A Prospective, Multi-site, International Comparison of F-18 fluoro-methyl-choline, multi-parametric magnetic resonance and Ga-68 HBED-CC (PSMA-11) in men with High-Risk Features and Biochemical Failure after Radical Prostatectomy: Clinical Performance and Patient Outcomes

Louise Emmett[1], Ur Metser[2], Glenn Bauman[3], Rodney J. Hicks[4], Andrew Weickhardt[5], Ian D. Davis[6], Shonit Punwani[7], Greg Pond[8], Sue Chua[9], Bao Ho[1], Edward Johnston[7], Frederic Pouliot[10] Andrew M. Scott[11].

[1]St. Vincent's Hospital, Sydney, Australia;
[2]University of Toronto, Toronto, Canada;
[3]London Health Sciences Centre, Ontario, Canada;
[4]Peter MacCallum Cancer Centre, Melbourne, Australia;
[5]Eastern Health, Melbourne, Australia;
[6] Monash University Eastern Health Clinical School
[7]University College London, London, UK
[8]McMaster University, Hamilton, Ontario Canada
[9]Royal Marsden Hospital, London, UK
[10]Université Laval, Quebec, Canada
[11]Austin Health, Melbourne, Australia;

Communicating Author: A/Prof Louise Emmett, Department of Theranostics, St Vincent's Hospital, Sydney, Australia.

Email: louise.emmett@svha.org.au Phone +61283821815 Fax +61283822619

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ABSTRACT:

Background: A significant proportion of men with rising PSA following radical prostatectomy (RP) fail prostate fossa salvage radiotherapy (SRT). This study assessed the ability of F18 fluoro-methyl-choline PET/CT(FCH) , Ga-68 HBED-CC PSMA-11 PET/CT (PSMA) and pelvic multi-parametric magnetic resonance imaging (pelvic MRI) to identify men who will best benefit from SRT.

Methods: Prospective, multisite, imaging study in men with rising PSA post RP, high-risk features (PSA > 0.2ng/mL and either Gleason Score (GS) > 7 or PSA doubling time <10 months, or PSA >1.0ng/mL) and negative /equivocal conventional imaging (CT and bone scan) being considered for SRT. FCH (91/91), Pelvic MRI (88/91) and PSMA (31/91) (Australia only) were performed within two weeks. Imaging was interpreted by experienced local and central reads blinded to other imaging results with consensus for discordance. Imaging results were validated using a composite reference standard. Expected management was documented pre and post- imaging, and all treatments, biopsies and PSA collected for 3 years. Treatment response to SRT was defined as > 50% PSA reduction without androgen deprivation therapy.

Results: Median GS, PSA at imaging and PSA doubling time were 8, 0.42(IQR 0.29-0.93) ng/mL, and 5.0 (IQR 3.3-7.6) months, respectively. Overall recurrent PCa was detected in 28% (25/88) with pelvic MRI, 32% (29/91) FCH and 42% (13/31) PSMA. This was within the prostate fossa (PF) in 21.5% (19/88), 13% (12/91) and 19% (6/31), with extra PF sites in 8% (7/88), 19% (17/91), and 32% (10/31) for MRI, FCH and PSMA (< 0.004). 94% (16/17) extra- PF sites on FCH were within the field of

view of pelvic MRI. The detection rate for intrapelvic extra-PF disease was 90% (9/10) for PSMA and 31% (5/16) for MRI compared to FCH. Imaging changed expected management in 46% (42/91) FCH, and 23% (21/88) MRI. PSMA provided additive management change over FCH in a further 23% (7/31). Treatment response to SRT was higher in men with negative or PF confined vs. extra PF disease. FCH 73% (32/44) vs. 33% (3/9) ($p< 0.02$), pelvic MRI 70% (32/46) vs 50% (2/4), p = ns) and PSMA 88% (7/8) vs. 14% (1/7) ($p<0.005$). Men with negative imging (MRI, FCH +/- PSMA) had high (78%) response rates to SRT.

Conclusion: FCH and PSMA had high detection rates for extra PF disease in men with negative/equivocal conventional imaging and BCR post RP. This impacted management and treatment responses to SRT, suggesting an important role for PET in triaging men being considered for curative SRT.

