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Vesicourethral anastomosis sampling – a forgotten tool for guiding salvage radiation post radical prostatectomy

Running title: VUA sampling to guide salvage radiation post radical prostatectomy

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Abstract

Objective

To review the utility of vesico-urethral anastomosis (VUA) directed biopsy in the setting of biochemical recurrence (BCR) following radical prostatectomy (RP) for prostate cancer (PC), in patients who have undergone evaluation by Gallium-68 prostate-specific membrane antigen positron emission tomography with computed tomography (^{68}Ga-PSMA PET/CT).

Methods

We completed a retrospective review of a prospectively kept dataset from January 2015 to August 2020. Patient demographics were recorded for those who had BCR defined by a prostate specific antigen (PSA) increase to over 0.2ng/ml, had a ^{68}Ga-PSMA PET/CT that did not demonstrate recurrence within the prostate bed and subsequently underwent a transperineal ultrasound (TP US) guided biopsy directed at the VUA. Histological reporting of the biopsies was undertaken in order to determine if the benefits of salvage radiation therapy (SRT) could be justified by the presence of cancer cells.

Results

18 patients were identified with BCR who had a ^{68}Ga-PSMA PET/CT and underwent VUA directed biopsy. ^{68}Ga-PSMA PET/CT scans demonstrated avidity at the VUA in 0%, although 11.1% (2/18) showed avidity in the seminal vesicles and 11.% (2/18) showed avidity within regional lymph nodes. Histology from the TP US guided, VUA directed biopsies demonstrated no prostatic tissue in 33.3% and presence of prostatic tissue in 66.7% of patients respectively. In 38.9% cases there was histologic evidence of recurrent PC in the absence of a positive ^{68}Ga-PSMA PET/CT scan at the VUA.

Conclusion

This study highlights the potential value of VUA directed biopsy. We are reminded that a negative ^{68}Ga-PSMA PET/CT does not exclude local recurrence and that the addition of a VUA directed biopsy may aid in the decision-making process for patients with BCR following RP, especially when ^{68}Ga-PSMA PET/CT is locally negative. When the result of both ^{68}Ga-PSMA PET/CT and VUA directed biopsy are negative, it should encourage clinicians to share decision making in regard to undertaking SRT versus continuing BCR

surveillance. This may delay the possible side effect profile consequent upon SRT, despite the excellent PSA-failure free survival.

Introduction

Investigation and treatment of prostate cancer (PC) is highly topical, as it is the second most common cancer in men worldwide (1, 2). While there has been an overall decrease in treatment of PC, attributable to active surveillance of low risk PC in younger age groups, in recent years we have seen an increase in patients over 65 years of age who are successfully treated for intermediate and high-risk PC by external beam radiotherapy (ERBT) or radical prostatectomy (RP) (3). However, a proportion of those patients who undergo treatment will go on to develop biochemical disease recurrence (BCR) (4).

Conventional imaging for investigating BCR following RP with computerised tomography (CT) and whole-body technetium bone scans is rapidly being superseded by emission tomography (PET). Initially the development of the ^{18}F-fluoromethylcholine PET/CT led to significant advantage over conventional imaging, although its market penetrance was limited due to the evolution of Gallium-68 prostate-specific membrane antigen (^{68}Ga-PSMA) PET/CT. ^{68}Ga-PSMA PET/CT out-performs the ^{18}F-fluoromethylcholine PET/CT by improving the specificity for PC recurrence at lower PSA and looks to become the imaging investigation of choice, although isotope availability and cost may be barriers to global uptake (5-7).

Increased use of ^{68}Ga-PSMA PET/CT has had a significant impact on clinical decision making in the investigation of BCR following RP, due to the concept of treatable oligometastatic PC. Accurate early detection of solitary or low volume PC recurrence in bones and lymph nodes has become paramount to planning metastasis directed therapy (MDT). The idea of MDT, such as stereotactic ablative body radiotherapy (SABR), has been offered as an alternative to salvage pelvic radiotherapy (SRT) with or without (+/-) androgen deprivation therapy (ADT) in an effort to avoid side effects and improve quality of life of patients suffering BCR following RP (8-10). SABR has been shown to be effective in treating oligometastatic deposits and decreasing PSA in 60-70% of patients without risks associated with widefield SRT (7, 11). A metanalysis of

^{68}Ga-PSMA PET/CTs specificity and sensitivity has demonstrated its ability to detect true recurrence in 33% of cases when PSA is 0.2ng/ml and up to 95% of cases when PSA is >2ng/ml (12).

