URN 2307a: Positron Emission Tomography – Computed Tomography (PET-CT) scanning for individuals with highrisk prostate cancer

Narrative summary of papers presented for review

Three papers were presented for review by NHS England. Paper 1 is a randomised controlled trial (RCT) conducted at ten centres in Australia. Men (n=302) with biopsy-proven prostate cancer and high-risk features were randomly assigned to gallium-68 (^{68}Ga) prostate-specific membrane antigen (PSMA)-11 PET-CT or conventional imaging. Patients were followed-up for six months. Paper 2 is a prospective single arm diagnostic efficacy trial conducted at two US centres. Men (n=764) with intermediate to high-risk prostate cancer underwent an imaging scan for staging with ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PETmagnetic resonance imaging (MRI). Follow-up duration was not reported. Paper 3 is a retrospective case series of 116 men with intermediate or high-risk prostate cancer who underwent an imaging scan for staging with ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PETMRI at one centre in Switzerland. Mean follow-up was 12 months.

Paper 1: Hofman et al 2020. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study

This paper reports a multi-centre phase III imaging RCT comparing ^{68}Ga-PSMA-11 PET-CT to conventional imaging in 302 men with newly diagnosed prostate cancer and high-risk features. Patients were recruited between March 2017 and November 2018 from ten centres in Australia. Eligible patients (≥18 years) had histopathologically-confirmed prostate cancer and were being considered for radical prostatectomy or radiotherapy with curative intent. All patients had high-risk features including at least one of either a prostate-specific antigen (PSA) concentration of ≥20 ng/mL within 12 weeks before randomisation, International Society of Uropathology grade group 3-5, or clinical stage T3 or worse. Key exclusion criteria included any imaging done for staging within eight weeks before randomisation, with an exception for MRI of the prostate before biopsy. Median patient age was 69.0 years (range 63.0 to 73.5).

Patients were randomly assigned to first-line imaging with either ^{68}Ga-PSMA-11 PET-CT (n=150) or conventional imaging (n=152). Conventional imaging consisted of the combined findings of abdomen and pelvis CT with intravenous contrast and technetium-99m bone whole body planar imaging with single-photon emission CT of the chest to pelvis. Patients crossed-over for second-line imaging within 14 days unless three or more unequivocal distant metastases were identified on first-line imaging. Additional confirmatory studies were done at the discretion of the treating clinician. Repeat imaging according to randomised group was done at six months (± 30 days) with cross-over imaging if evidence of node positive (N1) or metastatic disease (M1) was found at baseline or if biochemical or clinical suspicion of residual or recurrent disease was found.

Paper 2: Hope et al 2021. Diagnostic accuracy of 68 Ga-PSMA-11 PET for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: a multicentre prospective phase 3 imaging trial

This paper reports a prospective multi-centre open-label phase III imaging trial with a single arm assessing the diagnostic accuracy of ^{68}Ga-PSMA-11 PET for initial staging in 764 men with intermediate to high-risk prostate cancer. Patients were being considered for prostatectomy between December 2015 and December 2019 at two centres in the United States. Eligible patients had histopathologically-confirmed prostate cancer and were planning to undergo radical prostatectomy. Patients had intermediate to high-risk disease including at least one of the following: elevated PSA >10 ng/mL, T stage ≥T2b, Gleason score >6 or other risk factors (not further defined). Key exclusion criteria included any prostate cancer therapy prior to prostatectomy. Median patient age was 69 years (interquartile range 63 to 73). 590 men (78%) were classified as having high-risk prostate cancer. No outcomes were separately reported for men classified as having intermediate or high-risk disease.

Patients were imaged using either ^{68}Ga-PSMA-11 PET-CT (n=612) (80%) or ^{68}Ga-PSMA-11 PET-MRI (n=152). Patients who did not undergo prostatectomy (n=487) were not included in the primary efficacy population. The ^{68}Ga-PSMA-11 PET scans of the patients who did undergo prostatectomy (n=277) were read by three blinded independent central readers. Histopathology was used as the reference standard. In the prostatectomy group, 214 patients (77%) received ^{68}Ga-PSMA-11 PET-CT and 63 patients received ^{68}Ga-PSMA-11 PET-MRI. Safety data were available for all 764 patients. No outcomes were separately reported for patients who received ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI respectively.