Introduction

Approximately 20-50% of pT2-3, node negative PCa patients experience biochemical recurrence (BCR) following radical prostatectomy (RP). Salvage radiation treatment (SRT) is the only potentially curative treatment option for these patients. The 5-year progression-free survival rate following SRT is approximately 50%, varying from 71% in men with pre-RT PSA level of 0.2ng/mL to 12% in men with high risk features [1-3]. Because SRT generally targets disease in the prostatic fossa (PF), and may have adverse effects on quality of life, patients with disease outside the prostatic fossa (extra PF) should ideally be spared futile salvage radiotherapy to the prostatic fossa alone, or considered for treatment intensification (addition of pelvic nodal radiotherapy to fossa irradiation and/or androgen deprivation therapy). SRT is most effective at low PSA levels (<1.0-2.0 ng/mL)[3, 4], at which conventional imaging (bone scan and computed tomography/CT) is insensitive. The aim of this study was to assess the ability of FCH, pelvic MRI and PSMA to identify those men with BCR post RP, negative conventional imaging and high risk clinical features who will best benefit from SRT.

Methods

Men with biochemical failure post RP and high-risk features being considered for SRT were prospectively recruited at 8 sites across Australia, Canada and the United Kingdom. The study protocol was approved by all institutional ethics boards (www.clinicaltrials.gov NCT02131649). Eligible consenting men had biopsy confirmed PCa, prior RP (pT1-T3, N0 or Nx) and a rising PSA (3 consecutive rises documented a minimum 2 weeks apart), with a PSA≥ 0.2ng/mL and at least one high-risk feature (PSA>1.0ng/mL, ≥pT3b, GS > 7 or PSA DT ≤ 10 months.). Diagnostic CT and bone scan within 12 weeks of enrolment were negative or equivocal for metastases with a planned management prior to enrollment of standard salvage fossa radiotherapy (SRT) with curative intent. A total of 91 men satisfied screening criteria and were enrolled in the study between July 2014 and January 2017. Enrolled men underwent both FCH and pelvic MRI within a 2 week period, with men in Australia undergoing an additional PSMA within the same time frame as part of study protocol. 3/91 men failed to complete the pelvic MRI component due to claustrophobia. All 91 men underwent FCH imaging, 88/91 completed pelvic MRI and 31/91 PSMA.

Radio-pharmacy and PET acquisition:

Radio-pharmacy production of Fluorine^{-18} fluoro-methyl-choline and gallium-^{68} HBED-CC -PSMA 11 (Australian sites only) was undertaken within each participating institution required to comply with local production and quality control requirements. Imaging protocols were harmonised across institutions for each modality. All men underwent immediate dynamic pelvic (10 mins) and then delayed

whole-body FCH PET/CT imaging at 60 minutes after intravenous administration of FCH (3.6 MBq/kg to a maximum of 400MBq at time of injection). A low-dose, non-contrast CT scan was initially performed for attenuation correction and image fusion with coverage from skull base to proximal thighs in the supine position. Initial dynamic scans frames were acquired over the pelvis at 4 x 30s, 4 x 1min and 2 x 2min. Subsequently, whole-body PET acquisition was acquired towards the head. In those undergoing PSMA, imaging from vertex to mid thighs was undertaken at least 60 minutes following the intravenous administration of Ga^{68} PSMA HBEDD -11 (2.0MBq/kg, to a maximum 200MBq at time of injection). PET imaging was stored on a centralised secure server for central review.

Pelvic MRI acquisition:

Multiparametric pelvic MRI was performed as per local institutional protocols but were harmonized to include small field-of-view, pelvic T2 axial and coronal sequences, axial diffusion-weighted imaging (DWI), axial pelvic dynamic contrast-enhanced MR after administration of gadolinium-based contrast, and axial pelvic diffusion weighted imaging with b50 and b1000 diffusion weightings. Following acquisition, MRI imaging was uploaded to a centralized online secure server and centrally reviewed for quality.

