Use of PSMA PET/CT in Response Assessment Following Upfront Chemohormonal Therapy in Metastatic Prostate Cancer.

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Ethics approval and consent to participate

Multi-site ethical approval for this study was provided by the Melbourne Health Human Research Ethics Committee (HREC/14/MH/254), as a sub-study of a broader research project, prior to the commencement of data collection. This included a waiver of the requirement for individual patient consent, given the retrospective, non-interventional and de-identified nature of the

research and the patient group (advanced cancer). The study was conducted in accordance with the National Health and Medical Research Council's (NHMRC, Australia) National Statement on Ethical Conduct in Human Research (2007) and was carried out according to the principles of the Declaration of Helsinki.

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Dear Editor,

Prostate-specific membrane antigen (PSMA) PET/CT imaging is increasingly being utilised in clinical practice, demonstrating greater sensitivity in the detection of metastatic prostate cancer (mPC) compared to conventional imaging [1]. Prior studies have primarily focussed on its use following biochemical recurrence to detect oligometastatic disease potentially amenable to salvage therapies [2-4]. However, the role of PSMA PET/CT in assessing treatment response remains unclear. Standardised criteria for metabolic response have not been established, particularly to account for whole body tumour burden and the effects of systemic therapies on PSMA expression [5, 6].

Furthermore, the mPC treatment landscape has dramatically changed within the past decade. The addition of docetaxel to androgen deprivation therapy (ADT) in the hormone-sensitive setting has demonstrated significant survival benefit, with prostate-specific antigen (PSA) ≤ 0.2ng/mL after 7 months of therapy associated with superior overall survival [7].

Our study investigated the use of PSMA PET/CT in patients with mPC who received upfront chemohormonal therapy. The aim was to compare metabolic response by PSMA PET/CT to the established favourable prognostic marker of PSA ≤ 0.2 ng/ml following chemotherapy.

Patients who underwent PSMA PET/CT at baseline and within 6 weeks following upfront docetaxel were identified from two Australian sites. Those who received additional cancer therapy prior to CRPC were excluded. Patient and disease-related data were retrospectively collected. Baseline and restaging PSMA PET/CTs were evaluated using four tools: SUVmax (maximum standardised uptake value of PSMA-avid disease), molecular tumour volume (MTV: sum of all PSMA-avid lesions with SUV ≥3), total lesional PSMA-expression (MTV x SUVmean) and visual analysis (total lesional PSMA expression of all visible lesions on maximum intensity images, including SUV <3). Anatomical response was assessed using RECIST v1.1 criteria. Descriptive statistics reported imaging response, post-treatment PSA levels and the development of castration-resistant prostate cancer (CRPC). Comparisons were made using Fisher's Exact Test and follow-up time calculated using the Kaplan-Meier method.

Twenty-five patients were included; 7 with de novo mPC and 18 with metastatic recurrence leading to ADT commencement. Median age at diagnosis was 63 years and median baseline PSA was 12ng/ml. At baseline, all had PSMA-avid disease but only 15 (60%) had measurable disease on CT imaging. The majority of patients (84%) had lymph node and/or bone metastases with no visceral disease.

All patients experienced a PSA response, including 13 (52%) with PSA <0.2ng/ml following chemotherapy. By PSMA PET/CT visual analysis, 14 patients (56%) achieved partial response (PR), 9 (36%) achieved complete response (CR) and 2 (8%) developed progressive disease (PD) (Table 1). An important observation was the variability in response assessment between criteria in 10 (40%) patients. All nine patients with CR by visual analysis had concordant responses between criteria, however patients with stable disease or PD had inconsistent response assessments between criteria. Only 3 of the 15 patients with concordant PSMA PET/CT response had correlating anatomical response on CT.

After a median follow-up of 37.7 months, 13 patients (52%) developed CRPC. Patients achieving CR by visual analysis were less likely to develop CRPC (22% vs 69%; p=0.04). CRPC rates in those with a post-chemotherapy PSA ≤ 0.2ng/ml were numerically lower (46% vs 58%) although not statistically significant (p=0.70). Post-treatment PSA corresponded with

PSMA PET/CT response by visual analysis; patients with PSA ≤ 0.2ng/ml following chemotherapy were more likely to achieve CR (p=0.01).