It is recognised however that ^{68}Ga-PSMA PET/CT does not have high sensitivity for PC recurrence. Lack of tracer avidity does not preclude recurrence of PC, especially in cases of low PSA and low volume PC (12, 13). Prior to the introduction of ^{68}Ga-PSMA PET/CT, vesico-urethral anastomosis (VUA) directed biopsies had been considered to evaluate whether local recurrence in the prostatic bed was present, and whether patients would benefit from SRT (14).

We reviewed a prospectively collected database from a group of surgeons who have performed VUA directed, transperineal ultrasound (TP US) guided biopsies of the prostatic bed as a way to bridge the sensitivity gap afforded by ^{68}Ga-PSMA PET/CT, in order to assist determine whether patients might avoid or delay SRT and its possible side effects.

Methods

Data collection

We completed a retrospective review of a multi-surgeon, prospectively kept dataset from January 2015 to August 2020 for patients who were discussed at a local multidisciplinary meeting (MDM), had a ^{68}Ga-PSMA PET/CT without tracer avidity clearly surrounding the VUA who, after being made aware of the published data potentially justifying this procedure, consented to undergo a TP US guided VUA directed biopsy for BCR defined by a PSA rise above 0.2ng/ml following previous RP for PC. Patient demographics, ^{68}Ga-PSMA PET/CT lack of tracer avidity at the VUA determined by two nuclear medicine radiologists, and histological outcome determined by an anatomical pathologist with specialisation in Genitourinary cancers were recorded. MDM discussion of all results followed to determine if salvage radiation therapy (SRT) could be justified by the presence of cancer cells. Follow up duration post-biopsy was measured, as was time from completion of SRT.

Biopsy strategy

All biopsies were performed under general anaesthetic in high lithotomy position with 2g of intravenous cephazolin antibiotic coverage. Biopsies were TP US guided and directed at the VUA, using a FlexFocus 800 with an Endocavity Biplane E14CL4b transducer (BK Medical). To better define the VUA, patients were instructed to keep a full bladder prior to biopsy, although if required, an in-out 12-16F catheter was placed under anaesthesia and 100-200ml of normal saline was instilled to improve the quality of US images obtained. 1-2 cores were sampled at the left and right anterior; left and right mid (1-2mm or needle width from urethra); and left and right posterior aspects of the VUA with cognitive direction towards the seminal vesicle beds for a total of 6-8 cores (Figure 1). If there was suggestion by magnetic resonance imaging (MRI) of a soft tissue target at the VUA, the template was adapted to include those areas.

Histologic analysis

All histology was read by anatomical pathologists with specialisation in genitourinary malignancy. The 6-8 cores were microscopically reviewed for nucleoli, gland formation and if equivocality to the presence of PC they were subsequently immunoassayed with PSA to further define presence of PC.

Imaging strategy

Full body ^{68}Ga-PSMA PET/CT scans were undertaken and read by two nuclear medicine radiologists from a high-volume centre (Initial report and secondary review at MDM) as to the presence of tracer avidity in the region of the VUA. 68Ga-PSMA injected dose ranged from 150-200MBq and imaging was completed within 40-60 minutes. Where possible, patients underwent pre-biopsy pelvic MRI using a Skyra 3-T scanner (Siemens) to look for soft tissue targets from which to modify the biopsy template.

Ethics

Ethics were approved for a retrospective review of the prospectively kept dataset through the Austin Health Office for Research against the principles of the National Statement on Ethical Conduct in Research (2007, updated 2018) HREC (Audit/20/Austin/40).

