

PSMA PET

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PET in prostate cancer

PET tracer	Which metabolic pathway
18F FDG	Glucose metabolism
11C-acetate	Lipid metabolism
11C or 18F Choline	Lipid metabolism
18F FLT	Cellular proliferation
18F FDHT	Androgen receptor
68Ga-bombesin	Gastrin-Releasing Peptide Receptor
11C Methionine	Amino acid transport
18F NAF	Ca analogue
18F-Fluciclovine (FACBC)	Amino acid transport
68Ga-PSMA	Prostate Specific Membrane Antigen

PSMA

Type II transmembrane protein

Short intracellular component compared to longer extracellular component

PSMA gene located on short arm chr 11

1,000-fold over- expression on the cell membrane of nearly all prostatic cancer cells

PSMA



Biodistribution



18F FDG



18F Choline



68Ga-PSMA



18F Fluciclovine

68Ga-PSMA PET

- 68Ga-PSMA is produced using a 68Ge/68Ga radionuclide generator
- Inject 1.8-2.2MBq/kg body weight as an IV bolus
- PET acquisition begins approximately 60minutes after tracer injection

- Clinical Nuclear Medicine, July 2017

Safety

ORIGINAL ARTICLE

A Comprehensive Safety Evaluation of ^{68}Ga -PSMA-11 PET/CT in Prostate Cancer

The Results of 2 Prospective, Multicenter Trials

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Karin M. Nielsen, MSc, PhD,* Kaija Dettmann, MD,§
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- **Aim:** to evaluate the clinical safety profile of the ^{68}Ga -PSMA (HBED).
- **Methods:** 2 Multicenter prospective studies on 88 patients with newly diagnosed or recurrent prostate cancer.
- PSMA-HBED-CC was administered as 2 MBq/kg body weight.
- AE, HR, BP assessment prior to injection (baseline); immediately after injection (postinjection); at 1, 10, and 60 minutes after injection; and postscan.
- **Results:** No patients developed hypotension. One patient developed transient tachycardia. No patients required medical intervention for cardiovascular disturbances.
- **Conclusion:** ^{68}Ga -PSMA-11 is very well tolerated and considered to be safe for human application.

Safety

- The radiation dose to the patients were calculated to be 3 mSv from ⁶⁸Ga-PSMA-11 PET plus approximately 3 mSv from the low-dose CT (total, 6 mSv) based on a 200-MBq dose of ⁶⁸Ga-PSMA-11.
- ‘Joint EANM and SNMMI procedure guideline for prostate cancer imaging’ stated that PSMA PET has an average effective radiation dose of 3 mSv for an administered activity of 150 MBq.

Eur J Nucl Med Mol Imaging

Table 2 Data available for radiation dosimetry for ⁶⁸Ga-PSMA

		⁶⁸ Ga-PSMA HBED-CC Pfob C et al. [55]	⁶⁸ Ga-PSMA HBED-CC Afshar-Oromieh et al. [56]	⁶⁸ Ga-PSMA 617 Afshar-Oromieh et al. [9]	⁶⁸ Ga-PSMA-I&T Hermann et al. [10]
Effective dose coefficient	mSv/MBq	1.71E-02	2.3E-02	2.1E-02	1.99E-02
Urinary bladder wall	mSv/MBq	1.73E-01	1.30E-01	9.03E-02	6.74E-02
Kidneys	mSv/MBq	1.22E-01	2.62E-01	2.06E-01	2.20E-01
Standard injected activity	MBq	150	150	150	150

⁶⁸Ga-PSMA-11 PET/CT interobserver agreement for prostate cancer assessments: an international multicenter prospective study

- Results: Agreement among all observers was substantial for T ($\kappa=0.62$, 95%CI 0.59-0.64) and N ($\kappa=0.74$, 95%CI 0.71-0.76) staging and almost perfect for Mb ($\kappa=0.88$, 95%CI 0.86-0.91) staging.
- Level of experience positively correlated with agreement for T ($\kappa=0.73/0.66/0.50$ for high/intermediate/low experience, respectively), N ($\kappa=0.80/0.76/0.64$), and Mc staging ($\kappa=0.61/0.46/0.36$).
- Interobserver agreement for Mb was almost perfect irrespective of prior experience ($\kappa=0.87/0.91/0.88$).
- Observers with low experience, when compared to intermediate and high experience, demonstrated significantly lower median overall agreement (54% versus 66% and 76%, $p=0.041$) and specificity for T staging (73% versus 88% and 93%, $p=0.032$).

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DOI 10.1007/s00259-017-3725-1

ORIGINAL ARTICLE

Development of standardized image interpretation for ^{68}Ga -PSMA PET/CT to detect prostate cancer recurrent lesions

	Sensitivity	Specificity
68Ga-PSMA	65.9- 80	97-98.9
Choline	49.2 - 59	92-95
CT	42	82
MRI	39	82

Evangelista, L et al Eur. Urol. 63, 1040–1048 (2013).

BCR Choline Vs PSMA

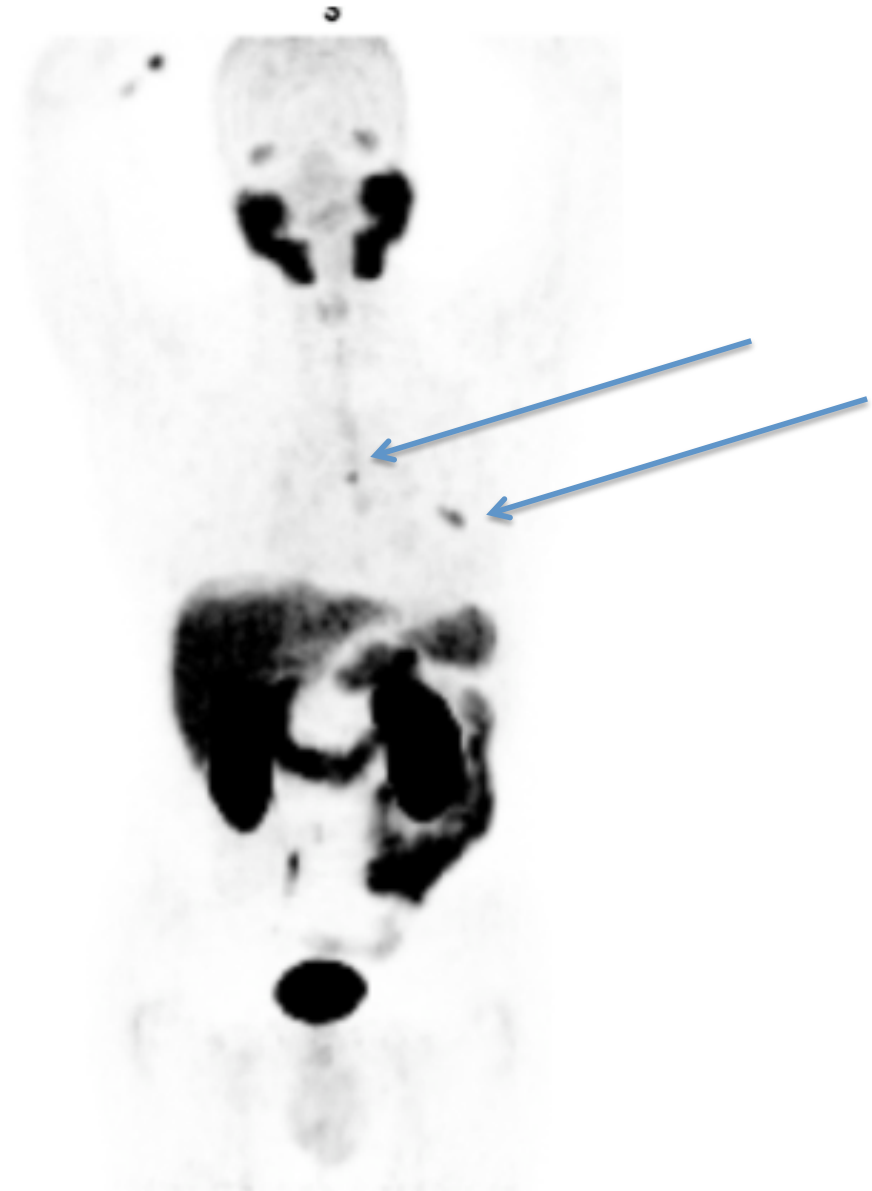
- Choline PET tracers have a detection rate ranging from 19-36% when serum PSA is below 1.5ng/mL
- n=37, PSMA PET was able to detect all lesions demonstrated on Choline PET as well as additional sites of disease, identifying 86.5% of patients with at least one site of disease characteristic for prostate cancer, compared with 70.3%
(Afshar-Oromieh, A. et al. Eur. J. Nucl. Med. Mol. Imaging 41, 11–20 (2014)).
- N=38, on lesion-based analysis, (68)Ga-PSMA detected significantly more lesions than (18)F-fluoromethylcholine (59 vs. 29 respectively, $P < 0.001$)

Morigi JJ et al. J Nucl Med. 2015 Aug;56(8):1185-90.

18F Choline



68Ga-PSMA



Factors influencing PSMA uptake

Detection Efficacy of Hybrid ^{68}Ga -PSMA Ligand PET/CT in Prostate Cancer Patients with Biochemical Recurrence After Primary Radiation Therapy Defined by Phoenix Criteria

•PSA

•ADT

[J Nucl Med.](#) 2017 Jul;58(7):1081-1087

BCR PSMA

- N=319 patients with BCR
- 82.8% of PSMA scans positive
- Probability of detecting disease increased with higher PSA levels e.g - 50% likelihood of positive scan at PSA <0.5 and 60% when PSA was 0.5-1 *Afshar- Oromi et al. Eur J Nucl Med Mol Imaging. 2015; 42: 197–209.*
- No significant association of positive studies with PSAdt, although a tendency towards positive scans with unfavourable PSA kinetics was noted.
- Others have shown a significant relationship correlation, although less marked than the correlation with PSA. *Ceci F et al. Eur J Nucl Med Mol Imaging. 2015;42:1284–1294).*

Nodal staging

- Previous studies have shown that up to 98% of lymph node metastases from prostate cancer demonstrate very high levels of PSMA. *Sweat SD et al Urology. 1998;52:637–40.*
- In 130 patients with intermediate to high-risk prostate cancer treated with prostatectomy and pelvic lymph node dissection, Ga-PSMA was shown to have a sensitivity of 65.9% and specificity of 98.9% for lymph node staging. *Maurer, T. et al. J. Urol. <http://dx.doi.org/10.1016/j.juro.2015.12.025> (2015).*

BCR salvage lymphadenectomy

- LNM were found in 68/179 resected LN fields (38.0%)
- The specificity of ^{68}Ga -PSMA HBED-CC PET and morphologic imaging was 97.3% and 99.1%, respectively
- However, ^{68}Ga -PSMA HBED-CC PET detected LNM in 53/68 histopathologically proven metastatic LN fields (77.9%) whereas morphologic imaging was positive in only 18/67 (26.9%)

Rauscher et al JNM 2016

Size of the lymph nodes?