Paper 3: Ferraro et al 2020. Impact of 68 Ga-PSMA-11 PET staging on clinical decision-making in patients with intermediate or high-risk prostate cancer

This paper reports a retrospective case series assessing the diagnostic accuracy of ^{68}GaPSMA-11 PET for initial staging in 116 men with intermediate or high-risk prostate cancer. Patients were scanned between April 2016 and May 208 at one centre in Switzerland. No definitions for intermediate or high-risk prostate cancer were reported. However, 30/116 patients (26%) had a PSA >20 ng/mL, 109/114 patients (96%) had a Gleason score >6 and
45/108 patients (42%) had a T stage ≥3 on initial staging. Median patient age was 66.6 years (range 51 to 84). No outcomes were separately reported for men classified as having intermediate or high-risk disease.

Patients were imaged using either ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET- MRI (proportion receiving each scan not reported). No outcomes were separately reported for patients who received ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI respectively. A simulated multidisciplinary tumour board made hypothetical treatment recommendations based on clinical information and conventional imaging alone. The information from ^{68}GaPSMA-11 PET staging was then added and a second treatment recommendation made. Data from conventional imaging from within six months of the ^{68}Ga-PSMA-11 PET was used where available. Information on additional therapies and follow-up PSA was collected 12 months after treatment.

Effectiveness

Accuracy of imaging

Hofman et al 2020 reported accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease[1] at six-month follow-up in men with prostate cancer and high-risk features. Data were available for 295 (of 302) men. ^{68}Ga-PSMA-11 PET-CT (n=150) had an absolute greater area under the curve (AUC) for accuracy than conventional imaging (n=145), reflecting the lower sensitivity and specificity for conventional imaging (Table 1). The difference of 27% (95% CI 23 to 31) was statistically significant (p<0.0001). **Table 1: Imaging accuracy results reported by Hofman et al 2020**

	^{68}Ga-PSMA-11 PET-CT	**Conventional imaging**
Area under the curve	92% (95% CI 88 to 95)	65% (95% CI 60 to 69)).
Sensitivity	85% (95% CI 74 to 96)	38% (95% CI 24 to 52)
Specificity	98% (95% CI 95 to 100)	91% (95% CI 85 to 97)

^{68}Ga-PSMA-11 PET-CT remained superior to conventional imaging in sensitivity analysis where lesions rated as equivocal were considered positive rather than negative (absolute greater AUC 28% [95%CI 23 to 33]).

The superiority of ^{68}Ga-PSMA-11 PET-CT was demonstrated for subgroups of patients with pelvic nodal (absolute greater AUC 32% [95%CI 28 to 35]) and distant metastasis (absolute greater AUC 22% [95%CI 18 to 26]). The authors reported that ^{68}Ga-PSMA-11 PET-CT was also superior in subgroup analysis of men with Gleason grade group 4 disease of higher, grade group 3 or lower and PSA concentration of ≥20 ng/mL.

Hofman et al 2020 also reported AUC for men who crossed-over to second-line imaging (n=291). The AUC of accuracy was 17% higher (95%%CI 13 to 22) for ^{68}Ga-PSMA-11 PETCT (84% [95%CI 80 to 88]) than conventional imaging (67% [95%CI 62 to 71]). No statistical comparison was reported.

Hope et al 2021 reported the accuracy of ^{68}Ga-PSMA-11 PET for the detection of regional nodal metastasis on a per-patient basis using nodal regional correlation in men with intermediate to high-risk prostate cancer (n=277). Patients received either ^{68}Ga-PSMA-11 PET-CT (n=214) or ^{68}Ga-PSMA-11 PET-MRI (n=63) (outcomes for each scan type not separately reported). Imaging results[2] were compared to a reference standard of pathology at radical prostatectomy:

Table 2: Imaging accuracy results reported by Hope et al 2021

	^{68}Ga-PSMA-11 PET
Sensitivity	0.40 (95% CI 0.30 to 0.51)
Specificity	0.95 (95% CI 91 to 97)
Positive predictive value	0.75 (95% CI 0.60 to 0.86)
Negative predictive value	0.81 (95% CI 0.76 to 0.85)