PSMA PET/CT provided additional information to conventional CT with 8 of 13 patients who developed CRPC having no measurable disease on pre-chemotherapy CT. This is pertinent in prostate cancer where metastases predominantly involve bones or lymph nodes, often not measurable on CT and limiting the ability to utilise traditional RECIST v1.1 assessment criteria. PSMA PET/CT has the potential to detect and evaluate treatment response in these lesions.

Our small, retrospective study is limited by the lack of standardised PSMA PET/CT protocols and tracers between patients. PSMA PET/CTs were also performed at different time intervals following treatment commencement. Systemic therapies, including ADT and novel antiandrogens influence PSMA expression and therefore the timing of imaging following treatment is relevant [8]. Furthermore, very few patients underwent bone scans at baseline, an important component of conventional imaging. Comparison between bone scan and PSMA PET/CT response would be of significant value. In particular, PSMA PET/CT may be better for assessing osseous disease given the difficulty in differentiating progression from treatment response on bone scintigraphy.

There are few data regarding the use of PSMA PET/CT in metastatic disease. In the hormone-sensitive setting, systemic therapy studies have traditionally used conventional imaging to stratify patients by disease volume. However, with increasing use of PSMA PET/CT and the potential to more accurately measure metastatic disease, the implications on treatment choice and outcomes requires further evaluation.

Overall, our findings suggest that PSMA PET/CT response by visual analysis is concordant with the established good prognostic marker of PSA ≤ 0.2ng/ml following chemohormonal therapy and may be a better predictor of CRPC. Our study demonstrates the potential benefits of PSMA PET/CT over conventional CT in the assessment of treatment response in mPC. However in patients without CR, significant variability between response assessment

methods was observed. This highlights the need to further explore the full potential of PSMA imaging parameters and importantly, their correlation with long-term outcomes.

Kind Regards,

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Imaging Response Assessment Tool						
	Total Lesion PSMA Expression	SUV Max	Molecular Tumour Volume	Visual Analysis	CT RECIST v1.1 Response	Post-Chemotherapy PSA (ng/mL)
Discordant PSMA PET/CT Assessments						
1	PR	SD	PR	PR	CR	3.7
2	PR	PD	PR	PR	PR	3.17
3	PR	SD	PR	PR	NM	2.1
4	PR	SD	PR	PR	PR	5.4
5	PD	PR	PR	PR	PD	7.9
6	PR	SD	PR	PR	NM	0.23
7	PD	PD	SD	PD	PR	1.56
8	PR	SD	PR	PR	NM	0.47
9	PD	PR	PR	PD	PD	0.024
10	CR	PR	CR	PR	CR	0.1
Concordant PSMA PET/CT Assessments						
11	CR	CR	CR	CR	CR	<0.01
12	PR	PR	PR	PR	CR	<0.01
13	CR	CR	CR	CR	NM	<0.01
14	PR	PR	PR	PR	CR	0.1
15	CR	CR	CR	CR	PR	0.03
16	CR	CR	CR	CR	NM	0.01
17	CR	CR	CR	CR	CR	<0.01
18	PR	PR	PR	PR	CR	0.91
19	PR	PR	PR	PR	CR	5.3
20	CR	CR	CR	CR	CR	0.97
21	PR	PR	PR	PR	NM	<0.01
22	PR	PR	PR	PR	NM	0.02
23	CR	CR	CR	CR	NM	0.017
24	CR	CR	CR	CR	NM	0.08
25	CR	CR	CR	CR	NM	0.3

NM= Non-Measurable by RECIST v1.1 criteria
CR= Complete Response: Absence of any PSMA activity
PR= Partial Response: ≤ 70% of baseline measurement
SD= Stable Disease: Between 70% and 130% of baseline measurement
PD= Progressive Disease: New PSMA-avid disease or ≥ 130% of baseline measurement