



CYCLOTEK
PET RADIOPHARMACEUTICALS
AUSTRALIA – NEW ZEALAND

F18 PSMA imaging

A viable option

Dr Rob Ware

Disclosure

- Clinical affiliation Peter MacCallum Cancer Centre
- I am a shareholder and Director of several CYCLOTEK companies whose principal business is the commercial production of PET Radiopharmaceuticals in Australia and New Zealand



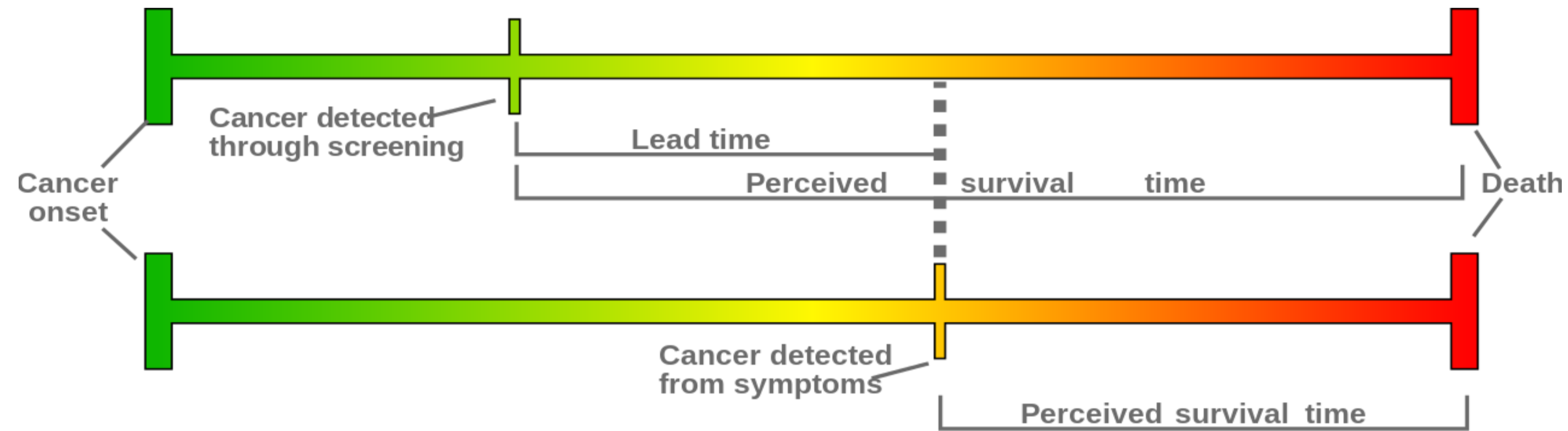
F18 PSMA imaging-a viable option

BACKGROUND

- Nuclear medicine long a main stay of prostate cancer management -bone scanning (WBBS)
- Status quo was shaken by advent of PSA screening
- Early detection raised hopes of cure, but exposed the inadequacies of ceCT and WBBS for staging/restaging and disease characteristion

F18 PSMA imaging-a viable option

BACKGROUND



- Problem of applying right treatment, to the right patient at the time persists
- Imaging remains crucial to the decision making process

F18 PSMA imaging-a viable option

BACKGROUND

- MRI improved primary assessment
- Advances have occurred in molecular imaging
 - F18 Bone scan
 - FDG can help identify “bad players” non invasively
 - Choline PET/CT
 - PSMA PET/CT

F18 PSMA imaging-a viable option

CHOLINE PET/CT evidence

- Systematic review indicates very good diagnostic performance

	Sensitivity	Specificity	Positive Likelihood ratio	Negative Likelihood Ratio
Staging				
Patient (N=637)	84%	79%	4	.2
Lesion (N=5117)	66%	92%	8.3	.4
Re-staging				
Patient (N=1005)	85%	88%	7	.2

Umbehr et al. European Association of Urology. 2013

- Peter Mac RCT evaluating independent and incremental value of FCHOL compared to CT/WBBS analysis awaited