Results

18 patients were identified with BCR who had a ^{68}Ga-PSMA PET/CT and underwent VUA directed biopsy. Median age was 64.5 [58 – 70] years and median time between prostatectomy and biochemical recurrence prompting VUA biopsy was 12.5 [8 – 24] months. Median PSA doubling time was 6 [6.0-6.75] months. 16.7% (3/18) of patients had pelvic lymph node dissection (PLND), 83.3% (15/18) of patients had involved margins at RP and 83.3% (15/18) of patients had pT3 PC where no PC was detected in the patients who underwent PLND. The PSA range prior to re-staging imaging was 0.3-4.4ng/ml with a median of 0.48 ng/ml [0.42 – 1.13]. (Table 1)

^{68}Ga-PSMA PET/CT scans were completed in all 18 patients. ^{68}Ga-PSMA PET/CT scans demonstrated tracer avidity at the VUA in 0% of scans. 11.1% (2/18) showed tracer avidity within the seminal vesicles and a further 11.1% (2/18) showed avidity within regional lymph nodes. In those patients who had tracer avidity visible beyond the prostate bed and VUA on ^{68}Ga-PSMA PET/CT, histology demonstrated no prostate tissue identified (NP) in 3/4 (75%) and benign prostate tissue (BN) in 1/4 (25%) respectively. The solitary case where BN was detected was where ^{68}Ga-PSMA PET/CT tracer avidity was present in a para-rectal lymph node. (Table 2)

MRI scans were completed in 72.2% (13/18) patients. 15.4% (2/13) of those scans demonstrated a soft tissue mass at the VUA, the other 84.6% (11/13) did not. The 9 patients with negative MRI scans demonstrated NP, BN and PC on histology in 36.4%, 18.2% and 45.4% respectively. (Table 3)

Histology from the TP US guided, VUA directed biopsies demonstrated no prostate tissue, benign prostate tissue and PC in 33.3% (6/18), 27.8% (5/18) and 38.9% (7/18) respectively. Patients who had demonstrable PC on VUA directed biopsy all had pT3 staging at RP and all excepting one had positive margins.

Of the two patients who had soft tissue masses detected on MRI suggestive of recurrence, one had histologic evidence of PC, although the other had benign prostate tissue only. ISUP grades of PC were 1,2,3 and 4. PC where ISUP ≤ 2 was present in 71.4% of the total PC specimens, where ISUP ≥3 was identified in 28.6% of PC specimens. (Table 3) In the PC ISUP ≥3 recurrence group, there was one ISUP 3with a PSA 0.33 and one ISUP 4 with a PSA of 0.66. The core measurements in ISUP 3 were 6 and 7mm in length; and the core measurements in the ISUP 4 recurrence was 2.5mm. There were no reported adverse outcomes recorded in terms of infection, erectile disfunction or urinary retention in the cohort.

77.8% (14/18) patients underwent SRT to the pelvis with minimum 6 months ADT (range 6-18months), 11.1% (2/18) patients had SABR to solitary lymph nodes without ADT and 11.1% (2/18) patients were put placed on surveillance. Those patients placed on surveillance shared in decision making on management following MDM discussion where, due to lack of ^{68}Ga-PSMA PET/CT tracer avidity and a VUA biopsy with either NP or BN was identified, an unclear treatment consensus existed. Patients on placed on surveillance both had stage pT3 and positive margins at RP where RP histology grade was ISUP 2 and 3 respectively.

Duration of follow up from time of salvage radiation ranged from 1-56 months with a median of 24 [12 – 46] months. Both patients who underwent SABR without ADT developed recurrence of PSA, where the first was within 3 months of SABR and had new lymphatic tracer avidity on repeat ^{68}Ga-PSMA PET/CT. The other patient developed PSA recurrence at 46months following SABR, although ^{68}Ga-PSMA PET/CT has yet to detect a site of recurrence and therefore he continues on surveillance. He is now 56 months post SABR with a PSA of 1.89ng/ml, although his first recurrence with ^{68}Ga-PSMA PET/CTs tracer avidity was not until his PSA reached 4.4ng/ml. One patient who underwent SRT with 18 months of ADT developed PSA recurrence 28months thereafter. ^{68}Ga-PSMA PET/CT at PSA 0.19ng/ml demonstrated widespread lymphatic deposits. His VUA directed TP US guided biopsy demonstrated no prostate tissue. (Table 4)

