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Ga-PSMA PET: Still just the tip of the iceberg

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Running head: Ga-PSMA PET for prostate cancer

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Abstract

Objectives

To assess the performance of Ga-PSMA PET for positive lymph nodes on imaging after curatively intended radical prostatectomy.

Patients and methods

Seventeen patients with biochemical recurrence after radical prostatectomy undergoing robot assisted salvage lymphadenectomy for positive lymph nodes on imaging were

included in this single surgeon study. The performance of Ga-PSMA PET was assessed on a per patient, per lesion, per landing site and per laterality level using sensitivity, specificity, negative and positive predictive value analysis.

Results

A total of 34 positive nodes were detected on Ga-PSMA PET with a median of 2 nodes per patient (IQR 1 - 3 nodes per patient). Sixty six nodes were pathologically disease positive from 14 patients, with a median of 2 positive nodes per patient (IQR 1 - 6). Three patients had no pathologically detectable disease. On a per patient basis the positive predictive value was 82%. Sensitivity, specificity and negative predictive value were not able to be calculated as all patients had disease recurrence with a detectable PSA.

On a “per lesion” basis, the sensitivity, specificity, positive predictive value and negative predictive value were 36.7%, 96.9%, 73.5% and 86.7%, respectively.

Conclusion

Our study indicates that sensitivity of Ga-PSMA PET in the salvage setting is not yet sufficient to detect all sites of metastasis. Therefore, imaging guided metastasis targeted treatment is likely to fail given the likely concomitant imaging negative more widespread disease.

Keywords: Ga-PSMA PET; Staging; Prostate cancer

Introduction

Prostate cancer is the most common solid organ malignancy affecting male patients in Western populations. Although PSA screening has lead to earlier stage diagnosis in most men, a significant number will fail local therapy and suffer biochemical relapse. Ga-PSMA PET has emerged as a more sensitive and specific investigation than any other imaging modality, generating renewed interest in a theoretical “oligometastatic” state. However, there is little data on the sensitivity of Ga-PSMA PET at an individual lesion level, as

distinct from overall sensitivity at the patient level. Successful treatment of the oligometastatic state is dependent on correctly identifying all metastases in an individual patient, otherwise further relapse is inevitable. The aim of this study was to determine the individual lesion sensitivity of Ga-PSMA PET in a patient population undergoing salvage pelvic lymph node dissection after failed local therapy with curative intent.

Patients and Methods:

From April 2015 to August 2017, 17 patients with pelvic and/or retroperitoneal node only recurrence on Ga-PSMA PET imaging were included in this prospectively recorded and retrospectively analysed single surgeon (PD) study.

All patients presented with biochemical recurrence (as defined by PSA >0.2ug/l) after curative intended radical prostatectomy without extended pelvic lymphadenectomy. All patients underwent a Ga-PSMA PET in addition to full body diagnostic computed tomography for re-staging. Selected patients with clinical suspicion of local recurrence also underwent pelvic magnetic resonance imaging to exclude local pelvic recurrence. Each patient was discussed in a dedicated prostate cancer multidisciplinary meeting and were deemed suitable for salvage treatment if they had lymph node only recurrent disease detected on Ga-PSMA PET imaging and the identified nodes were considered surgically resectable. Although all patients were consented to the experimental nature of the treatment, there were no patients who declined to undergo surgery. Included patients underwent robot assisted salvage pelvic +/- limited retroperitoneal lymph node dissection. Three patients had concomitant retroperitoneal node dissection. Only two patients had undergone pelvic node dissection at the time of radical prostatectomy (limited obturator node dissection in one patient and unilateral node dissection in a second patient), 4 patients had received and then ceased prior androgen deprivation and four patients had received prior salvage external beam radiotherapy. One patient had received stereotactic radiotherapy to a pelvic bone metastases at the time of radical prostatectomy and 3 years

prior to salvage lymphadenectomy. Patients were followed up with a clinical review one week after surgery. PSA was first performed 3 months postoperatively, then every 3 months.

Surgery:

Port placement and robotic arm set-up was identical to that performed for robotic assisted radical prostatectomy if extended pelvic lymphadenectomy only was performed. When limited retroperitoneal node dissection was performed in conjunction with extended pelvic lymphadenectomy, the camera port and arms were placed approximately 7cm proximally. All patients underwent a systematic bilateral extended pelvic lymphadenectomy, including tissue over the common iliac vessels to the crossing of the ureter, the external iliac vessels down to the node of Cloquet, the obturator fossa and the internal iliac vessels. Presacral tissue was sent only when suspicious nodes were identified in this region on imaging. When Ga-PSMA PET positive lymph nodes were identified in the retroperitoneum, the dissection included the tissue over the common iliac arteries and the retroperitoneum, bounded by the ureters laterally, to the level of the inferior mesenteric artery. Tissue was sent in separate packets from each anatomical region unless the hemi-pelvis was node negative on imaging, in which case the tissue was sent as a single packet from that side only. When limited retroperitoneal dissection was performed, tissue was sent from the pre-aortic, paracaval and interaortocaval regions separately. Thirteen landing sites were described per patient (Fig. 1).