F18 PSMA imaging-a viable option

CHOLINE PET/CT evidence

- Sensitivity limited, especially in patients with PSA < 2ng/ml. Surgically controlled studies have indicated per lesional sensitivity as low as 39%.
- Poor guide to grade of prostatic carcinoma
- False positives- inflammation

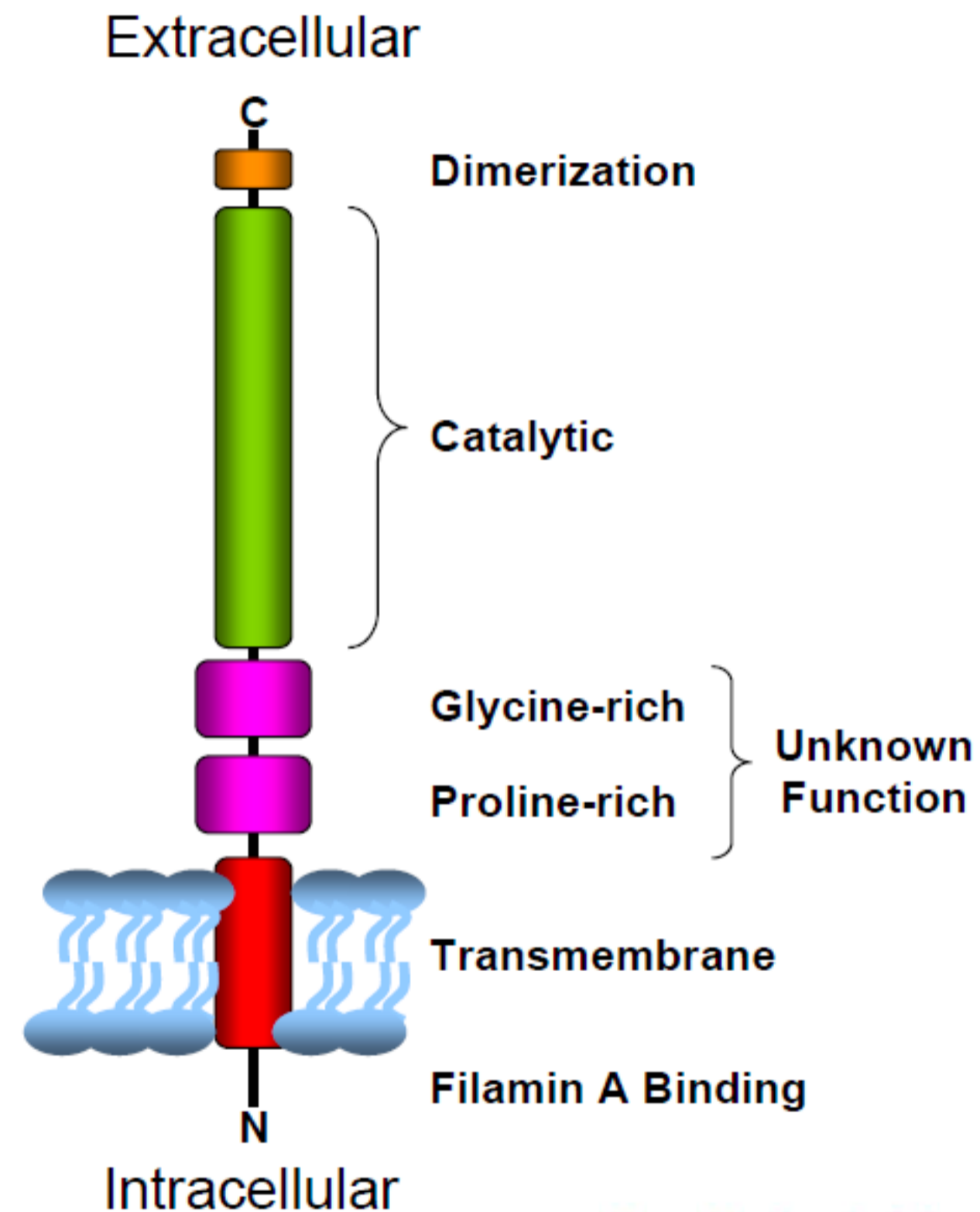
F18 PSMA imaging-a viable option

PSMA Biology

- Integral membrane carboxypeptidase II
- Expressed on 90-100% prostate cancers
- Function in tumour biology uncertain
- Increased expression higher grade, metastatic and castrate resistant tumours
- 100-1000 fold lower expression on normal cells except small intestine, renal tubular cells and salivary glands
- High expression also in renal cell carcinoma and tumour neovasculature