Discussion

Incomplete resection of the prostate at RP is a risk that patients accept when choosing to have surgical treatment of their PC. It is accepted that 20-40% of patients having RP for clinically T2 PC will ultimately be shown to have non-organ confined (pT3) PC (15). Lightfoot et al remarked that at RP, 47% of stage pT3 PC cases resulted in a positive margin resection (16). Those patients with a positive margin and pT3 PC are at increased likelihood of BCR due to failure of local control. Shekarriz et al were so convinced of likely local recurrence following their study of this, they stated that where a patient has stage pT3 PC at resection and PSA post-operatively rises above 1ng/ml, a VUA directed biopsy was not required to confirm local recurrence (14).

These findings invite us to openly adopt the views provided by Emmett et al that where a ^{68}Ga-PSMA PET/CT is negative or shows recurrence isolated to the prostatic fossa, SRT has shown excellent treatment response and durability without ADT, compared to those with identifiable distant disease (17, 18). Despite this, SRT alone is not without its significant side effect profile in both the short term (nausea, vomiting, abdominal pain) and the long term (haematuria, bladder neck contracture, and radiation proctitis). In an effort to avoid the side effects of SRT, despite its track record as the only curative intent treatment for BCR following RP for PC (19), there may

be those strong believers in MDT who favour surveillance with plans to act once tracer avidity declares itself on serial ^{68}Ga-PSMA PET/CTs or PSA surpasses 1.0ng/ml.

With the advent of TP US guided biopsy, the significant infection rates of 1-3% faced by transrectal ultrasound guided biopsy have been reduced to as low as 0.076% in addition to improving the likelihood of sampling PC within the anterior gland (20-22). This makes the decision to offer TP US guided sampling of the VUA region a safe and reasonable option for patients with BCR following RP where a ^{68}Ga-PSMA PET/CT which is negative for recurrence in the prostatic fossa.

All 18 patients in the cohort underwent ^{68}Ga-PSMA PET/CT to evaluate their BCR following RP as we are currently led to believe it is the best modality for identification of possible PC recurrence. Perera et als metanalysis on ^{68}Ga-PSMA PET/CTs specificity and sensitivity has potentially falsely reassured us of the lack of disease recurrence within the prostate bed in the scans ability to detect true recurrence in 33% of cases when PSA is 0.2ng/ml and up to 95% of cases when PSA is >2ng/ml (12). In our cohort 22.2% (4/18) of patients had identifiable tracer avidity on ^{68}Ga-PSMA PET/CT, although none at the VUA/bladder base as was the case with the remaining 77.8% (14/18). Despite this 38.9% (7/18) of patients had demonstrable PC detected and a further 27.8% (5/18) had benign prostatic tissue identified on VUA directed, TP US guided biopsy.

The question of MRI evaluation of the pelvis following a negative ^{68}Ga-PSMA PET/CT may be posed. 72.2% (13/18) of our cohort underwent MRI scan prior to biopsy. Further definition of possible VUA recurrence of PC can be identified by MRI as it may inform on soft tissue recurrence with high accuracy that may be targeted for sampling when undergoing TP US guided, VUA directed biopsy to prove recurrence is PC (23). The addition of MRI has also been shown to be useful when planning for SRT delivery (24).

Only 15.4% (2/11) of those MRI scans identified possible disease recurrence where the remaining 84.6% (9/11) did not. Of those 9 patients with negative MRI scans for recurrence, NP, BN and PC was detected in 36.4%, 18.2% and 45.4% respectively. In the two patients with MRI scans detecting possible recurrence BN was detected in one and PC was detected in the other. We suggest that while an MRI indicative of recurrence warrants targeted biopsy, an MRI lacking suggestion of recurrence does not preclude the possibility of both BN or PC presence.