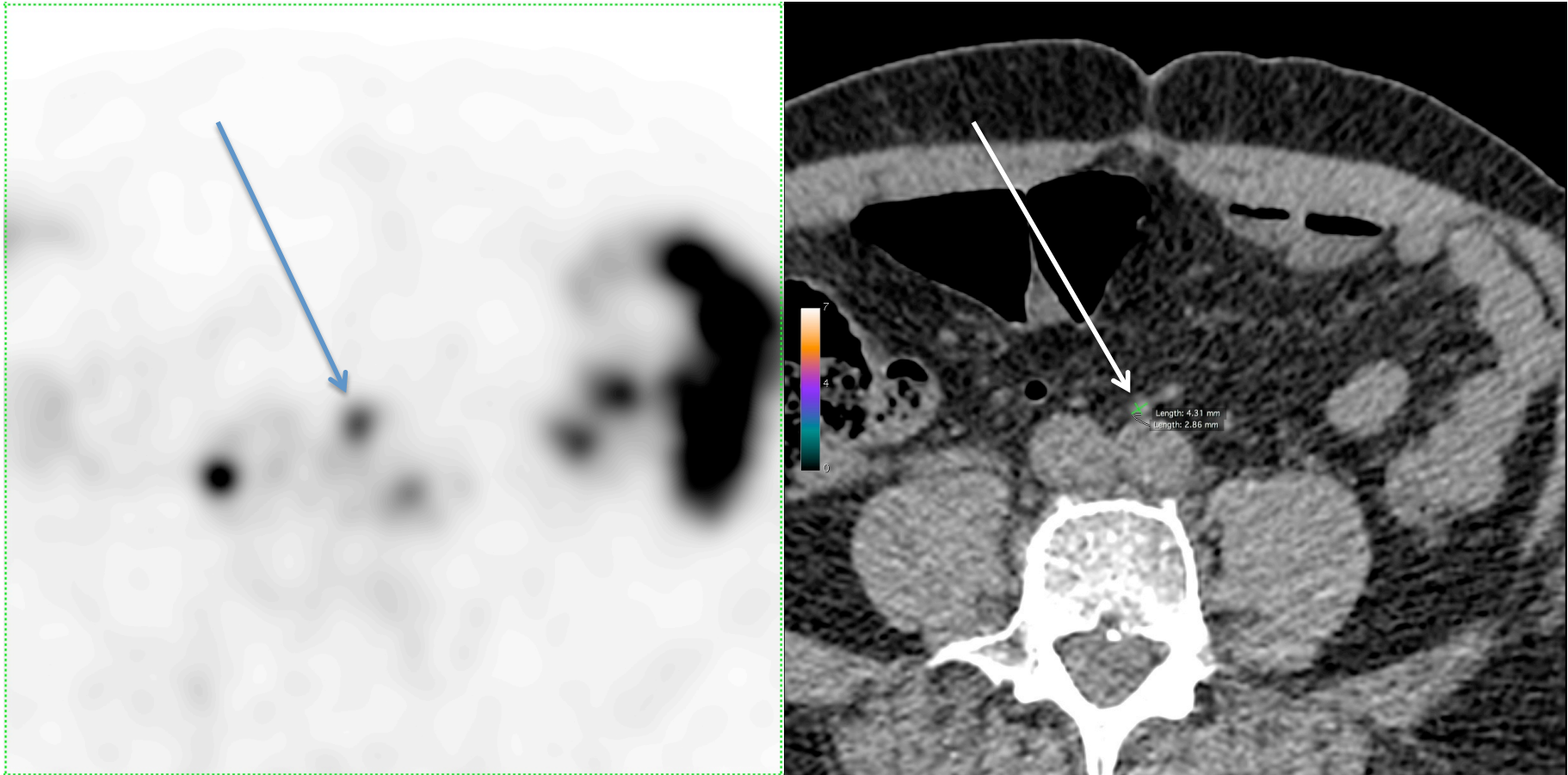
Journal of Nuclear Medicine, published on June 21, 2017 as doi:10.2967/jnumed.116.185033

⁶⁸Ga-PSMA PET/CT and volumetric morphology of PET-positive lymph nodes stratified by tumor differentiation of prostate cancer

- N=147 mean SUVmax in this study was 12.4 (range 2-49) and the SAD was 9.4 mm (range 1.9-33.5 mm)
- Rauscher et al / JNM 2016 - 53/68 positive lymph nodes showed an SUVmax of 12.7 (range 2.4-51.0) with a corresponding node size of 8.3 mm (range 4-25 mm). LNs which were suspicious only in CT or MRI, presented with a mean size of 13.0 ± 4.9 mm (range, 8-25 mm).

- ⁶⁸Ga-PSMA imaging led to a reclassification of N staging in 61% of patients

Small nodes



When should ^{68}Ga -PSMA be used - Are there guidelines?

March 2017

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DOI 10.1007/s00259-017-3670-z



GUIDELINES

^{68}Ga -PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0

Localization of tumour tissue in recurrent prostate cancer

Most studies, mainly retrospective data, are available on the use of ^{68}Ga -PSMA PET/CT for localization of prostate cancer in the setting of biochemical recurrence [8, 9, 15–21]. Here, the use is especially recommended in patients with low PSA values between 0.2 and 10 ng/mL to identify the site of recurrence and to potentially guide salvage therapy. Higher sensitivities are noted in patients with shorter PSA doubling times and those with higher initial Gleason scores [21].

Primary staging in high-risk disease before surgical procedures or planning external beam radiation

In patients with high-risk disease (Gleason score >7 , PSA >20 ng/mL, clinical stage T2c – 3a) the likelihood of lymph node and bone metastases is increased. Several studies demonstrate the superiority of ^{68}Ga -PSMA PET/CT as compared to CT, magnetic resonance imaging (MRI) or bone scan for detection of metastases for initial staging at primary diagnosis [22–25]. The detection of radiologically occult lymph node metastases can significantly influence patient management, although the impact on overall survival of improved sensitivity by ^{68}Ga -PSMA PET/CT remains unanswered. A contrast-enhanced ^{68}Ga -PSMA PET/CT can replace abdomino-pelvic

Emerging clinical applications

Staging before and during PSMA-directed radiotherapy (mainly in metastatic castration-resistant prostate cancer)

Imaging before PSMA-directed therapy (e.g. radioligand therapy) is crucial to determine the presence and intensity of target expression [26–29]. Low PSMA expression in target lesions poses a contraindication for radioligand therapy. Of note, ^{68}Ga -PSMA PET can produce false negatives in up to 5% of patients with prostate cancer. In addition, it has been reported that in advanced metastatic castration-resistant prostate cancer, metastases (mainly in the liver) can lose PSMA expression [30–32].

Targeted biopsy after previous negative biopsy in patients with high suspicion of prostate cancer

Initial data indicate ^{68}Ga -PSMA PET may be valuable for guidance of repeated biopsy in patients with high suspicion of prostate cancer and prior negative biopsies as it has been shown to add in localization of primary prostate cancer [33, 34], and may add value for directed biopsies in the prostate cancer surveillance population who undergo repeated biopsies. Preferably, ^{68}Ga -PSMA PET should be combined with multiparametric MRI for this application to allow for a) potential image-guided fusion biopsy using the MRI for anatomical correlation and b) adding information from multiparametric MRI to potentially increase the diagnostic confidence [33].

Monitoring of systemic treatment in metastatic prostate cancer

RECIST 1.1 is limited by the high prevalence of non-measurable lymph node and bone metastases. Bone scan is limited by a potential flare phenomenon. Monitoring of systemic disease might become a potential application for ^{68}Ga -PSMA PET/CT. However, whether ^{68}Ga -PSMA PET/CT overcomes limitations of other modalities and proves superior

Evidence-based indications for the use of PET-CT in the United Kingdom 2016

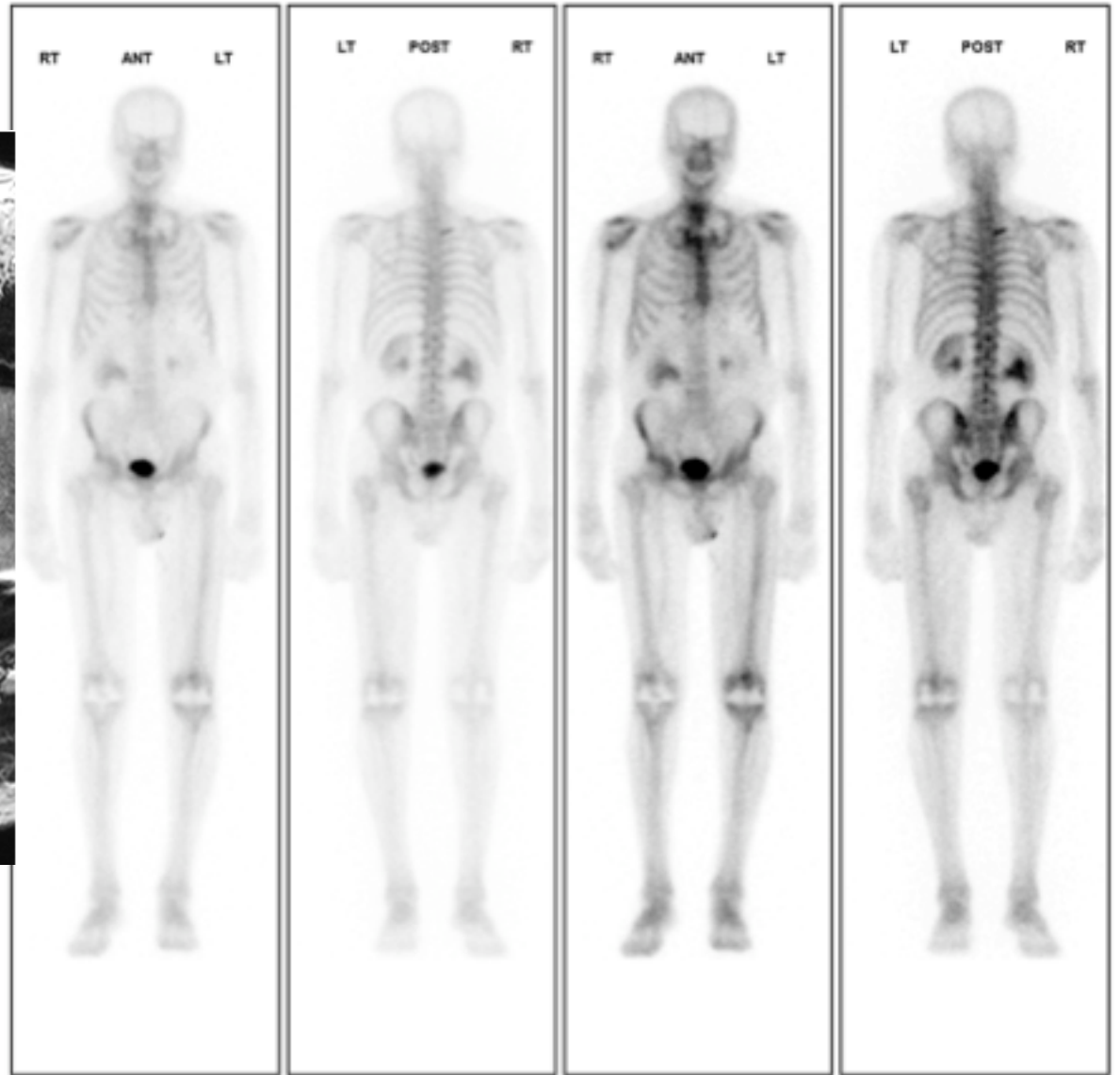
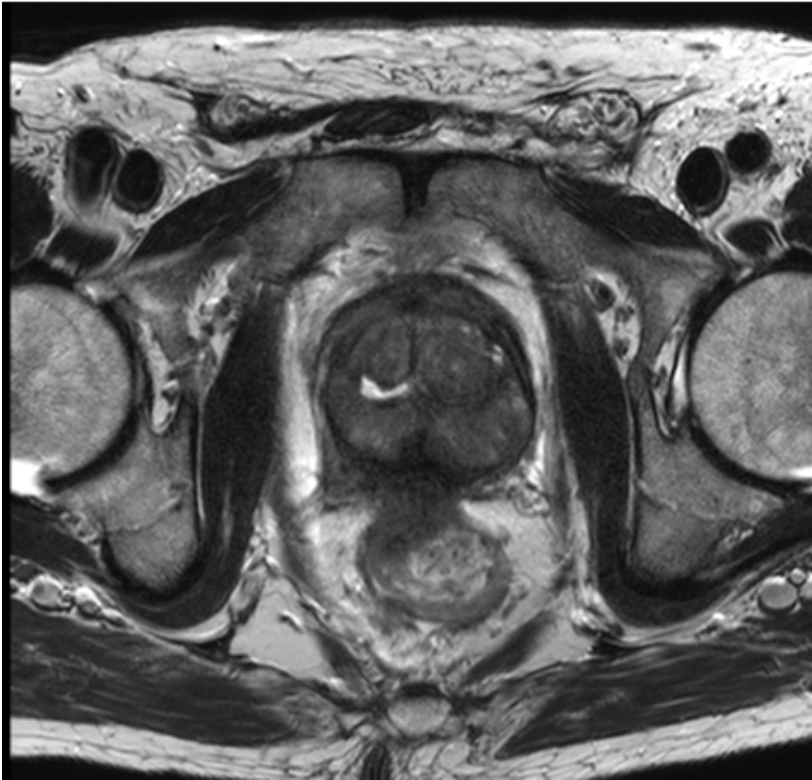
The Royal College of Radiologists, Royal College of Physicians of London, Royal College of Physicians and Surgeons of Glasgow, Royal College of Physicians of Edinburgh, British Nuclear Medicine Society, Administration of Radioactive Substances Advisory Committee