F18 PSMA imaging-a viable option

PSMA Biology



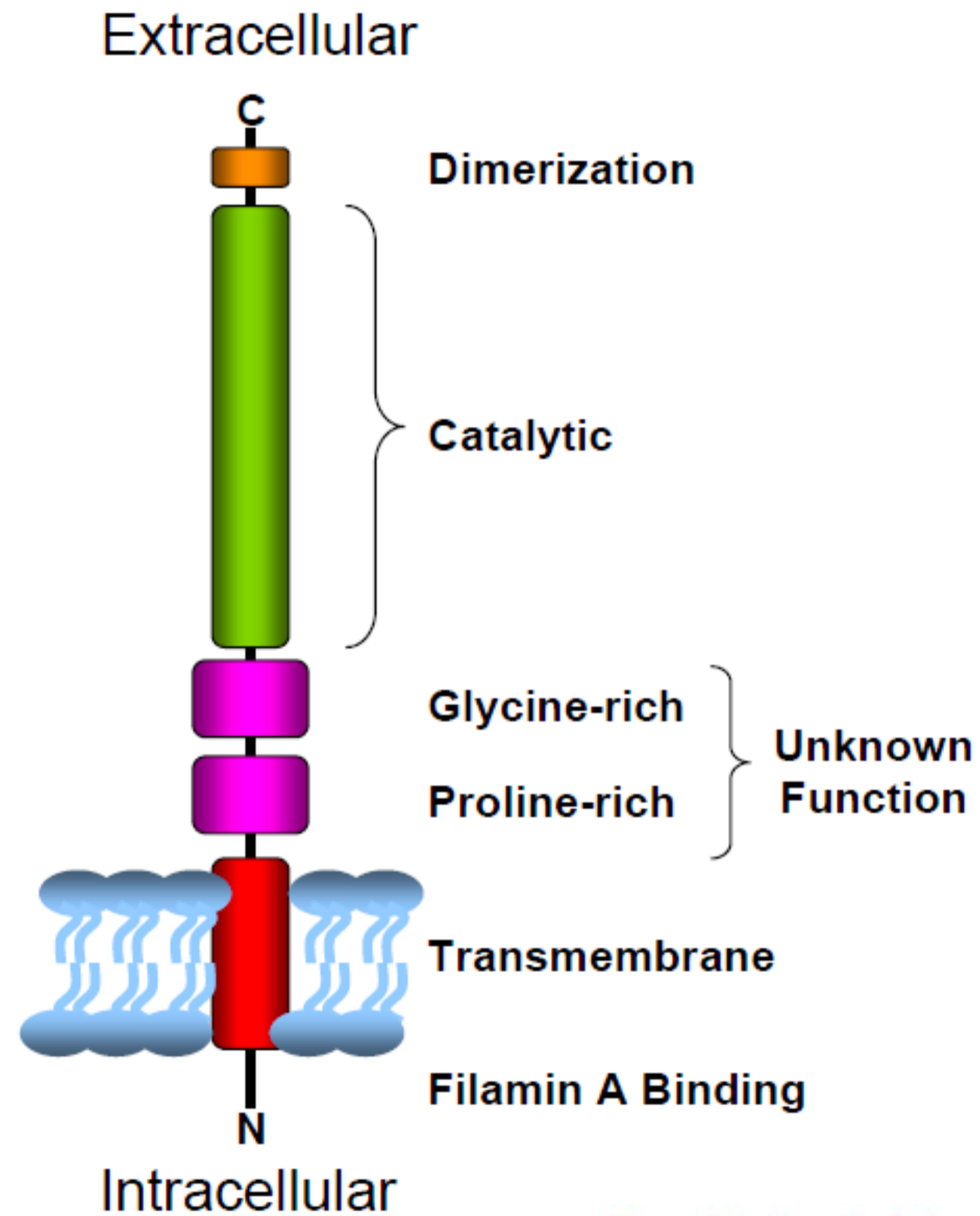
- Large number of agents developed

– *Monoclonal antibodies*

- In111-capromab recognised intracellular epitope and has limited sensitivity
- In111-J591 targets extracellular epitopes, accurately detects bone and soft tissue metastases
- Lu177-J591 has been used safely for therapy