[1] Assessed by the area under the curve (AUC) of the receiver-operating curve using a predefined reference standard including histopathology, imaging and biochemistry. The AUC was calculated as the mean of the estimated sensitivity and specificity

[2] Based on the majority read of the three blinded independent central readers

Post-hoc analysis found that larger pelvic nymph node metastasis size (>10mm) was associated with higher sensitivity for the detection of pelvic nodal metastasis. The authors reported that there was insufficient evidence to conclude that Gleason score, PSA level category or D'Amico risk were associated with sensitivity.

Ferraro et al 2020 reported that ^{68}Ga-PSMA-11 PET detected the primary tumour in 113 of 116 patients (97%) with intermediate or high-risk prostate cancer. One false positive ^{68}GaPSMA-11 PET finding of a single pelvic positive node was proven with histopathology. The patients were imaged using either ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET- MRI (proportion of patients receiving each scan type not reported; outcomes for each scan type not separately reported).

One of the included papers reported statistically significantly higher accuracy with ^{68}Ga-PSMA-11 PET-CT (n=150) compared to conventional imaging (n=145) in men with prostate cancer and high-risk features. Sensitivity was 85% vs 38% and specificity 98% vs 91% respectively. A second included paper (n=277) reported a sensitivity of 0.40 and specificity of 0.95 for men with intermediate to high-risk prostate cancer receiving ^{68}Ga-PSMA-11 PET-CT (n=214) or ^{68}Ga-PSMA-11 PET-MRI (n=63). A third included paper (n=116) reported that ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI detected the primary tumour in 97% of patients with intermediate or high-risk prostate cancer. In the third paper the proportion of patients receiving PET-CT or PET-MRI was not reported.

Reporter agreement

Hofman et al 2020 reported that reporter agreement was high with ^{68}Ga-PSMA-11 PET-CT (n=148) for nodal (pairwise kappa value (κ) =0.87 (95% CI 0.81 to 0.94)) and distant (κ =0.88 (95% CI 0.84 to 0.82)) disease in men with prostate cancer and high-risk features.

Hope et al 2021 reported inter-reader agreement for ^{68}Ga-PSMA-11 PET for men with intermediate to high-risk prostate cancer (n=277). This was reported as substantial for rightsided nodes (κ =0.61 (95%CI 0.55 to 0.67)) and left-sided nodes (κ =0.66 (95% CI 0.60 to 0.71) and moderate for other nodes (κ =0.52 (95% CI 0.46 to 0.58)). Patients received either ^{68}Ga-PSMA-11 PET-CT (n=214) or ^{68}Ga-PSMA-11 PET-MRI (n=63) (outcomes for each scan type not separately reported).

One of the included papers (n=148) reported high agreement between readers with ^{68}Ga-PSMA-11 PET-CT for nodal and distant disease in men with prostate cancer and high-risk features. A second included paper (n=277) reported substantial to moderate inter-reader agreement for nodal disease with ^{68}Ga-PSMA-11 PET-CT (n=214) or ^{68}GaPSMA-11 PET-MRI (n=63) in men with intermediate to high-risk prostate cancer.

Equivocal findings

Hofman et al 2020 reported statistically significantly fewer equivocal findings with ^{68}Ga-PSMA-11 PET-CT (11/148; 7% [95% CI 4 to 13]) compared to conventional imaging (35/152; 23% [95% CI 17 to 31]), p<0.001 in men with prostate cancer and high-risk features. The authors reported similar results for subgroups of men with pelvic nodal and distant metastasis.

One of the included papers reported statistically significantly fewer equivocal findings with ^{68}Ga-PSMA-11 PET-CT (n=148) (7%) compared to conventional imaging (n=152) (23%).