11C-Choline or 18F-fluoro-choline and 68Ga-prostate specific membrane antigen (PSMA)

68Ga-PSMA is a rapidly emerging alternative tracer for assessment of prostate malignancy with superior diagnostic accuracy compared to choline.

- Evaluation of high-risk patients before curative treatment or to evaluate equivocal findings such as possible nodal or metastatic disease in patients with prostate cancer where confirmation or exclusion of distant disease would directly influence patient management
- Suspected recurrence in patients with a rapidly rising PSA and negative or equivocal conventional imaging where the results would directly influence patient management

Cases



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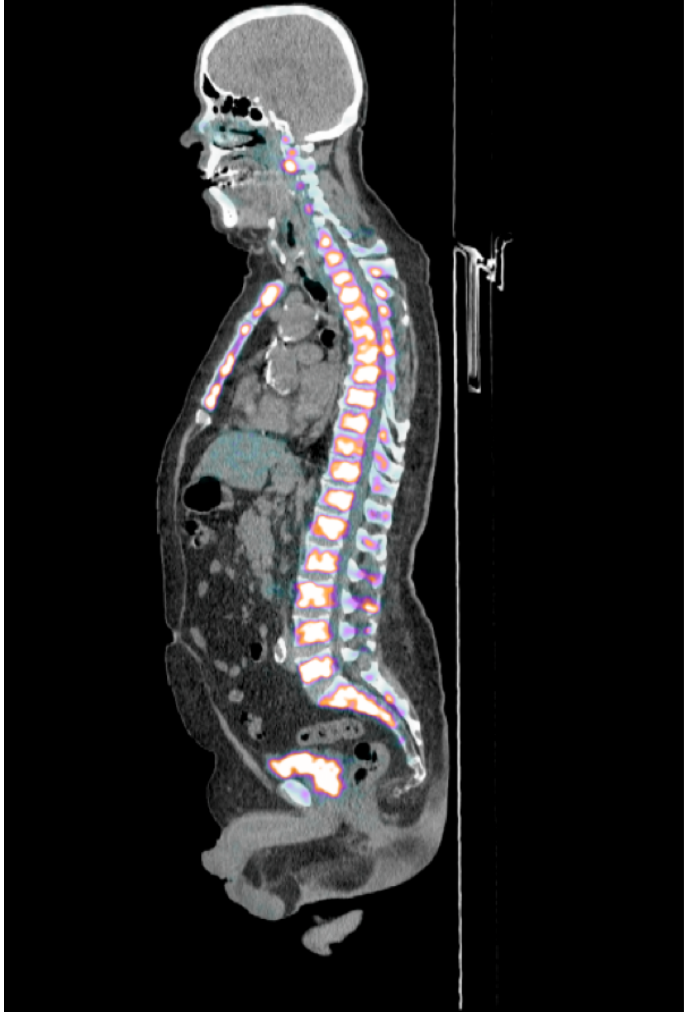
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S-I: 0.0
L-R: 6.2
Roll: 0.0



Case PD

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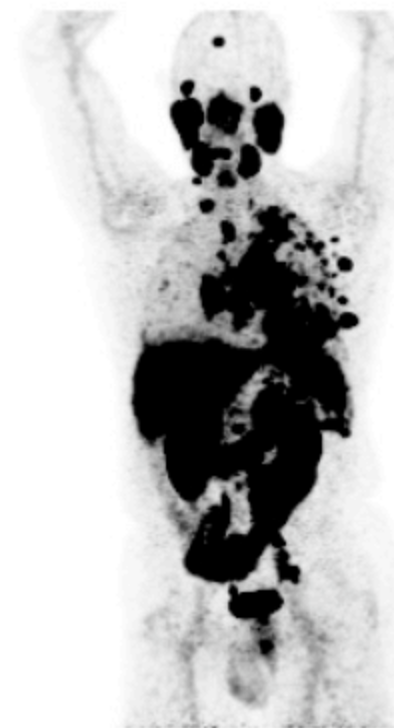
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RA



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L-R: 14.4
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Case PR

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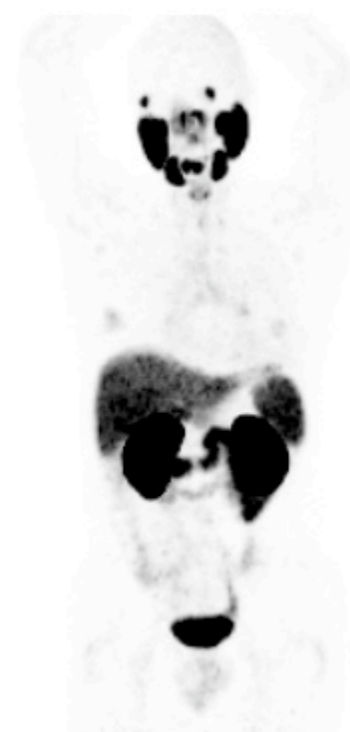
S

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I

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L



I

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L-R: 9.8
Roll: 0.0

Case PR

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S

From: 0.0000 To: 10.0532

S

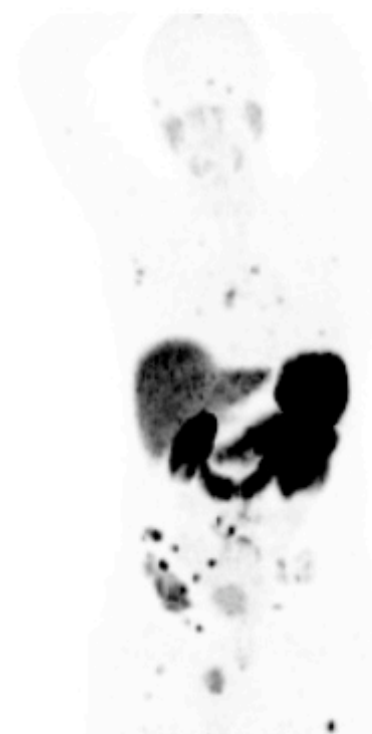


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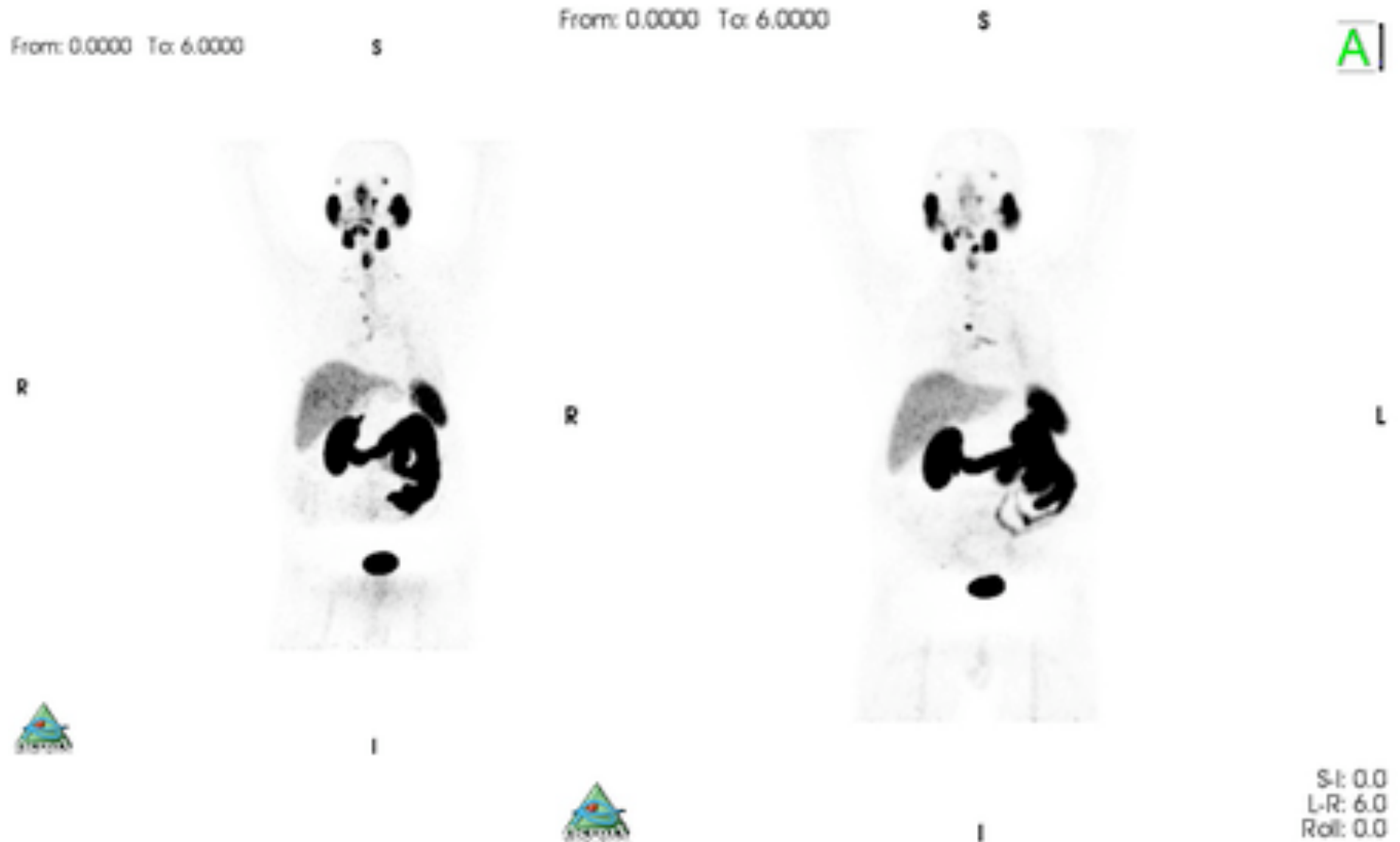