F18 PSMA imaging-a viable option

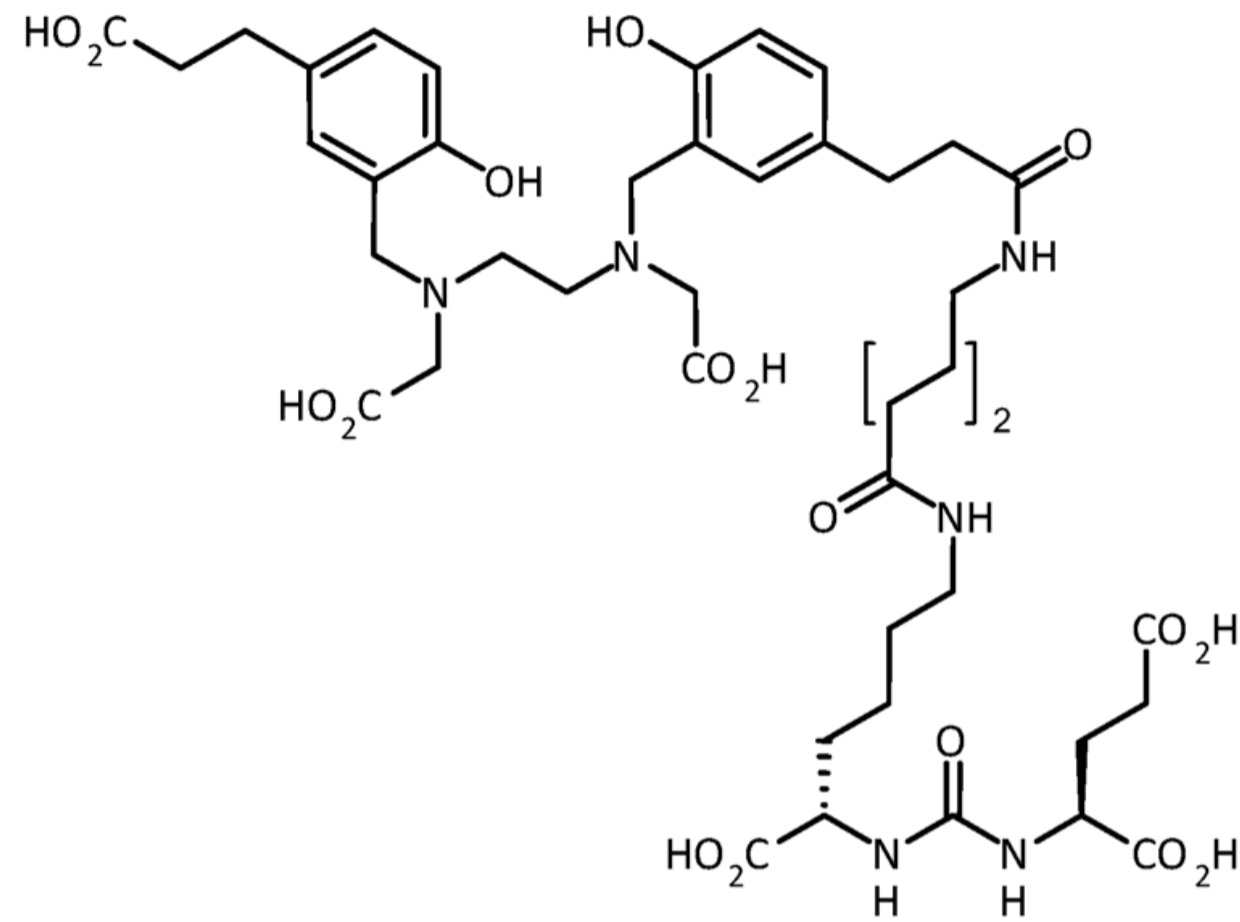
PSMA Biology



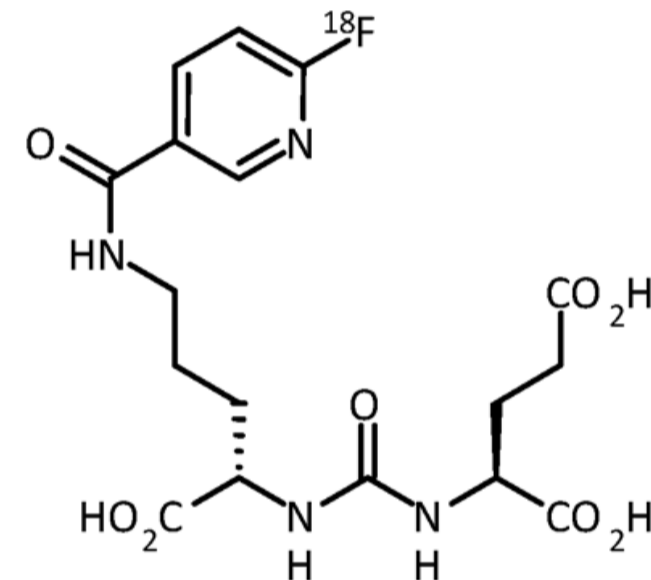
- Large number of agents developed
 - Monoclonal antibodies