In patients who have already chosen to have surgical treatment of their PC, it may be hard to assuage anxieties where biopsy reveals NP or BN that PC was not missed or that BN will not progress to PC. These anxieties were apparent in our cohort where many patients were eager to pursue SRT (14/18) where under half (7/18) had demonstrable PC. This is additionally reflective of the time period of the study, where recommendations guiding urologists suggested that if the PSA was increasing and a ^{68}Ga-PSMA PET/CT was negative, patients should be offered SRT (17, 18). The appeal of surveillance compared with SRT +/- ADT in the context of patients without PC lies in the possible significant detrimental side effects encountered with treatment (19).

In our cohort 3/18 patients had BN demonstrated at TP biopsy. Two of those when offered shared decision making following a negative ^{68}Ga-PSMA PET/CT and MRI chose to have SRT. In the patient who chose surveillance, he is now 22 months on from when his PSA broached 0.2ng/ml. His PSA has progressed from 0.51ng/ml at biopsy to 0.92ng/ml. He has had two further ^{68}Ga-PSMA PET/CT scans which have not demonstrated any tracer avidity and he is content with his choice as he believes it allowed him to avoid the side effects of SRT +/- ADT. In the two patients who chose SRT following biopsy revealing BN, both received ADT. The first patient has been followed for 48 months and has suffered severe bowel frequency and urgency since the time of his SRT for which he regularly takes loperamide, he has also continued to experience hot flushes and fatigue despite testosterone normalisation following ceasing ADT. The second patient has been followed for 8 months, is currently on ADT to be completed following a total of 18 months of treatment. He suffers from fatigue, depression and has had significant weight gain from treatment initiation.

Conclusion

While this is a limited cohort study without the ability to make significant recommendations on the sensitivity of ^{68}Ga-PSMA PET/CT or effectiveness of SRT compared to SABR, it does highlight the potential utility of VUA directed biopsy. A negative ^{68}Ga-PSMA PET/CT does not exclude local recurrence and the addition of a VUA directed biopsy may aid in the decision-making process for patients with BCR following RP, especially when ^{68}Ga-PSMA PET/CT is locally negative. When the result of both ^{68}Ga-PSMA PET/CT and VUA directed biopsy are negative, it should encourage clinicians to share decision making in regard to giving SRT versus continuing BCR surveillance with serial PSAs and ^{68}Ga-PSMA PET/CTs in an effort to delay the possible side effect profile of SRT,+/- ADT despite its excellent PSA-failure free survival.

Conflict of interest statement

We declare no conflict of interest in the presentation of these works.

Figure 1 – Vesicourethral anastomosis directed, transperineal ultrasound guided biopsy on BK Medical FlexFocus 800 with an Endocavity Biplane E14CL4b transducer

[Legend – A) Urethral catheter in place to fill bladder and define VUA, highlighted; B) Urethral catheter removed, bladder volume 150ml with VUA highlighted; C) Anterior to VUA directed biopsy pre-fire; D) Anterior to VUA directed biopsy fired; E) Mid VUA lateral to urethra – needle thickness away- directed biopsy pre-fire; F) ; Mid VUA lateral to urethra – needle thickness away- directed biopsy fired; G) Posterior to VUA directed biopsy pre-fire; H) Posterior to VUA directed fired]

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Table 1 – Demographics

(Legend - RP: radical prostatectomy; ISUP: international society of urological pathology; BCR: biochemical recurrence; PSA: prostate specific antigen)

Demographics	N= 18
Median patient age (years, IQR)	64.5 [58 – 70]
Grade ≥ ISUP 3 at RP	61.5%
Stage ≥ pT3 at RP	88.9%
Positive margin at RP	83.3%
Median time to BCR from RP (months, IQR)	12.5 [8 – 24]
PSA at biopsy 0.2-0.5	50%
PSA at biopsy 0.5-1.0	22.2%
PSA at biopsy >1.0	27.8%
Median PSA Doubling Time (months, IQR)	6.0 [6.0 – 6.75]

Table 2 - Suggestion of disease recurrence elsewhere by ^{68}Ga-PSMA PET/CT, locality and histology

(Legend - 68Ga-PSMA PET/CT: Gallium-68 prostate-specific membrane antigen positron emission tomography with computed tomography; PSA: prostate specific antigen; VUA: vesicourethral anastomosis; NP: no prostate cells detected; BN: benign prostate tissue)