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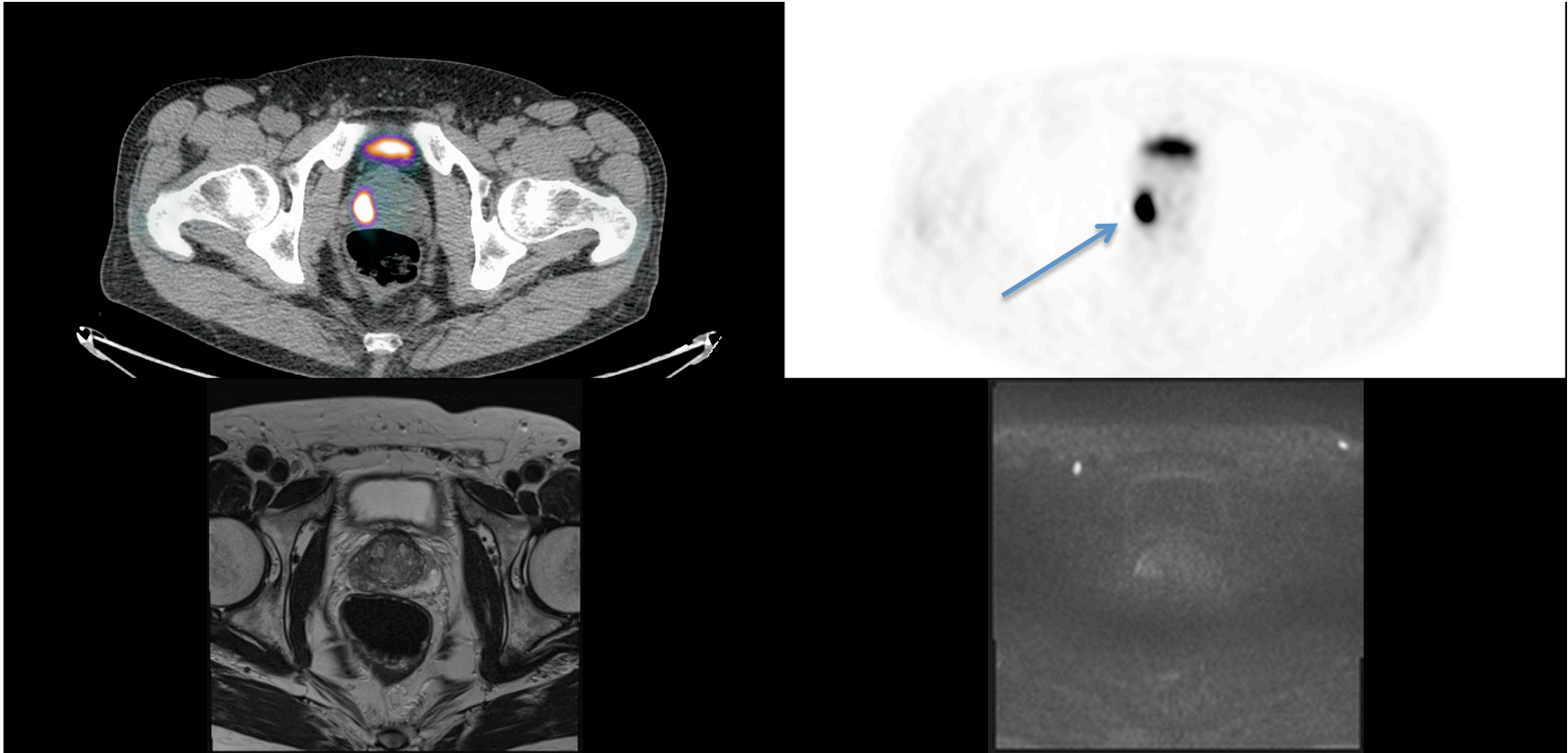
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Roll: 0.0

Mixed response



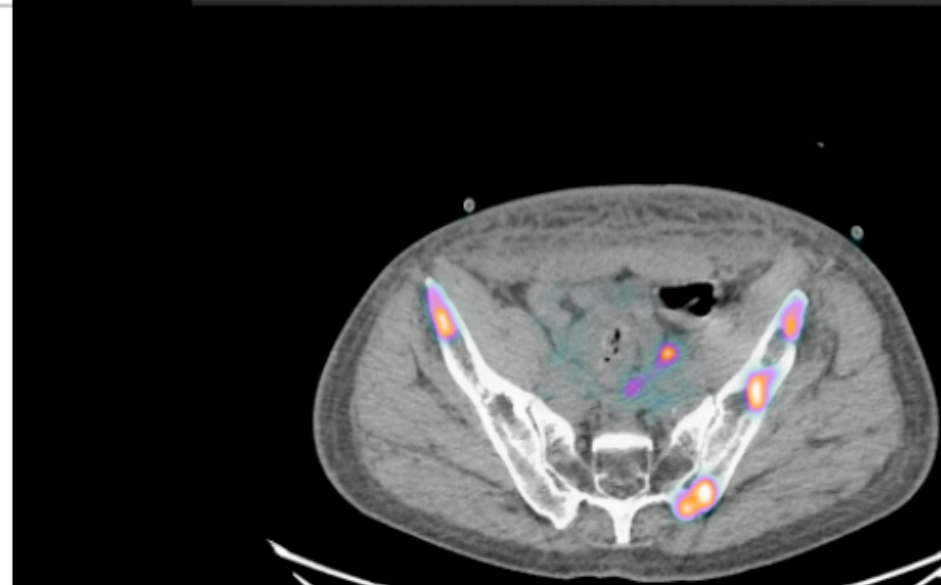
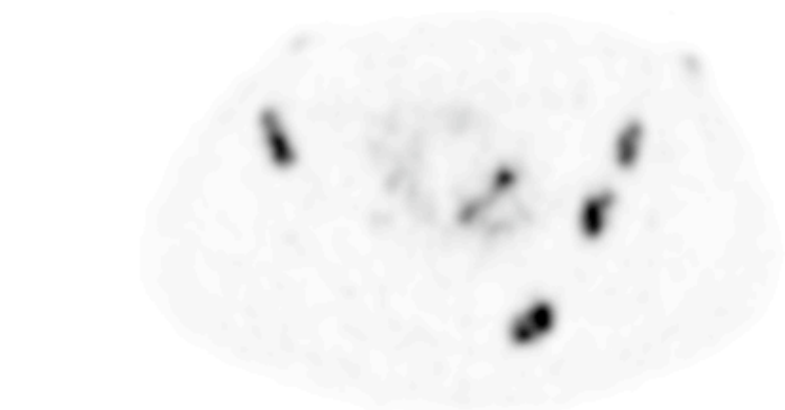
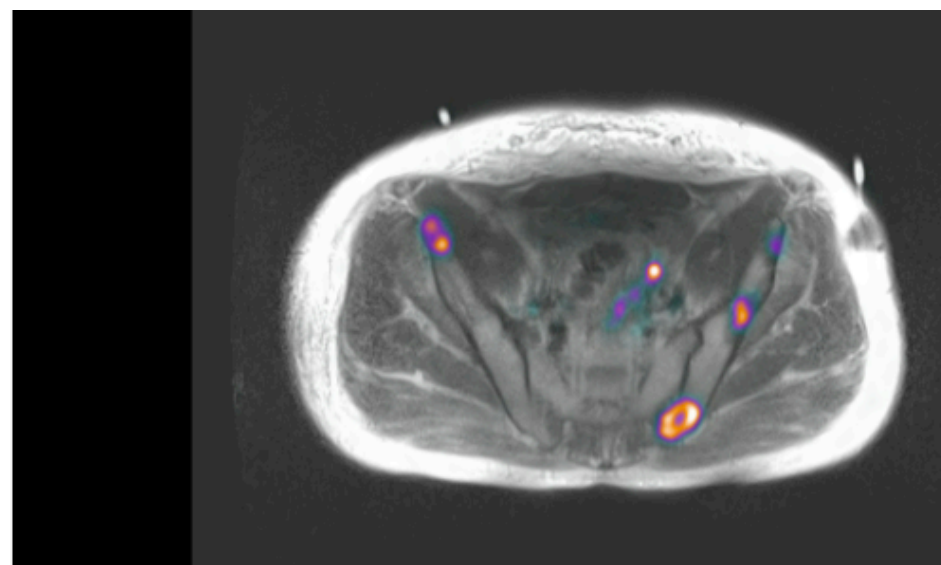
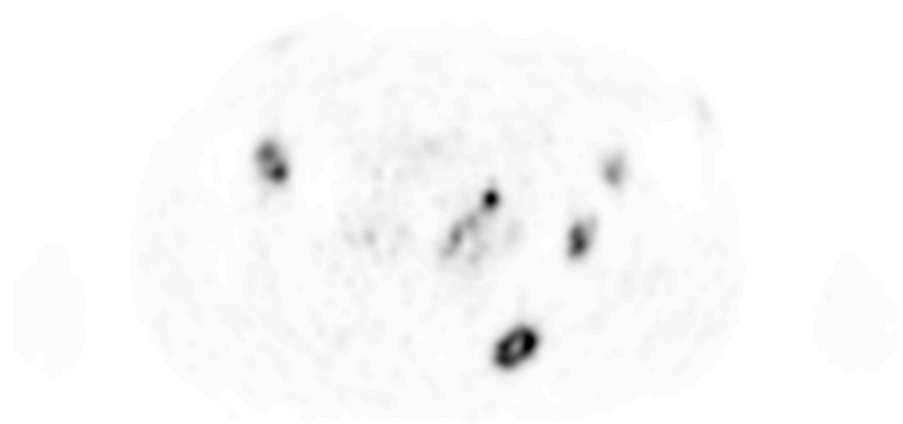