Change in staging

Hofman et al 2020 reported a change of stage or nodal or distant metastasis for men with prostate cancer and high-risk features who crossed-over to second-line imaging (n=291). Stage was changed for more men following second-line imaging with ^{68}Ga-PSMA-11 PET-CT (33/146; 22% [95% CI 16 to 30]) than after second-line conventional imaging (20/135; 14% [95% CI 9 to 22]). Change in stage was compared to the reference standard. The change in stage was judged correct more often with ^{68}Ga-PSMA-11 PET-CT (26 men) than conventional imaging (3 men). No statistical comparisons were reported.

Ferraro et al 2020 reported that ^{68}Ga-PSMA-11 PET brought new information in 42 of 116 men with intermediate or high-risk prostate cancer. The most frequent new findings were lymph node metastasis (n=20) and suspected bone metastasis (n=11). Patients were imaged using either ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET- MRI (proportion of patients receiving each scan type not reported; outcomes for each scan type not separately reported).

One of the included papers (n=291) reported a change of stage for 22% of patients after ^{68}Ga-PSMA-11 PET-CT and 14% of patients after conventional imaging. The change of stage was judged correct more often with ^{68}Ga-PSMA-11 PET-CT. No statistical comparison was reported. A second included paper reported that ^{68}GaPSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI brought new information in 42 of 116 men with intermediate or high-risk prostate cancer (proportion of patients receiving PETCT or PET-MRI not reported).

Change in patient management

Hofman et al 2020 reported that a statistically significantly greater number of men with prostate cancer and high-risk features had a change in their management with high or medium effect[3] with first-line ^{68}Ga-PSMA-11 PET-CT (41/148; 28% [95% CI 21 to 36]) compared to conventional imaging (23/152; 15% [95% CI 10 to 22]), p=0.008. Following first line ^{68}Ga-PSMA-11 PET-CT, 20 (14%) of 148 patients were directed from curative to palliative-intent treatment, 11 patients (7%) had a change in radiotherapy technique and 11 patients (7%) had a change in surgical technique.

Hofman et al 2020 also reported changes in patient management for men who crossed-over to second-line imaging (n=291). The number of men who had a change in their management with high or medium effect was higher with second-line ^{68}Ga-PSMA-11 PET-CT (39/146; 27% [95% CI 20 to 35]) compared to conventional imaging (7/135; 5% [95% CI 2 to 10]).

Ferraro et al 2020 reported that for 32 of 116 men (27%) with intermediate or high-risk prostate cancer, the new information gained from ^{68}Ga-PSMA-11 PET staging had an impact on disease management. The patients were imaged using either ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI (proportion of patients receiving each scan type not reported; outcomes for each scan type not separately reported). The new information led to a

[3] A change in treatment intent (e.g. curative to palliative), addition or removal of a treatment modality or change in surgery or radiotherapy technique

modification of some detail within the same therapy modality in 17 of these patients (14%). For the remaining 15 patients (13%), the previously intended therapy was not considered the best treatment option anymore. The changes in disease management are summarised in Tables 3 and 4.

Table 3: Change in intended therapy reported by Ferraro et al 2020

Change made with ^{68}Ga-PSMA-11 PET	**Patients (n=15)**
Change from local therapy to local treatment plus additional or metastasestargeted treatment due to new bone metastasis	6 (40%)
Change from local therapy plus androgen deprivation therapy (ADT) to systemic treatment only or additional chemotherapy due to more extensive disease	3 (20%)
Change from local therapy plus ADT to local therapy alone due to ruling out bone metastasis or showing oligometastatic disease	4 (27%)
Change from active surveillance to local therapy due to location of the prostatic lesion for targeted biopsy	1 (7%)
Change from focal therapy to surgery due to more extensive tumour	1 (7%)

Table 4: Change in therapy modality reported by Ferraro et al 2020

Change made with ^{68}Ga-PSMA-11 PET	**Patients (n=17)**
Change in radiation field due to previously undetected nodal metastasis	7 (41%)
Change in whether radiation of the lymphatic drainage was included or excluded	3 (18%)
Change to additional stereotactic body radiotherapy for bone metastasis	3 (18%)
Change in modality detail in surgical approach due to extracapsular extension or additional common nodes included in lymphadenectomy	4 (24%)

The new information gained from ^{68}Ga-PSMA-11 PET was not relevant to management for 10 patients (of 42 with new information). For example, because the additional bone metastasis or lymph node metastasis within the surgical/radiotherapy field.