Pathologic processing:

Identified lymph nodes were sampled and processed using routine protocols. Sampled nodal tissue was sectioned at 3um and stained with routine H&E. Histopathological assessment was performed, with quantification and reporting of total number of nodes, number of involved nodes and size of individual deposits. PSMA immunohistochemical

staining with Dako 3E6, 1:50 dilution was performed on representative metastatic tumour deposits.

Ga-PSMA PET acquisition:

Ga68-PSMA-HBED-CC was produced using an IRE Galli Eo 68Ge/68Ga generator with Scintomics GRP module. ITLC, HPLC and pH testing was performed to assure radiotracer purity.

Patient dose was 1.3-2.0 MBq/kg, IV 20 mgs Lasix was administered 10 minutes after tracer injection, unless significant urinary symptoms were reported.

During the uptake phase of 60-90 minutes, patients were hydrated orally with water.

Images were obtained using a Siemens Biograph mCT(20) Excel scanner.

After voiding, imaging was started with a low dose CT scan acquisition (120 KV, 30-50mAs, 16x1.2 mm collimation with 1.0 pitch, rotation time of 0.5 for 780 mm FOV for attenuation correction) with 3mm slice thickness in 2 mm increments using Siemens CARE Dose 4D.

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

PET slices were reconstructed using iterative reconstruction and TOF (2 iteration/21 subsets) with a transaxial spatial resolution in the reconstructed PET images of 7.0mm at FWHM.

The lung field was additionally separately reconstructed using a lung kernel and a maximum intensity reconstruction.

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

All images were analysed prior to surgery by a certified nuclear medicine radiologist and reviewed at a multidisciplinary conference including urologists, radiation and medical oncologists, general radiologist and a nuclear medicine radiologist.

Statistics:

Categorical data are presented as counts or percentages. The continuous variables are presented with median and interquartile range. The performance of Ga-PSMA PET was assessed at the patient level, “per lesion”, by anatomical landing site and by laterality using sensitivity, specificity, positive predictive value and negative predictive value. Statistical analysis was performed using GraphPad Prism 7 (GraphPad Software Inc.).

Results:

Patient characteristics at the time of radical prostatectomy and at the time of salvage lymph node dissection are presented in table 1. Sixteen of seventeen patients had node only recurrence detected on Ga-PSMA PET and 1/17 patient had node only recurrence on computed tomography with negative Ga-PSMA PET imaging. The median PSA pre-operatively was 1.6ng/mL (IQR 0.81 - 2.70ng/mL) with a median PSA doubling time of 4.85 months (IQR 3.55 - 7.2 months). A total of 34 positive nodes were detected on Ga-PSMA PET with a median of 2 nodes per patient (IQR 1 - 3 nodes per patient). The median time from radical prostatectomy to salvage node dissection was 4 years.

A total of 356 nodes were removed from 17 patients with a median node count of 20 nodes per patient (IQR 14 - 25). Sixty six nodes were pathologically disease positive from 14 patients, with a median of 2 positive nodes per patient (IQR 1 - 6). The average node deposit was 7.92mm (range 0.7 - 28mm). Three patients had no pathologically detectable disease; two of these patients had 1 Ga-PSMA PET avid node and one patient had 2 Ga-PMSA PET avid nodes. One patient had a PET positive mesorectal node that was unresectable and a further patient had a deep internal iliac node that was unresectable. Both patients had post-operative Ga-PSMA PET confirming the persisting presence of respective nodes.

The median size of Ga-PSMA PET positive node deposits was 10mm in comparison to 4mm for Ga-PSMA PET negative node deposits (p=0.0026). The smallest node deposit

detected on Ga-PSMA PET was 4.5mm whilst the smallest node deposit resected was 0.7mm.

On a per patient basis the positive predictive value was 82%. One patient was considered true positive without histologic correlation as they had an unresectable internal iliac node that had persisting Ga-PSMA PET avidity post-operatively. This patient was subsequently treated with stereotactic radiotherapy to the internal iliac node, which resulted in a PSA decline from 1.2ng/mL to 0.194ng/mL. Sensitivity, specificity and negative predictive value were not able to be calculated for this cohort of patients as there were no true negative patients who underwent surgery and by definition, all patients had disease recurrence with a detectable PSA following primary extirpative treatment.