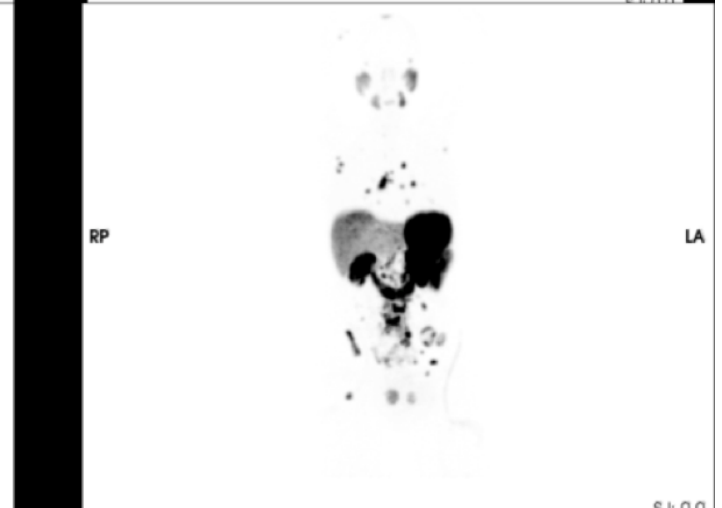
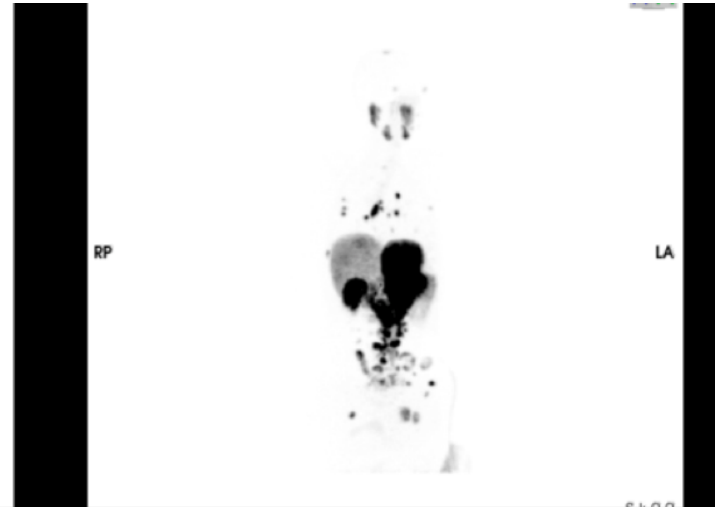
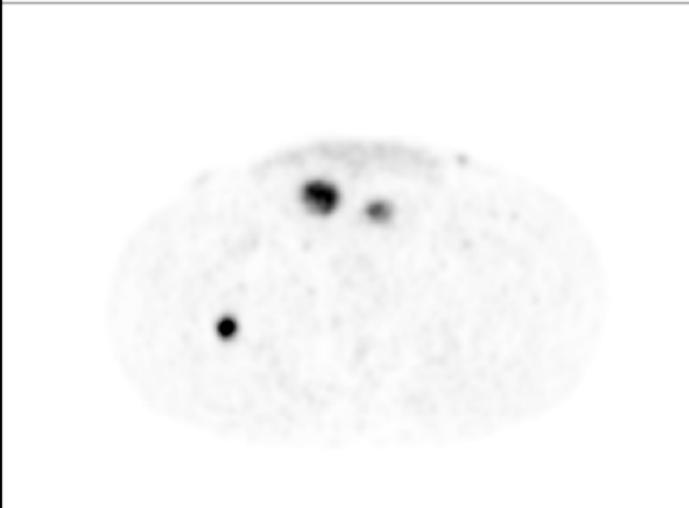
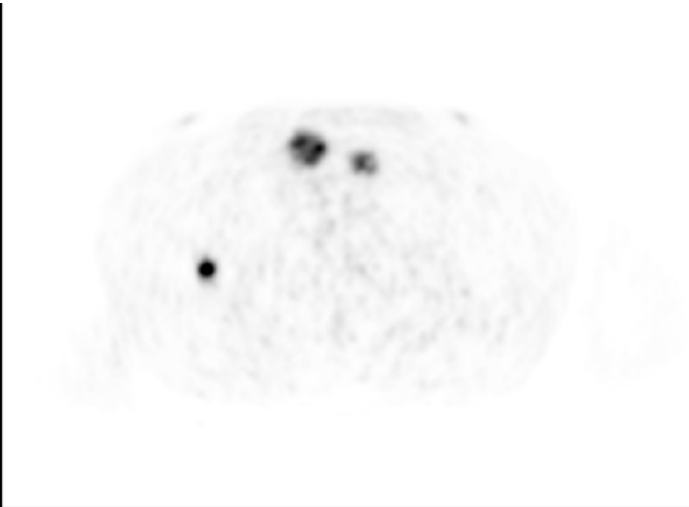
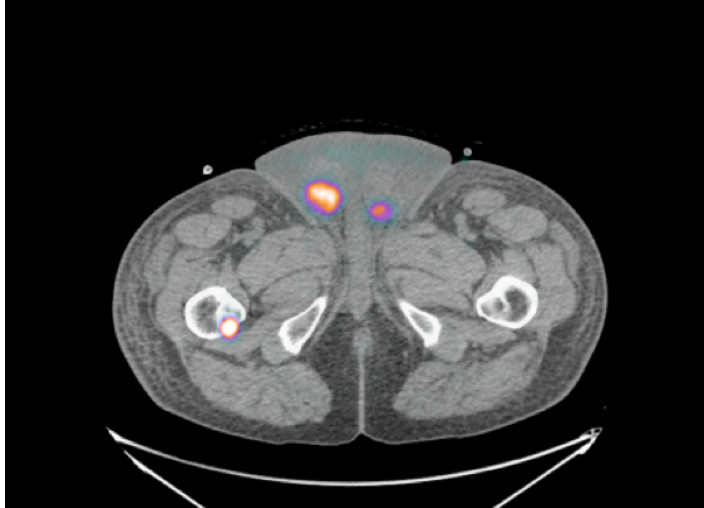
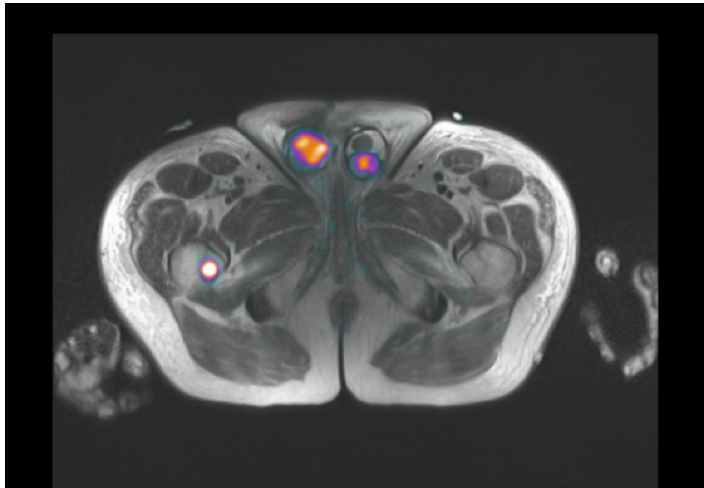
Primary tumour evaluation



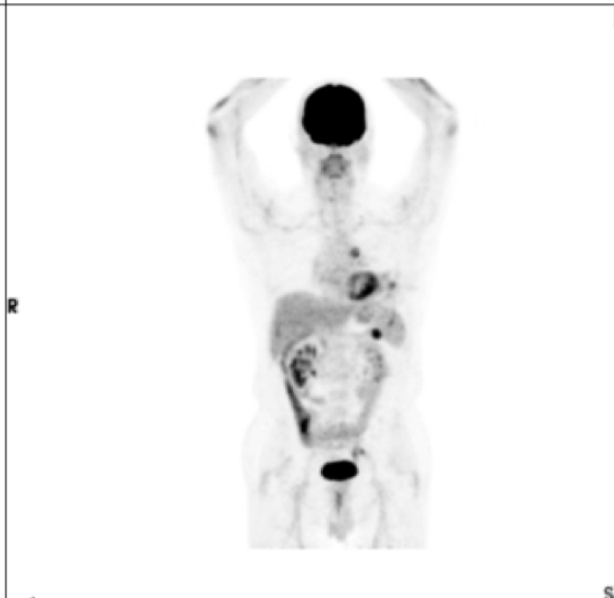
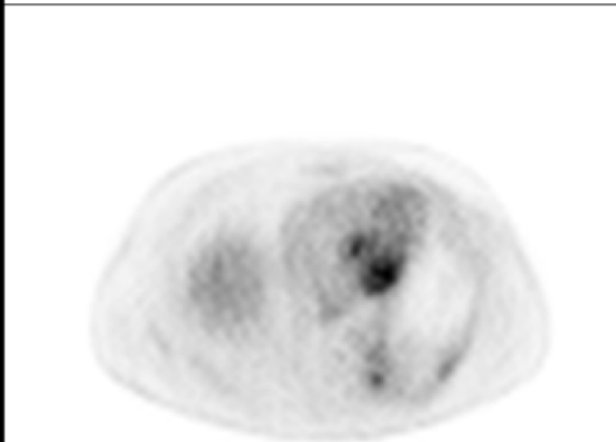
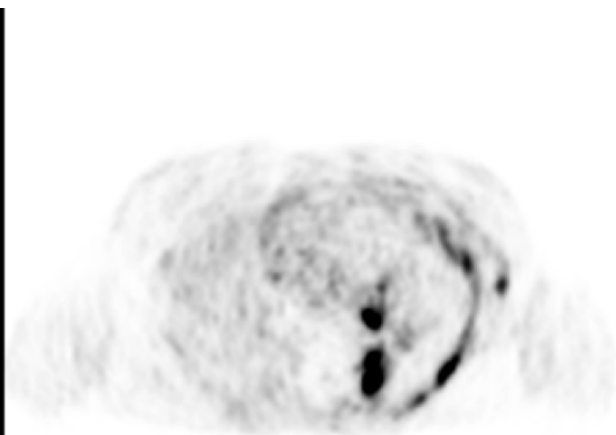
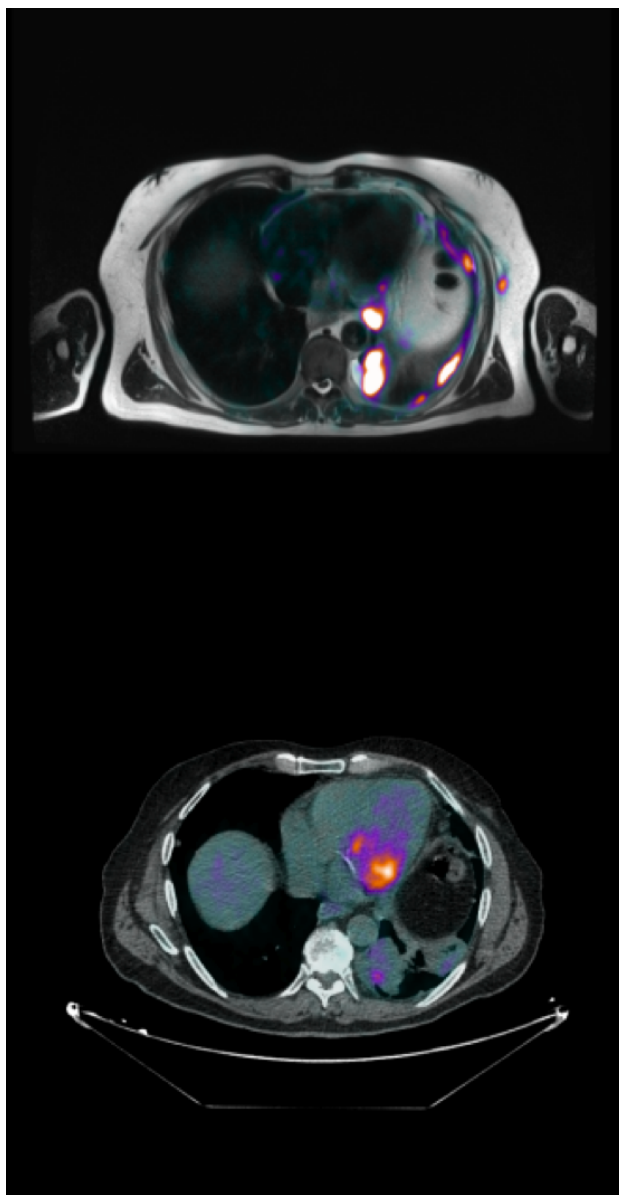
PET/CT, PET/MRI