Reporting of Imaging Procedures:

Following the completion of each imaging procedure, both local and central reads were acquired for each imaging modality. All PET (FCH and PSMA) reading was undertaken by prostate imaging experienced nuclear medicine physicians blinded to results of other imaging with consensus on discordant reads between the local

sites and central read sites (Peter MacCallum Cancer Centre, Melbourne). MRI was read by local MRI specialists with a central read by a prostate specialist MRI radiologist and consensus read with a second prostate MRI specialist for discordance. FCH, PSMA and pelvic MRI were scored by site of disease (prostate fossa, pelvic lymph nodes, distant lymph nodes, bone or viscera) with a 4-point certainty score assigned to each positive finding (definitely negative, probably negative, probably positive and definitely positive) [5]. Inter - reader agreement for the detection of fossa confined and extra -PF disease was substantial for PSMA (k 0.83), and fair to good for both pelvic MRI (k 0.59) and FCH (k 0.61).The consensus results were utilised for statistical analysis.

Management Impact questionnaires:

All treating investigators undertook a pre-imaging management questionnaire documenting the intended management, including planned site, fractions and dose of radiotherapy, whether ADT was planned, and duration of ADT. Following completion of imaging, and dissemination of the FCH PET/CT report to the investigating clinician, a questionnaire was completed providing information on changes in intended management. A second questionnaire detailing the management impact of pelvic MRI was completed by treating investigators. In the subgroup of men undergoing PSMA, a separate questionnaire evaluated the incremental management impact of PSMA findings over FCH. Serial PSA was documented in all men 3-monthly for the first 12 months after treatment, then 6-monthly PSA for 3 years. Biopsy results (where available) and documented sites of disease progression by imaging were also collated.

Documentation of treatments undertaken:

All men were being actively considered and eligible for standard salvage fossa radiotherapy. Quality control of investigative site SRT radiotherapy plans were undertaken by expert radiation oncologists appointed by the trial management committee prior to commencement of the study through completion and central review of a standardized trial PF radiotherapy case. As per protocol, men without disease or disease confined to the PF on PET imaging were expected to proceed to salvage fossa RT. For men with extra -PF sites identified , the study did not dictate the treatment to be received. Accordingly, based on clinician preference, some men underwent no treatment, others received conformal or intensity modulated (IM) RT to the prostate bed +/- pelvic lymph nodes, ADT or a combination of RT and ADT. All treatment undertaken was documented, including volume, timing and fractions of radiotherapy administered, duration and type of systemic therapy and any biopsies undertaken.

Treatment response:

Treatment response was defined as a drop in PSA of >50% from pre- treatment levels in the absence of ADT at the time of PSA assessment at least 6 months post-treatment. Men who were placed on ADT as part of treatment were not included in assessment of initial treatment response, although their PSA levels continue to be collected for up to 3 years following commencement of therapy on the trial. Full assessment of biochemical failure will be undertaken once 3-year follow-up is complete (median follow-up 16.1 months, IQR13.2 - 25.8 months).

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Composite reference standard:

As per protocol, biopsy of imaging-positive lesions was recommended within the study protocol, but, given the difficulties in biopsy of small lesions in biochemical failure post RP, was not mandated. Composite standard of reference incorporating biopsy and targeted treatment response is presented in figure 1 and was applied to all imaging modalities. For the composite reference standard, patients that received ADT without a biopsy outside of the prostate bed were excluded. Patients that underwent surveillance without having a biopsy performed outside of the prostate bed were also excluded. Thus, the composite reference was based on either biopsy or response to SRT to either fossa only or to fossa plus regional nodes.

Statistical Analysis:

Descriptive statistics were used to summarize baseline characteristics and outcomes of interest. Fisher's exact tests were used to evaluate differences in proportions between two groups of patients, while McNemar test was used to examine different rates of detection between imaging modalities within the same patient. Cohen's Kappa was used to measure inter observer agreement for all modalities. Wilcoxons signed rank test was used for non-parametric data in assessing number of lesions detected by different modalities. All tests were two-sided and a p-value of 0.05 or less was deemed statistically significant. Diagnostic accuracy was determined using the composite reference standard detailed above.

Results:

Baseline characteristics are summarized in Table 1. 91 men were eligible, consented and enrolled in this study. All men were enrolled to the trial between June 2014 and January 2017.