In subgroup analysis, Ferraro et al 2020 found a statistically significant association between PSA and clinical TNM stage and therapy change (Table 5).

Table 5: Patients with a change in their management by subgroup reported by Ferraro et al 2020

	Patients with change in management
PSA level ≤5 ng/mL	1/21 (4%)
PSA level between >5 and <10 ng/mL	5/26 (19%)
PSA level between ≥10 and ≤20 ng/mL	13/39 (33%)
PSA level of >20 ng/mL	13/30 (43%)
Tumour, node and metastasis (TNM) staging group II	5/42 (12%)
TNM staging group III	16/54 (30%)
TNM staging group IV	8/15 (53%)

D'Amico and Gleason score risk groups did not show a statistically significant correlation with a change in management.

One of the included papers reported that a statistically significantly greater number of men with prostate cancer and high-risk features had a change in their management with first-line ^{68}Ga-PSMA-11 PET-CT (n=148) compared to conventional imaging (n=152) (28% vs 15%). A greater proportion of men also had a change in management after cross-over to second-line ^{68}Ga-PSMA-11 PET-CT (27%) compared to conventional 5%). A second included paper (n=116) reported that the new information gained from ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI staging had an impact on disease management for 27% of men with intermediate or high-risk prostate cancer (proportion of patients receiving PET-CT or PET-MRI not reported).

Radiation exposure

Hofman et al 2020 reported that radiation exposure from first line diagnostic imaging was lower with ^{68}Ga-PSMA-11 PET-CT (n=148) (8.4 millisieverts (mSv) (95%CI 8.1 to 8.7)) compared to conventional imaging (n=152) (19.2 mSv (95%CI 18.2 to 20.3)). The difference of 10.9 mSv (95%CI 9.8 to 12.0) was statistically significant (p<0.001).

One of the included papers reported statistically significantly lower radiation exposure with ^{68}Ga-PSMA-11 PET-CT (n=148) (8.4mSv) compared to conventional imaging (n=152) (19.2mSv).

Biochemical recurrence

Ferraro et al 2020 reported that 11 of 58 men (19%) men with intermediate or high-risk prostate cancer selected for radical prostatectomy based on ^{68}Ga-PSMA-11 PET had biochemical recurrence after a mean (standard deviation) follow-up of 12 months (± 2.4). The patients were imaged using either ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET-MRI (proportion of patients receiving each scan type not reported; outcomes for each scan type not separately reported).

One of the included papers reported biochemical recurrence after a mean follow-up of 12 months in 19% of 58 men with intermediate or high-risk prostate cancer selected for radical prostatectomy based on ^{68}Ga-PSMA-11 PET. Patients were imaged using either ^{68}Ga-PSMA-11 PET-CT or ^{68}Ga-PSMA-11 PET- MRI (proportion of patients receiving PET-CT or PET-MRI not reported).

Safety

Hofman et al 2020 stated that no adverse events were reported with ^{68}Ga-PSMA-11 PET-CT for 150 men with prostate cancer and high-risk features. No statement was made regarding adverse events with conventional imaging.

Hope et al 2021 reported no Grade 2 or higher adverse events for men with intermediate to high-risk prostate cancer with ^{68}Ga-PSMA-11 PET. Grade 1 adverse events were reported in 44 of 764 patients (6%), none of which required intervention. The most common adverse events were diarrhoea (n=16), fatigue (n=6), rash (n=4) and nausea (n=4). The authors reported that these events were possibly related to contrast administration. Of the 764 patients, 612 received ^{68}Ga-PSMA-11 PET-CT and 152 ^{68}Ga-PSMA-11 PET-MRI (outcomes for each scan type not separately reported).

One of the included papers (n=150) reported no adverse events with ^{68}Ga-PSMA-11 PET-CT. A second included paper (n=764) reported no adverse events with ^{68}GaPSMA-11 PET that were Grade 2 or higher and Grade 1 adverse events in 6% of patients. Of the 764 patients, 612 received ^{68}Ga-PSMA-11 PET-CT and 152 ^{68}Ga-PSMA11 PET-MRI.

References

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