- n=20, prostate cancer diagnosis was easier and more accurate on PET/MRI than PET/CT.
- Unclear findings on PET/CT were able to be clarified on PET/MR, although the latter were performed at a later uptake time (3 hours rather than 1-hour post injection) EJNMI 2014;41:887-897
- n=26, PET/MR reliable and accurate when compared to PET/CT for node and bone lesion detection (Freitag et al 2015)

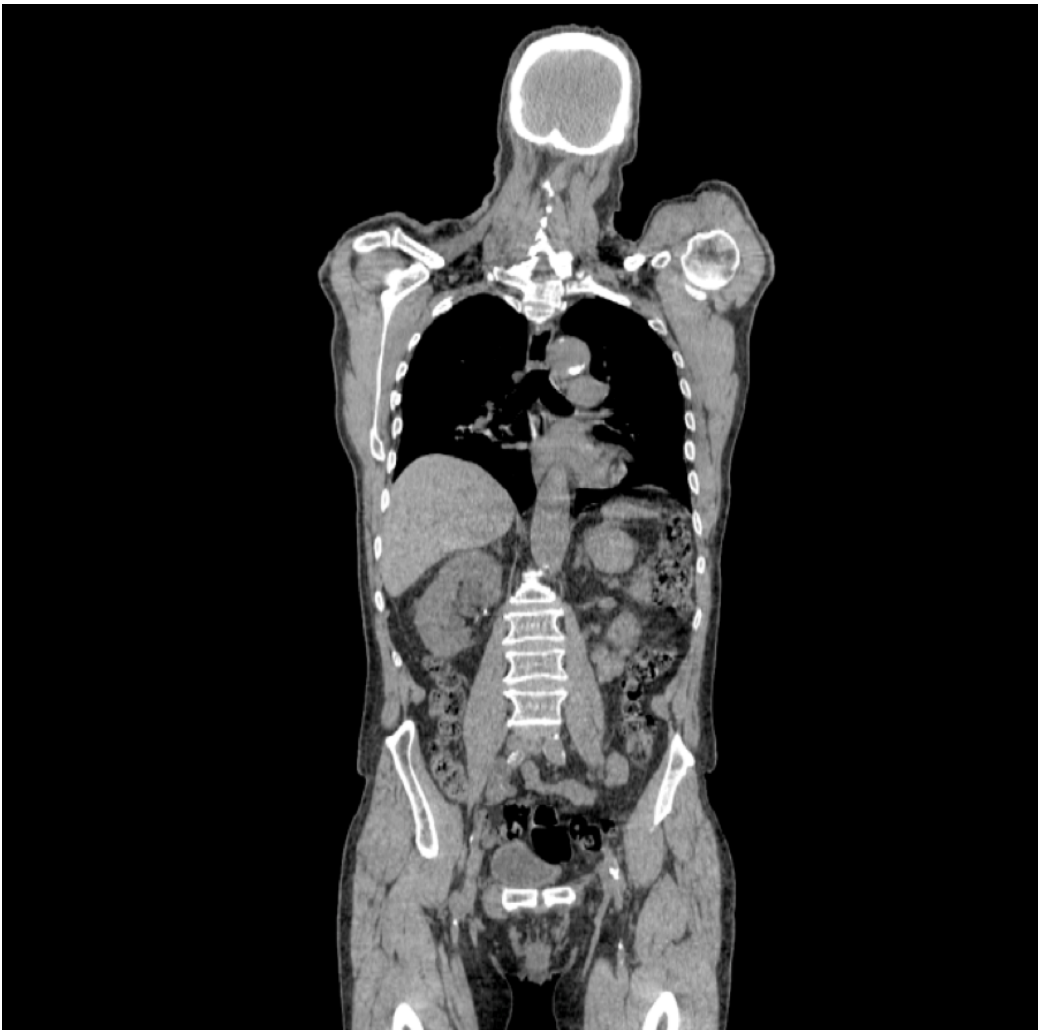




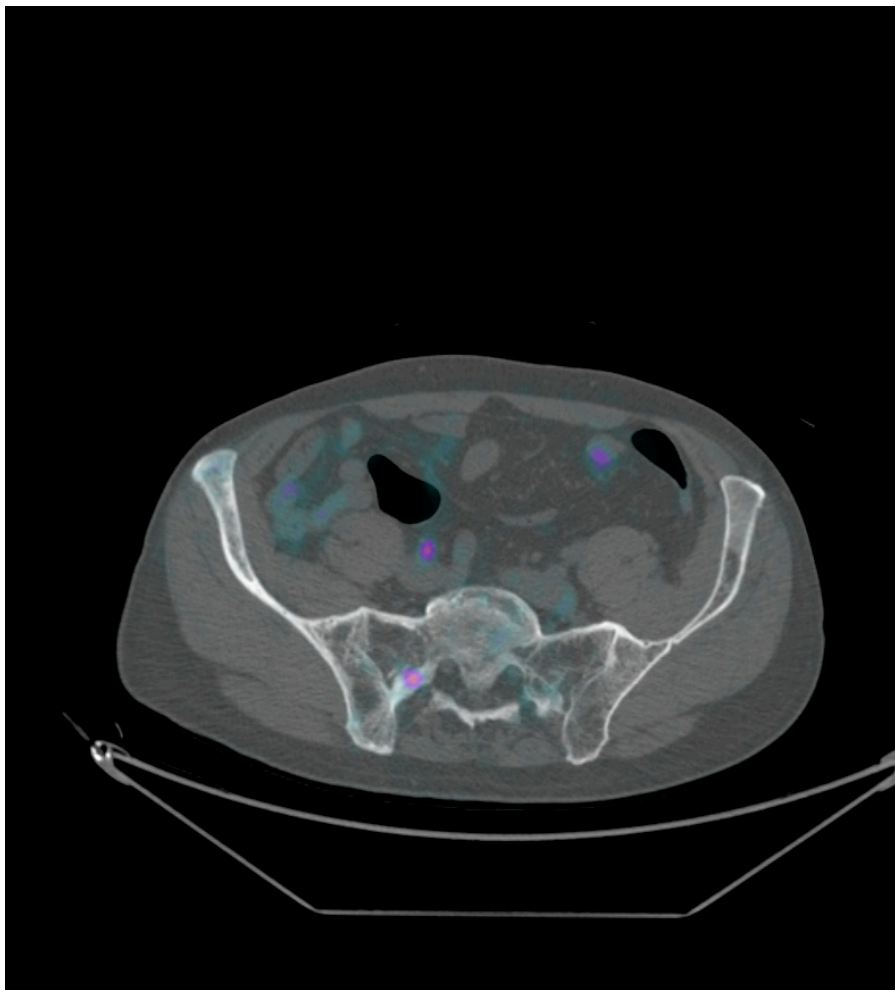
Pitfalls



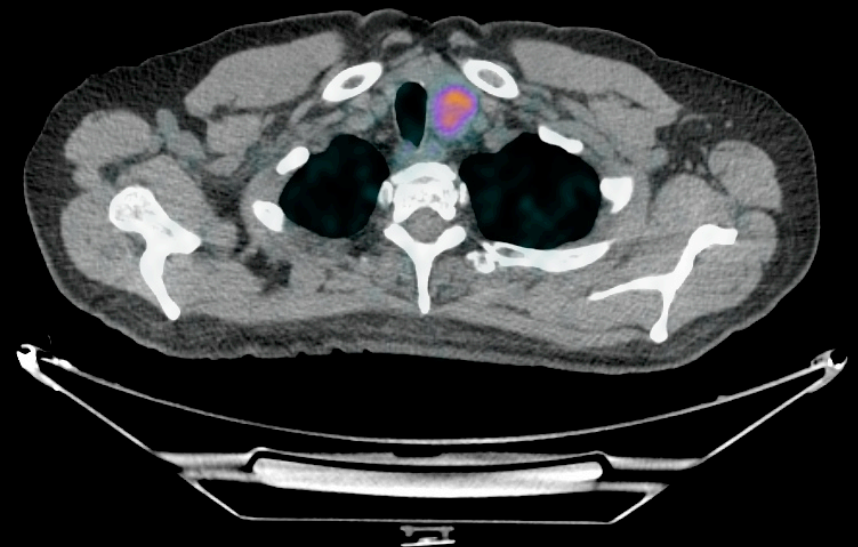
Lung cancer



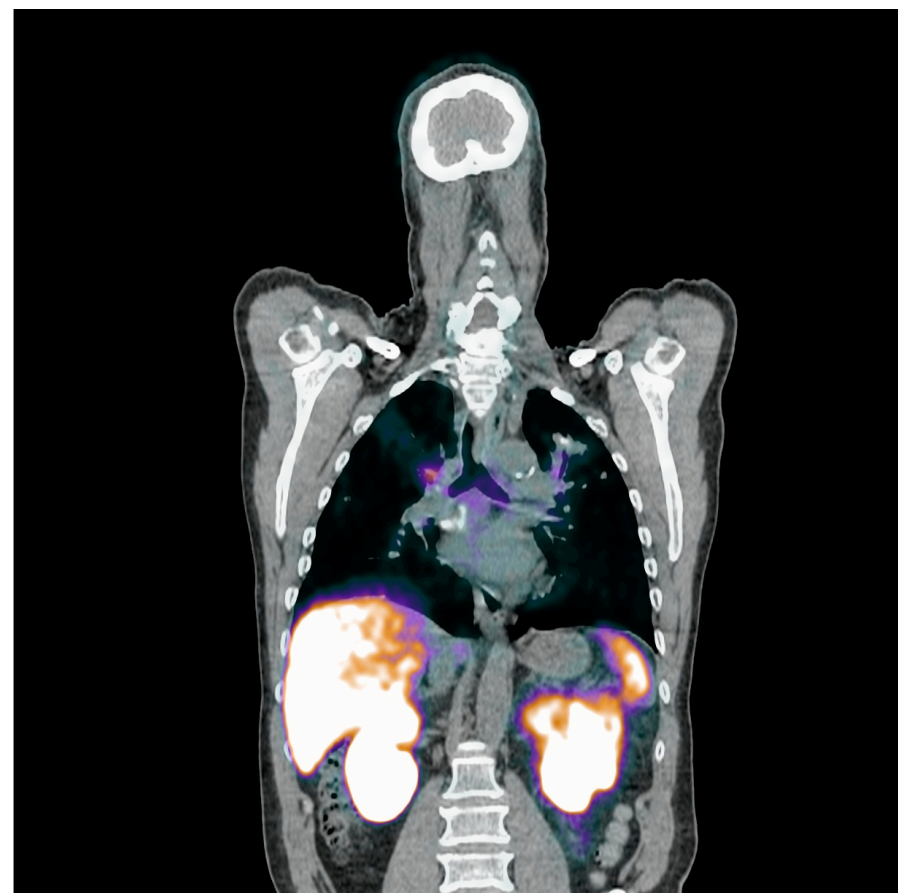
TCC Right ureter



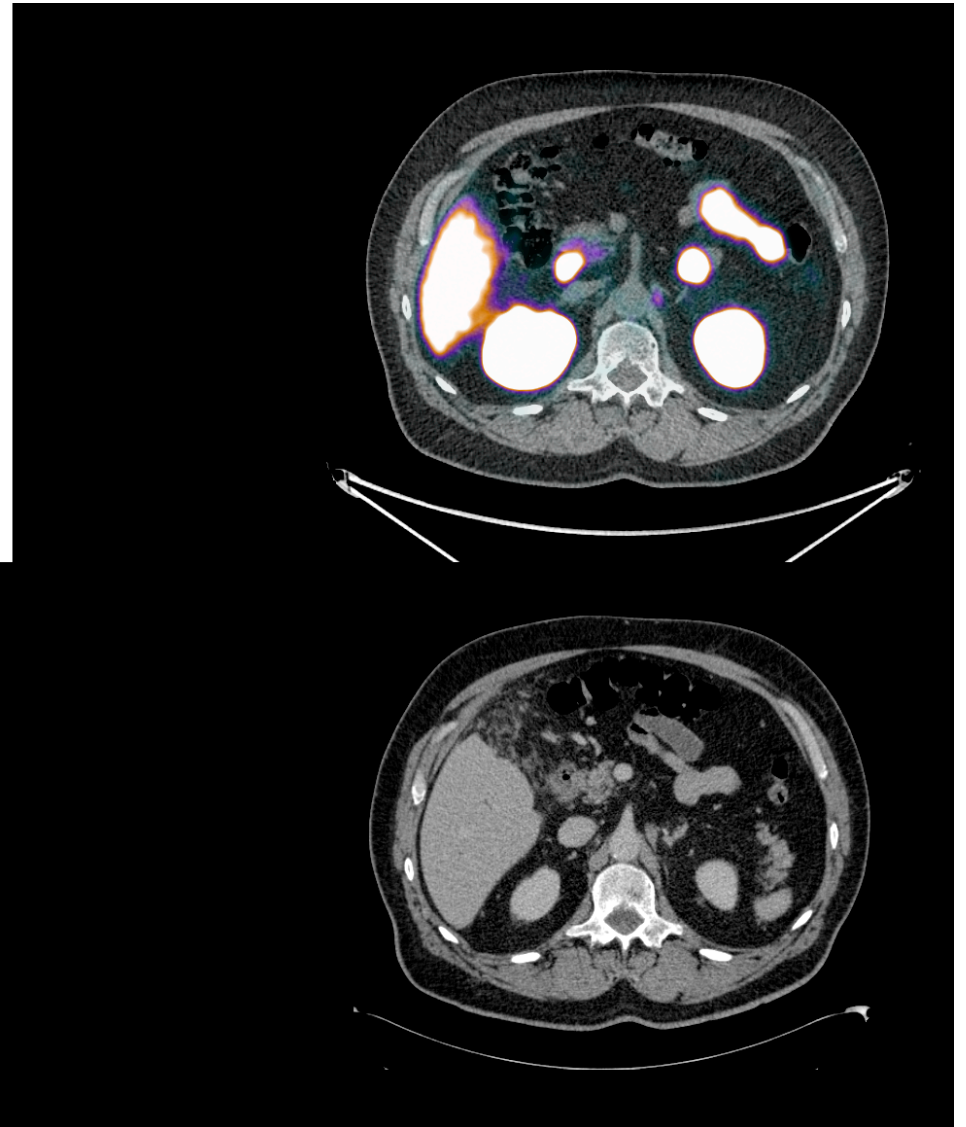
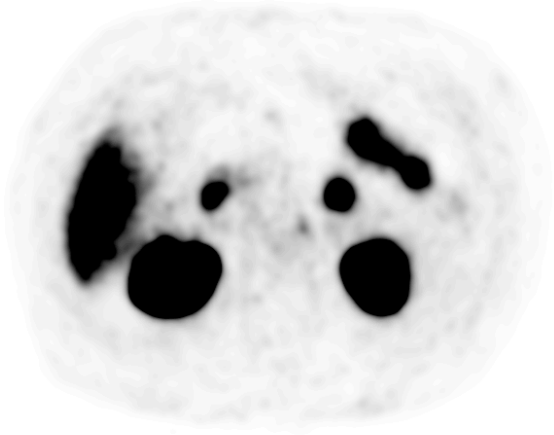
Paget's



Thyroid nodules



Sarcoidosis



Coeliac ganglion

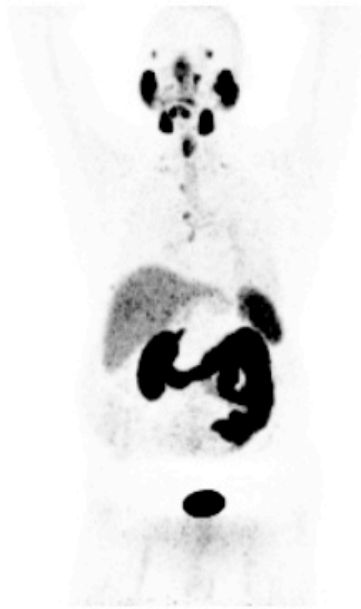
Artefact

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L-R: 9.2
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Halo artefact

⁶⁸Ga-PSMA PET/CT impact on prostate cancer management

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Athar Haroon⁵, Heather Payne⁶, Hashim Ahmed⁷, Shonit Punwani⁸,
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Abstract

Aim: To assess the impact of ⁶⁸Ga-Prostate Specific Membrane Antigen (PSMA) Positron Emission Tomography/ Computed Tomography (PET/CT) on management of prostate cancer in patients with biochemical recurrence (BCR). **Methods:** Documented management plans were retrospectively reviewed before and after ⁶⁸Ga-PSMA PET/CT in 100 patients with BCR and change in plans recorded. **Results:** Management changed after ⁶⁸Ga-PSMA PET/CT in 39 patients (39%). These occurred in 23/68 (33.8%) of patients with radical prostatectomy (RP) and 16/32 (50%) of patients previously treated with radical radiotherapy. Positive scan ($P < 0.001$) and higher Prostate Specific Antigen (PSA) ($P = 0.024$) were associated with management changes. No significant association with management change was found with Gleason grade, stage, presence of metastatic disease, PSA velocity or doubling time. **Conclusion:** ⁶⁸Ga-PSMA PET/CT altered management in 39% of patients with BCR, and occurred more often in patients with radical radiotherapy treatment, a positive ⁶⁸Ga-PSMA scan and higher PSA level.

This Article

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Aim

- To assess the impact of ^{68}Ga -PSMA PET/CT on management of prostate cancer in patients with biochemical recurrence (BCR).

Methods

- Documented management plans were retrospectively reviewed before and after ^{68}Ga -PSMA PET/CT in 100 patients with BCR and change in plans recorded.

Results

- Management changed after ^{68}Ga -PSMA PET/CT in 39 patients (39%)
- 23/68 (33.8%) of patients with (RP) and 16/32 (50%) of patients treated with (RT)
- Positive scan ($p < 0.001$) and higher PSA ($p=0.024$) were associated with management changes
- No significant association with management change was found with Gleason grade, stage, presence of metastatic disease, PSA_v or PSA_{dt}

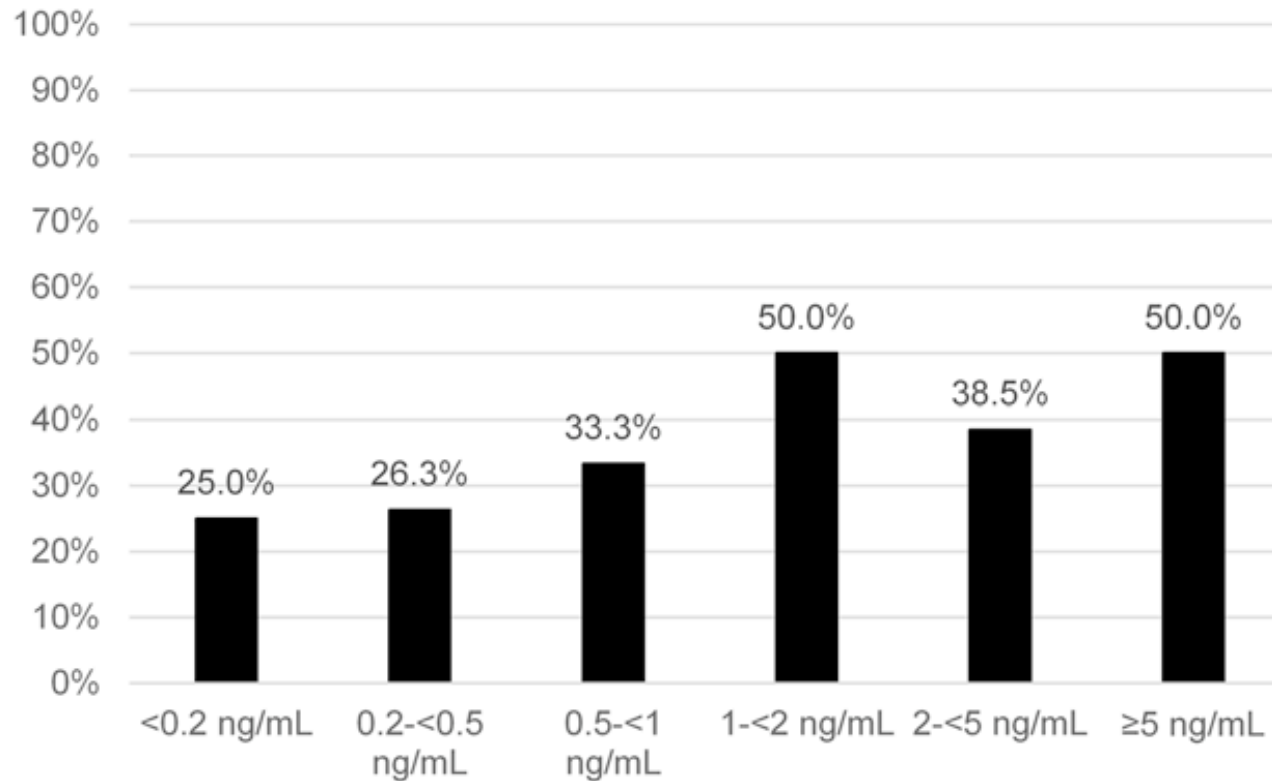


Figure 1. Management changes occurring at different PSA levels. A greater proportion of changes occurred with higher PSA levels and this was significant ($p=0.024$).