Detection Rates for recurrent prostate cancer:

Overall detection rates for recurrent prostate cancer were 28% (25/88) for pelvic MRI, 32% (29/91) for FCH, and 42% (13/31) for PSMA. Pelvic MRI and PSMA had the highest detection for local recurrence (PF) at 21.5% (19/88), and 19% (6/31); with 13% (12/91) for FCH (p = ns) (Table 2). Extra-PF sites were identified in 19% (17/91) with FCH, 8% (7/88) by pelvic MRI and 32% with PSMA (10/31) ($p < 0.004$) . The per patient extra- PF disease identified (all modalities) was pelvic nodal disease in 82% (14/17), osseous disease 12% (2/17), and lung 6% (1/17). 16/17 (94%) of extra-PF disease on FCH was within the field of view of pelvic MRI. Among men imaged with FCH and PSMA, PSMA detected the majority (9/10) of pelvic extra -PF lesions identified by FCH. For FCH and MRI, MRI detected only 5/16 (31%) pelvic extra-PF sites identified by FCH. In men with pelvic MRI findings confined to the prostate fossa or with negative scans, 15% (12/81) had additional sites of distant disease detected on FCH. Similarly, in those with negative or PF confined disease on FCH, pelvic MRI demonstrated extra-PF disease in 3% (2/74) ($p <0.003$) (Table 3A). In those men who underwent PSMA imaging, FCH and PSMA identified recurrent disease in 10/31 men (Table 3B), although PSMA identified 36 sites of disease compared to 20 on FCH ($p <0.02$). 1/13 men had an FCH positive

pelvic lymph node not identified on PSMA, which was biopsy negative (FCH false positive) and 1/13 was a PSMA positive thoracic spinal lesion not identified on FCH (PSMA true positive) (Figure 2).

Reference standard and diagnostic accuracy

A composite reference standard was applied to all imaging modalities to determine diagnostic accuracy. 68% (62/91) of men were assessed using the composite reference standard. 32% (29/91) were excluded as they did not undergo biopsy and either did not undergo treatment after imaging or were placed on ADT as part of treatment. Overall, 12% (11/91) men underwent biopsy of scan positive sites of disease. Using the reference standard, specificity was high with all modalities, with sensitivity of the PET agents higher than MRI on a per patient analysis (Table 3).

Management Impact:

Treating investigators reported that FCH imaging changed planned management in 46% (42/91) of men, while pelvic MRI changed expected management in 24% (21/88) ($p < 0.003$). As a result of the FCH, there was an expected increase in radiation field size or dose in 23% (21/91), the addition of ADT in 8% (7/91), a biopsy in 9% (8/91) and a reported de-escalation to no planned treatment in 10% (9/91) (Table 3). PSMA added an additional management change over that of FCH in 23% of men (7/31).

Following completion of imaging (FCH, pelvic MRI and PSMA) the actual treatment administered differed from that planned prior to imaging in 47% (43/91) of men enrolled. While the expected treatment in all men prior to imaging was SRT, this changed to no treatment in 21% (19/91), an increase in radiation field or dose in 9% (8/91), and the addition of ADT in 22% (20/91). Overall, 53% (48/91) had negative scans on all available imaging modalities. In men with negative scans, actual management changed from SRT to no treatment in 23% (11/48), while the remainder underwent SRT (33/48 SRT fossa alone ,4/48 SRT fossa + nodes, 5/48 SRT +ADT).

Treatment response.

Men given ADT 22% (20 /91) were excluded from response assessment; as were an additional 21% (19/91) of men who received no treatment. The remaining 57% (52/91) underwent SRT without ADT. Overall treatment response among patients treated only with radiotherapy (SRT or SRT+N) was 67% (35/52). Treatment responses to SRT were higher among men with negative scans or scans showing disease confined to the PF versus those demonstrating extra-PF disease: 70% (32/46) vs. 50% (2/4) with pelvic MRI ($p=0.45$); 75% (32/43) vs. 33% (3/9) with FCH ($p< 0.02$), and 88% (7/8) vs. 14% (1/7) with PSMA ($p<0.005$) (Figure 3).