^{68}Ga-PSMA PET/CT scans completed			N=18
Tracer avidity suggesting PC elsewhere			22.20%
Tracer avidity at seminal vesicle			11.10%
Tracer avidity at regional lymph node			11.10%
	PSA (ng/ml)	Location of avidity	VUA Biopsy Histology
Patient 1	0.34	Para-rectal lymph node	BN
Patient 2	4.4	Para-rectal lymph node	NP
Patient 3	0.46	Left seminal vesicle	NP
Patient 4	0.63	Right seminal vesicle	NP

Table 3 – ^{68}Ga-PSMA PET/CT avidity, MRI soft tissue, VUA biopsy histology by proportion of case numbers and percentage

(Legend - PSA: prostate specific antigen; MRI: magnetic resonance imaging; VUA: vesicourethral anastomosis; NP: no prostate cells detected; BN: benign prostate tissue; PC: prostate cancer; 68Ga-PSMA PET/CT: Gallium-68 prostate-specific membrane antigen positron emission tomography with computed tomography; ISUP: international society of urological pathology; - : no MRI completed)

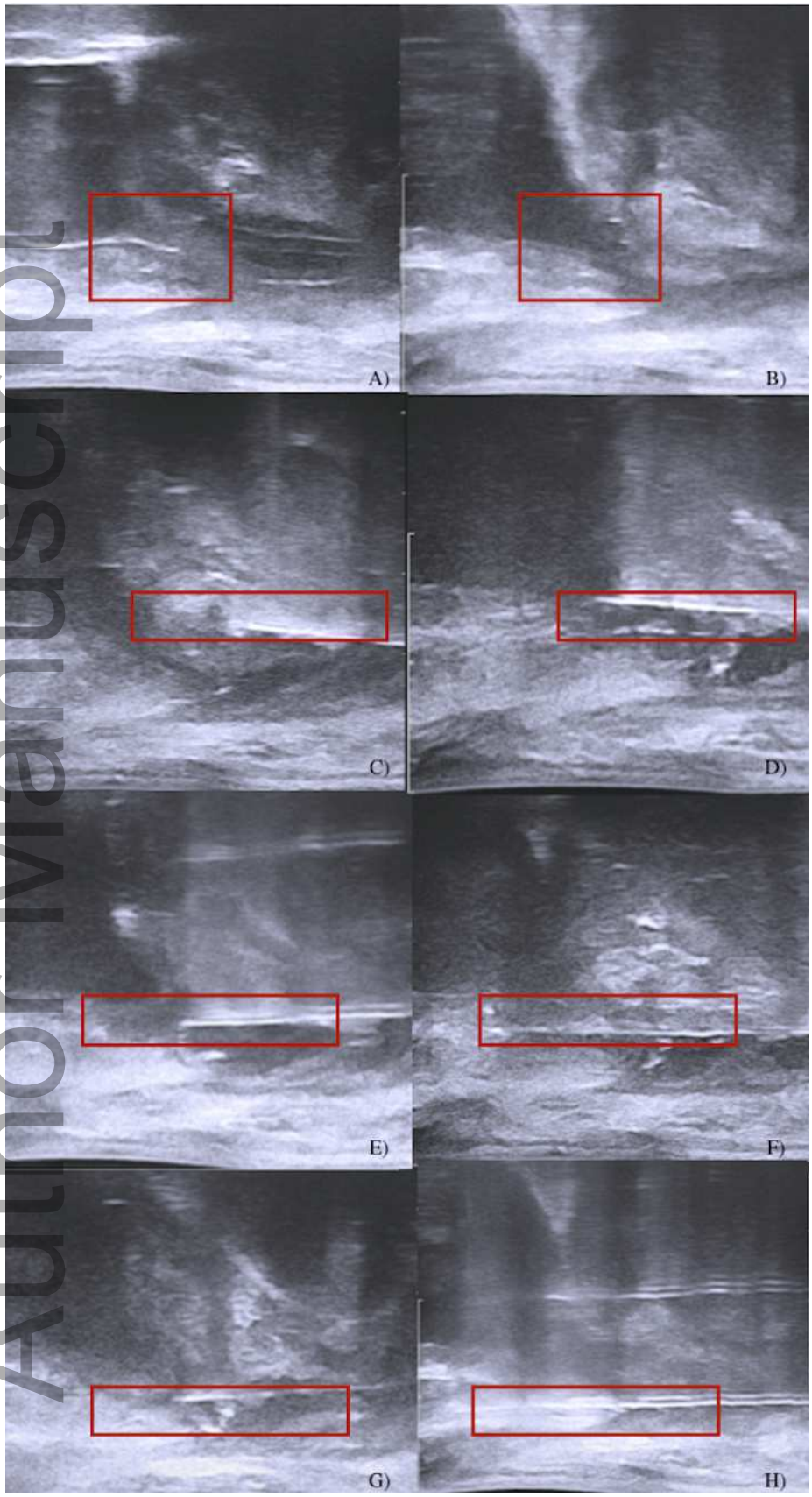
	PSA ≤0.5 ng/ml	PSA 0.5-1.0 ng/ml	PSA ≥1.0 ng/ml	Number of total	%
Total Number of Patients	9	4	5	18/18	-
MRIs completed	9	1	3	13/18	72.2%
MRI no recurrence suggested	9	-	2	11/13	84.6%
VUA histology - NP	2	-	2	4/11	36.4%
VUA histology - BN	2	-	0	2/11	18.2%
VUA histology - PC	5	-	0	5/11	45.4%
MRIs recurrence suggested	-	1	1	2/13	15.4%
VUA histology - NP	-	0	0	0/2	0%
VUA histology - BN	-	0	1	1/2	50%
VUA histology - PC	-	1	0	1/2	50%
68Ga-PSMA PET/CT completed without VUA tracer avidity	9	4	5	18/18	-
Tracer avidity elsewhere	2	1	1	4/18	37.6%
Tracer avidity elsewhere - NP	1	1	1	3/4	75%
Tracer avidity elsewhere - BN	1	0	0	1/4	25%
Tracer avidity elsewhere - PC	0	0	0	0/4	0%
Histology Overall					
No prostate tissue identified	2	1	3	6/18	33.3%
BN identified	2	1	2	5/18	27.8%
PC identified	5	2	0	7/18	38.9%
PC ISUP ≤2 identified	4	1	0	5/7	71.4%
PC ISUP ≥3 identified	1	1	0	2/7	28.6%