On a “per lesion” basis, the sensitivity, specificity, positive predictive value and negative predictive value were 36.7%, 96.9%, 73.5% and 86.7%, respectively. When each of the 13 nodal basins were considered rather than each individual node in isolation, sensitivity and negative predictive value improved to 64.7% and 92.9% respectively, but specificity and positive predictive value were slightly worse at 94.0% and 68.8%. When results were considered by laterality only (i.e. right versus left), sensitivity and positive predictive value improved again at 86.9% and 83.3%, but this was at the expense of specificity and negative predictive value at 66.7% and 72.7% respectively.

Discussion:

There has been increasing interest in metastasis directed therapy in patients presenting with limited metastatic burden either at the time of primary therapy, or in patients presenting with disease recurrence following definitive primary therapy. Both surgical extirpation and stereotactic radiotherapy have been utilised in this context, but surgery has been reserved only for patients presenting with lymph node only recurrences. Although long term biochemical recurrence free survival is possible following oligometastatic treatment, the majority of patients suffer biochemical recurrence and many progress to

clinical recurrence. Such an approach is clearly dependent on the sensitivity of imaging to detect all recurrences in an individual patient in order that they can be treated. Traditional staging for prostate cancer patients has included computed tomography, MRI and Tc-labelled whole body bone scan. Each of these investigations have poor sensitivity, particularly in patients with low PSA values. More recently, choline and fluorocholine PET have been utilised for staging, particularly in the setting of disease recurrence, but sensitivity is low, especially in patients with PSA values <1.0ng/mL[1,2].

Ga-PSMA PET has emerged over the last few years as a highly sensitive and specific investigation, particularly in the setting of biochemical recurrence following definitive primary treatment and even with very low PSA. An original report by Afshar-Oremieh et al in 2014 on the diagnostic performance of Ga-PSMA PET in 319 patients indicated very high sensitivity and specificity, even in patients with very low PSA values[3]. Histopathologic correlation, however, was obtained in very few patients. Their update in over 1000 patients reported similarly high sensitivity, but again without histopathologic correlation in most patients[4]. Maurer et al reported on 130 patients with primary staging PSMA PET yielding a sensitivity of 65.9% based on template extended pelvic lymphadenectomy and a specificity of 98.9%, but they reported on the diagnostic performance at the patient level and not the individual lesion level[5]. The same group published on histopathologic correlation in the salvage setting, with field based sensitivity 77.9% and PPV 94.6%[6]. However, only 11 of 48 patients received an extended template based lymphadenectomy, with the remaining undergoing node dissection based on pre-operative imaging, which leaves the possibility of undetected metastatic disease in remaining lymph node fields.

Other groups have reported on histopathologic correlation with pre-operative PSMA imaging. Jilg et al reported a sensitivity 93.2% and PPV of 100% on the basis of “main regions” (left and right hemipelvis and retroperitoneum). On a subregion basis however, in which each hemipelvis was divided into 5 commonly used anatomical descriptors and the

retroperitoneum divided into 4 subregions, sensitivity fell to 81.2% but PPV remained high at 99.5%[7]. In their series, only 24/30 patients underwent a full bilateral tempate lymphadenectomy. In a comparison of FEC and Ga-PSMA PET, Pfister et al performed a systematic template based lymphadenectomy, but it is not clear if bilateral template dissection was performed[8]. They report sensitivity of 86.9% on a “per lesion” basis, but of note, a mean of only 11 lymph nodes were removed per patient.

Most reports on the sensitivity of Ga-PSMA PET are at the population level. This may be useful for patients considering salvage radiotherapy for example, where the presence of metastatic disease may render this approach futile[9]. However, when considering an aggressive oliometastatic approach, an inability to identify all individual lesions within a given patient will lead to biochemical persistence post treatment. The “per lesion” sensitivity is therefore a much more useful reference. Only two other studies that we could identify reported on the “per lesion” sensitivity of Ga-PSMA PET following pelvic lymphadenectomy[10,11]. In both of these studies, the sensitivity was higher than what we report, but the average number of nodes resected per patient was 12 and 12.6 respectively. Indeed, one of these studies also included retroperitoneal node dissection to a testis cancer template[10]. This compares to a median lymph node yield of 20 per patient in the current study. The low lymph node yield in these previous studies may reflect an incomplete pelvic lymphadenectomy, or it may be because of prior primary lymphadenectomy. In the setting of incomplete lymphadenectomy, the sensitivity is likely to be overestimated. Alternatively, prior lymphadenectomy may improve the diagnostic accuracy of Ga-PSMA PET because of a lower node density and fewer potential drainage sites. It is interesting to note that both of the studies assessing diagnostic accuracy of Ga-PSMA PET in the primary setting (at which time all patients have an intact pelvic nodal basin), showed a lower sensitivity in comparison to studies assessing diagnostic accuracy of Ga-PSMA PET in the salvage setting[5,7,10-14].