In the men with negative results for all 3 imaging modalities 43% (43/91), SRT resulted in a significant treatment response in 78% (25/32), compared to only 9% (1/11) in those men who did not receive SRT ($p < 0.0005$).

Discussion

Salvage prostate fossa radiation treatment (SRT) is current standard of care in men with biochemical failure following radical prostatectomy. At this time, it remains the last chance for cure in these men, with around half of men achieving complete biochemical response at 5 years following SRT ([2, 3, 6]).This chance of cure is significantly lower in men with high risk features on clinical risk nomograms, dropping as low as 18% in men with rapid PSA doubling times and high Gleason scores [4, 6]. Conventional imaging has a low sensitivity for detecting sites of recurrent disease at times where salvage therapies are most likely to be successful (PSA <1-2 ng/mL) [7]. It has not been clear if complex imaging in men with high-risk biochemical recurrence can improve prediction of which men will benefit from SRT, or which imaging modality is optimal. Ideally, imaging at the time of biochemical failure post RP would identify those men who will achieve the most benefit from SRT, maximizing the chance of long term response. The major findings from this study were that the PET tracer agents had a higher detection rate for prostate cancer that had spread beyond the prostate fossa than pelvic MRI. Further, men with negative scans, or those with disease confined to the prostate fossa on PET (PMSA or FCH) exhibited higher SRT treatment response rates suggesting successful identification of men most likely to benefit from fossa only radiotherapy.

This is the first study that has undertaken a direct prospective comparison of three imaging modalities now frequently used in the assessment of BCR post RP, in the presence of negative or equivocal conventional imaging. The combination of all modalities identified disease recurrence in around half of these men for whom conventional imaging had not been helpful. However, there was significant

variation in detection rates by the imaging modalities undertaken concurrently in this study. MRI and PSMA had the highest identification of disease confined to the fossa. PET (FCH and PSMA) detected significantly higher rates of disease outside the PF than MRI, with an associated overall higher sensitivity.

With the exception of the recent Australian guidelines [8], most currently published guidelines do not recommend imaging for BCR with PSA < 1.0ng/ml [7]. This stance has been challenged recently with several studies reporting high detection rates for recurrent disease in men with BCR at low PSA levels using PSMA PET[9-14].This study confirms the high detection rate for disease recurrence with PSMA both in the prostate fossa and distantly. Consistent with the previous comparisons of FCH and PSMA PET, the number of extra fossa lesions visualised on PSMA was higher than FCH in men who underwent imaging with both modalities [15, 16]. However, the difference in detection rate for FCH and PSMA was not as high as reported previously, likely due to the high-risk nature of our current patient cohort. FCH performs better with more aggressive prostate cancer phenotypes (shorter doubling time or higher grade disease) at low PSA levels [17]. The men enrolled in this study had high-risk features and a high likelihood of poor response to SRT. We found the detection rate of FCH in this patient cohort, despite a low median PSA (0.42ng/mL), was substantial (32%), with more than half of these sites being extra-PF.

The use of pelvic MRI to better target or boost radiotherapy fields in the setting of BCR is appealing [18, 19]. However, little data has been published on detection rate or utility of pelvic MRI in the setting of BCR at PSA levels at which men are still curable[20-22]. A retrospective review of 473 men who underwent

pelvic MRI prior to SRT for BCR found up to 57% of men had a positive MRI, 49% of recurrences were local and 8% distant to the fossa [21]. This current study also showed that pelvic MRI detected predominately local prostate fossa recurrences with a low detection rate for pelvic nodal disease. Further, we found a significant proportion of men with negative or fossa-confined MRI scan results had pelvic nodal or distant disease that was identified on PSMA or FCH. The majority of these recurrences identified by PET alone occurred within regional pelvic nodes, within the field-of-view of a pelvic MRI study, with only 2 men in this cohort with disease identified outside the field of view of a pelvic MRI. This suggests that while pelvic MRI may be useful in helping to plan radiotherapy fields and boosting sites of fossa recurrence, it is less helpful in determining if the SRT will be successful, and should therefore be used as an adjunct to PET imaging, not in isolation.