Table 4 - Treatment assigned and follow up outcomes

(Legend - PSA: prostate specific antigen; 68Ga-PSMA PET/CT: Gallium-68 prostate-specific membrane antigen positron emission tomography with computed tomography; SABR: stereotactic ablative body radiotherapy; NP: no prostate cells detected; BN: benign prostate tissue; PC: prostate cancer; SRT: salvage radiotherapy)

	PSA ≤0.5 ng/ml	PSA 0.5-1.0 ng/ml	PSA ≥1.0 ng/ml	BCR following salvage	Mean Time to BCR following salvage (months mean +/- SD)	Mean duration of follow up (months mean +/- SD)	Recurrence site defined by 68Ga-PSMA PET/CT
Cases which underwent SABR to affected lymph node	1	0	1	100%	24.5±29.8	-	-
Cases with NP cells on biopsy	0	0	1	100%	3±0	Not continued post salvage	Para-aortic lymph node
Cases with BN on biopsy	1	0	0	100%	46±0	56±0	None defined, PSA currently1.89
Cases with PC on biopsy	0	0	0	0%	-	-	-
Cases which underwent SRT	8	3	3	76.90%	28±0	23.1±8.4	-
Cases with NP on biopsy	2	1	1	25.00%	28±0	18±5.9	Widespread lymph nodes
Cases with BN on biopsy	1	0	2	0.00%	-	26±18.8	-
Cases with PC on biopsy	5	2	0	0.00%	-	29±16.8	-
Cases under surveillance	0	1	1	-	-	13±12.5	-
Cases with NP on biopsy	0	0	1	-	-	4±0	-
Cases with BN on biopsy	0	1	0	-	-	22±0	-

Cases with PC on biopsy	0	0	0	-	-	-	-



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