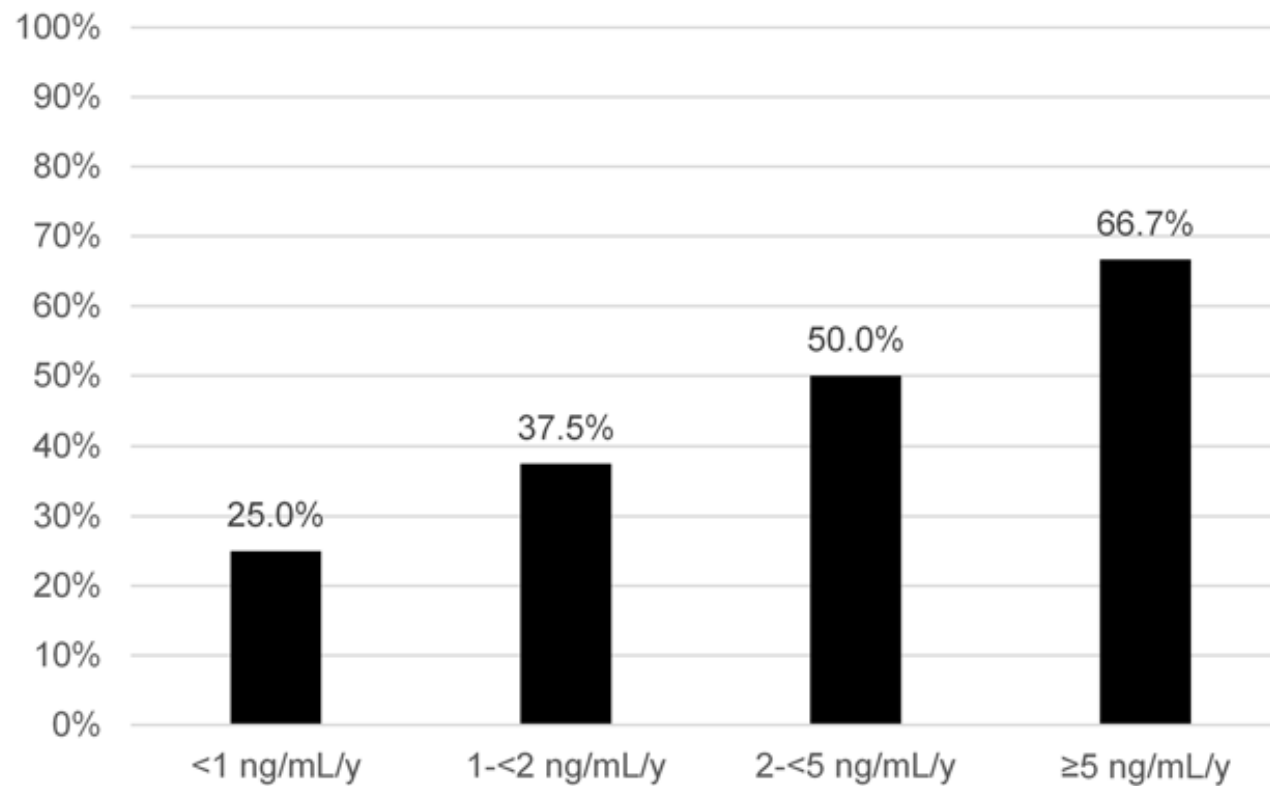


Figure 2. A higher PSA velocity was seen when a greater proportion of management changes occurred but this did not reach statistical significance ($p=0.086$).

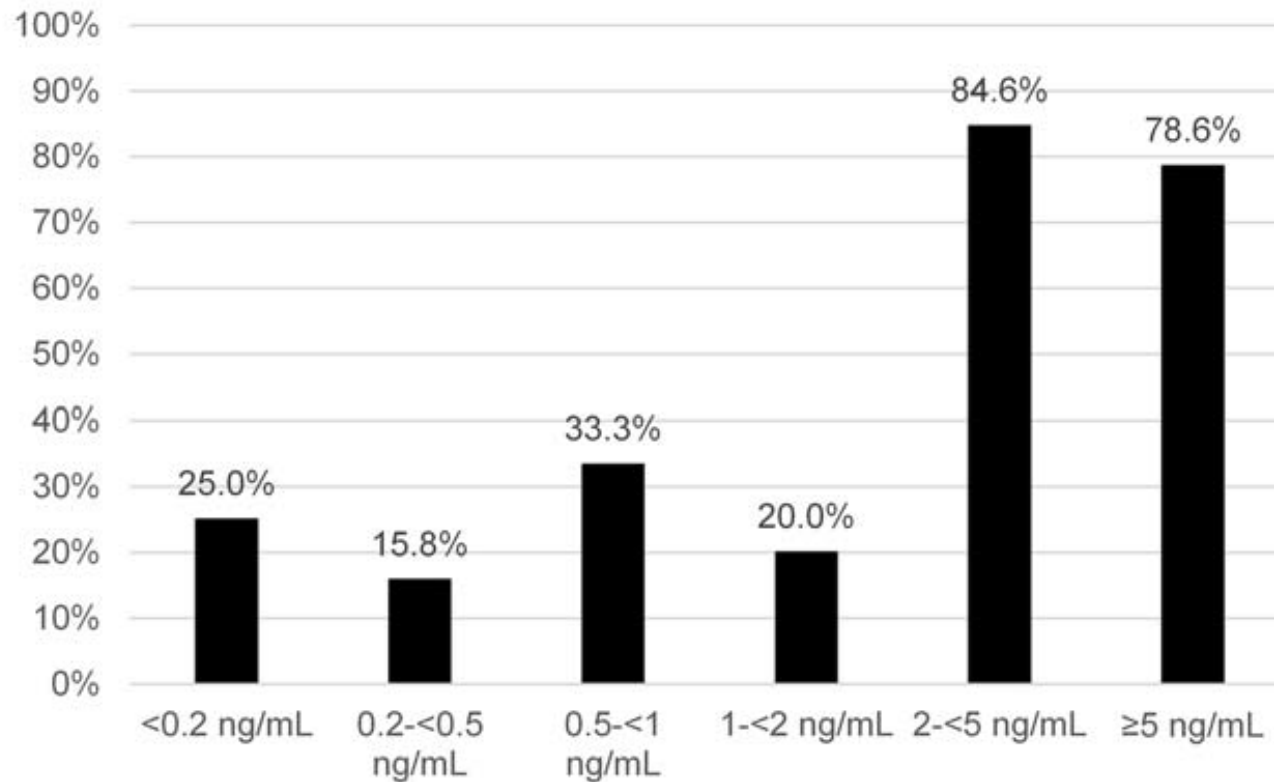


Figure 3a The proportion of positive ^{68}Ga -PSMA PET/CT at different PSA levels. A significantly higher rate of positive scans was seen at high PSA levels ($p < 0.001$).

Initial management plan	Revised management plan (n=39)
PSA surveillance	Prostate/ bed radiotherapy (1) Prostate/ bed and pelvic lymph node radiotherapy (1) Hormone therapy (3) Focal therapy (1) Cyberknife (2) Follow up of avid site (7) Follow up of non avid site (2) Radical prostatectomy and extended lymph node dissection (1)
Prostatectomy	Hormone therapy (1)
Prostate/bed radiotherapy	PSA surveillance (1) Prostate/ bed and pelvic lymph node radiotherapy (2) Radiotherapy to oligometastatic disease (1) Hormone therapy (1) Follow up of non avid site (1) Chemotherapy (1)
HIFU	Prostatectomy (2)
Hormone therapy	Prostate bed radiotherapy (2) Prostate/ bed and pelvic lymph node radiotherapy (1) Radiotherapy to oligometastatic disease (2) Focal therapy (2) Targeted biopsy (1) Radical prostatectomy and extended lymph node dissection (1) Alteration to hormone therapy regimen or introduction of enzalutamide(2)

Conclusion

- ^{68}Ga -PSMA PET/CT altered management in 39% of patients with BCR
- Changes occurred more often in patients with previous radical radiotherapy treatment, a positive ^{68}Ga -PSMA scan and higher PSA level.

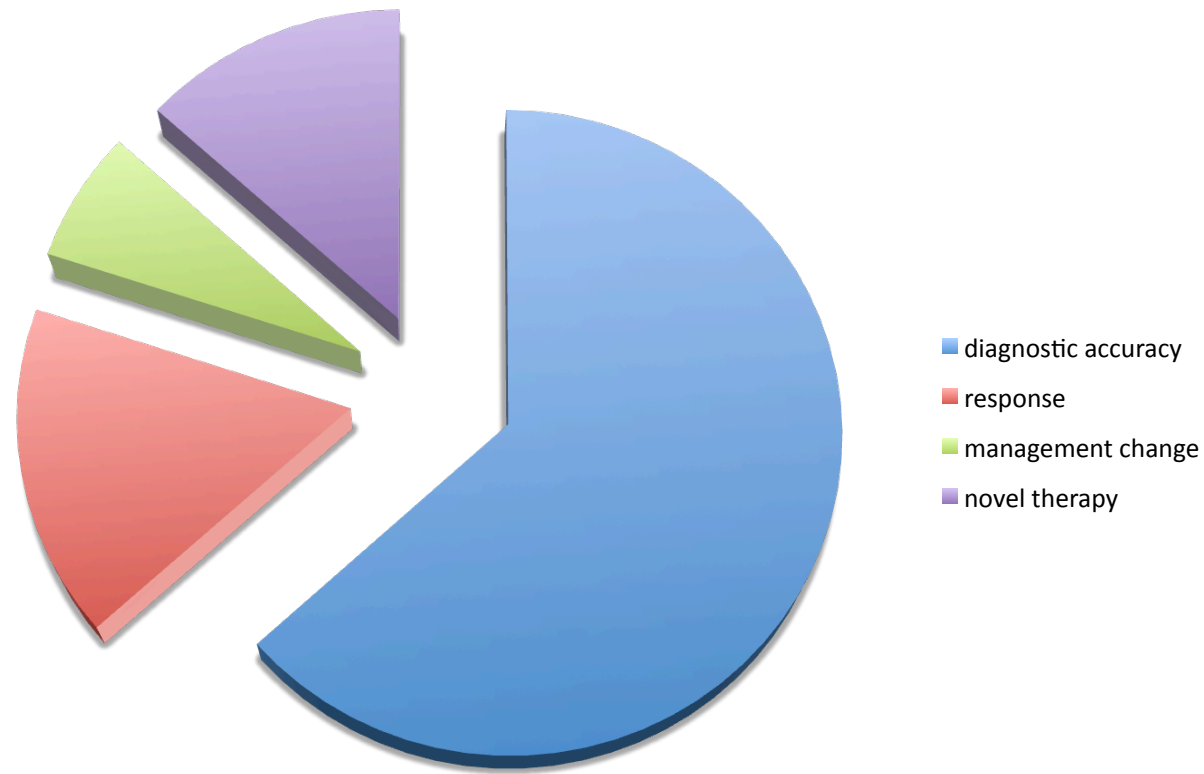
Clinical impact

Study	n=	Change in management %	Comments
Bluemel et al EJNMMI 2016	45	40%	Patients scheduled for SRT
Hope et al JNM 2017	150	53%	BCR
Albisinni et al BJUI 2017	131	76%	BCR
Afaq et al JNM 2017	100	39%	BCR

Future

- Clinical trials
- Outcomes
- Response assessment validation
- Guidelines

Current clinical trials (clinicaltrials.gov)



Summary 68Ga-PSMA PET

- Detection at low PSA levels
- Superior to Choline PET
- BCR & High risk patients are indications
- Significant impact on management of patients

Thank you

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- INM
- UCLH Oncology
- UCLH Urology
- UCL Experimental Cancer Medicine Centre