The high rates of extra fossa disease identified on FCH led to a consequent high management impact of 46% in these men. Treating investigators reported an additional 23% management impact of PSMA above and beyond FCH in the subgroup of men who underwent both types of imaging, suggesting the higher potential of PSMA PET even in this high risk patient population. MRI had a significantly lower management impact of 23%, likely due to the relatively reduced detection of extra fossa disease compared to PET. Management changes predominately involved changing radiotherapy fields or adding systemic ADT. However, an unexpected management impact was that a significant proportion of men had a de-escalation of treatment with 21% of men not undergoing their intended SRT nor any other systemic treatments. The majority of men who did not receive planned SRT had negative scans on all modalities. These men with negative

scans who did not undergo further systemic or targeted treatment over the course of the trial had a consequent rise in PSA to above (potentially) curative levels in the majority (92%). The significant rise in PSA in these men contrasts starkly to the high PSA responses in men with negative scans treated with SRT. As an imaging study, this study enrolled men eligible and planned for SRT, but did not dictate final treatment. The substantial response rate among men with negative imaging receiving SRT suggests salvage RT should still be considered. The negative imaging likely reflects the presence of micro-metastatic disease still confined to the prostate fossa that would be optimally managed with targeted treatment.

All men enrolled in this study had clinical characteristics previously associated with poor biochemical response to SRT, presumably due to disease outside the fossa that would not be controlled by local treatment that until recently we could not accurately identify. Both PSMA and FCH findings of disease outside the prostate fossa was able to predict whether or not a patient would have a treatment response to SRT. This ability to stratify men into high and low treatment responses was demonstrated most strongly with PSMA. Men with negative or fossa confined disease on PSMA had an 88% treatment response to salvage fossa radiotherapy, compared to just 14% in men with extra fossa sites of disease on PSMA. This ability of PSMA to effectively stratify patients who will have a significant treatment response to SRT in the setting of biochemical failure has previously been demonstrated, but not in such a high risk cohort, or in comparison to both FCH and pelvic MRI[11]. There is ongoing follow-up for up to 3 years following SRT in these men, which will be important in determining if this early treatment response remains clinically significant.

Study limitations:

Only a subset of men (31/91) were able to undertake PSMA in addition to FCH due to the differing availability of the tracer across continents. All PSMA was undertaken in the 4 sites within Australia where men enrolled underwent MRI, FCH and PSMA within the study timeframe. The limited number of men undergoing all 3 imaging modalities restricts the ability of the study to draw strong conclusions over the relative benefits of FCH or PSMA in this patient cohort.

In this initial study, analysis of treatment response was assessed rather than biochemical failure at 3 years. Furthermore, a significant number of men on ADT at the time of their radiotherapy were not included in the treatment response analysis. Data collection is ongoing with the study, with a view to evaluating 3 year biochemical failure rates post SRT, rather than the currently reported treatment response, and this will include men who were treated with short term ADT around the time of SRT.

A further limitation of the study was the proportion of men with negative imaging who did not undergo subsequent treatment with SRT. The study did not mandate SRT in men with negative or fossa confined disease on trial imaging, however, planned SRT was part of the trial inclusion criteria, so the de-escalation of therapy among this subset of men was unexpected. While this diminished the study's ability to evaluate the benefit of imaging in identifying those men who will have a treatment response to SRT, it served to highlight the benefit that treatment with SRT affords in men with negative scans.

In this study, the detection rate of pelvic MRI has been compared to whole body imaging with PSMA and FCH. The lower detection rate of pelvic MRI may at least in part be explained by the limited field of view of pelvic MRI compared to whole body PET. However, a separate analysis of metastatic foci within the field of view of pelvic MRI confirmed the detection rate of MRI for pelvic lymph nodes is significantly lower than either FCH or PSMA. This is important in this patient cohort where over 80% of extra-PF disease was nodal.

CONCLUSION

Both FCH and PSMA PET had high detection rates for extra PF disease in men with high risk BCR post RP and negative/equivocal conventional imaging. The impact on management and the higher therapy treatment responses among men with negative PET or disease confined to the prostatic fossa on PET suggests an important role for PET in triaging men being considered for curative SRT.

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