The smallest node deposit detected by Ga-PSMA PET in the current study was 4.5mm. This is almost identical to that reported by Budaus et al, in which the limit of detection of Ga-PSMA PET was 4mm[12]. The median node deposit in Ga-PSMA PET positive and negative metastases was 13.6 and 4.3mm, similar to the current study[12]. It would appear then, that the limit of detection of nodal disease on Ga-PSMA PET imaging is around 4mm, which would explain why most patients suffer biochemical recurrence following oligometastatic treatment. It is not known if the limit of detection is the same for bone metastases, but it would seem logical that there is a similar limit of detection.

Another consideration in the assessment of imaging performance is that of inter-interpreter variation. Maximum standardised uptake values (SUV_{max}) are higher with Ga-PSMA PET in comparison to FEC PET, which allows lesions to be seen more clearly and is likely to reduce inter-interpreter variation[3]. However, even on Ga-PSMA PET, some lesions may be weakly avid and therefore difficult to characterise. To our knowledge there is no data about inter-interpreter variation in the reporting of PSMA PET scans in the salvage setting for prostate cancer.

Conclusion

Although Ga-PSMA PET has shown superior diagnostic accuracy than other imaging modalities in prostate cancer, the current study indicates that the sensitivity is not yet sufficient to detect all sites of metastasis in most patients. These findings need to be considered in patients undergoing metastasis directed treatment given that imaging negative and therefore untreated metastasis might negatively influence the outcome.

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Table 1) Patient characteristics

At time of radical prostatectomy	
Median age, years (IQR)	66 (60-70)
Median follow up, months (IQR)	27 (9-37)
Pathological Gleason Score, n	
3+4	1
4+3	6
4+4	6
4+5	4
Pathological T stage, n	
pT2a	1
pT2c	3
pT3a	7
pT3b	6
Margin status, n	
negative	12
positive	5
Salvage Radiotherapy, n	
No	13
Yes	4
ADT before salvage LND, n	
No	13
Yes	4
At time of salvage lymph node dissection	
Median age, years (IQR)	69 (67-75)
Median time from RP to sLND, years (IQR)	4 (1.5-8)
Median positive nodes on Ga-PSMA-PET, n (IQR)	2 (1-3)
Median pathologically positive LND, n (IQR)	
Extracapsular extension (n)	2 (1-6)
10	

ADT: androgen deprivation therapy; (s)LND: (salvage) lymph node dissection; RP: radical prostatectomy

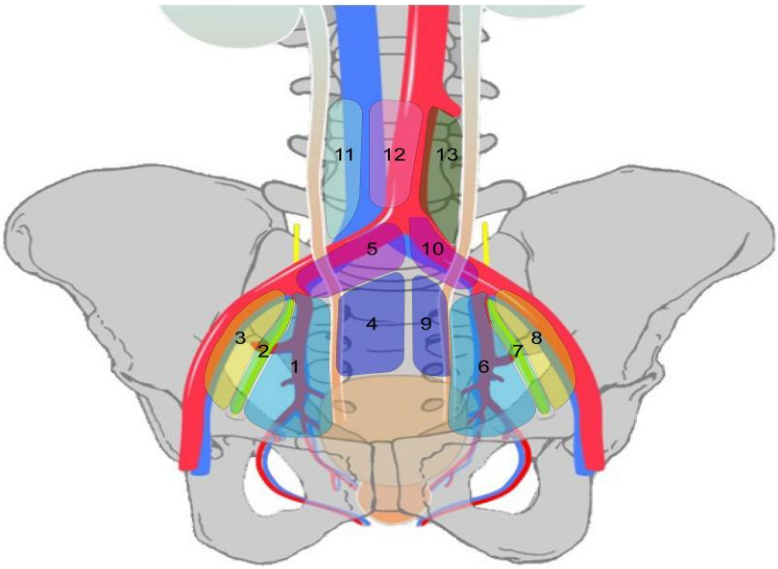

Figure 1: Defined landing sites for salvage lymphadenectomy (1:Right internal iliac; 2: right obturator; 3: right external iliac; 4: right presacral; 5: right common iliac; 6: left internal iliac; 7: left obturator; 8: left external iliac; 9: left presacral; 10: left common iliac; 11: paracaval; 12: interaortocaval; 13: preaortic