 - ***Small molecule inhibitors of catalytic site***
- Tc
- I123/I124/I131
- C11
- Ga68
- F18

F18 PSMA imaging-a viable option

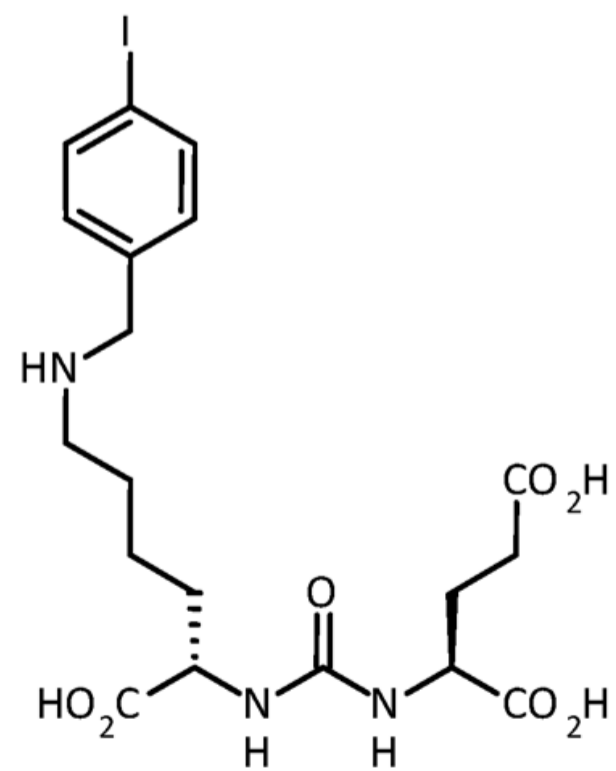
Glutamate-Urea-Lysine based PSMA Ligands



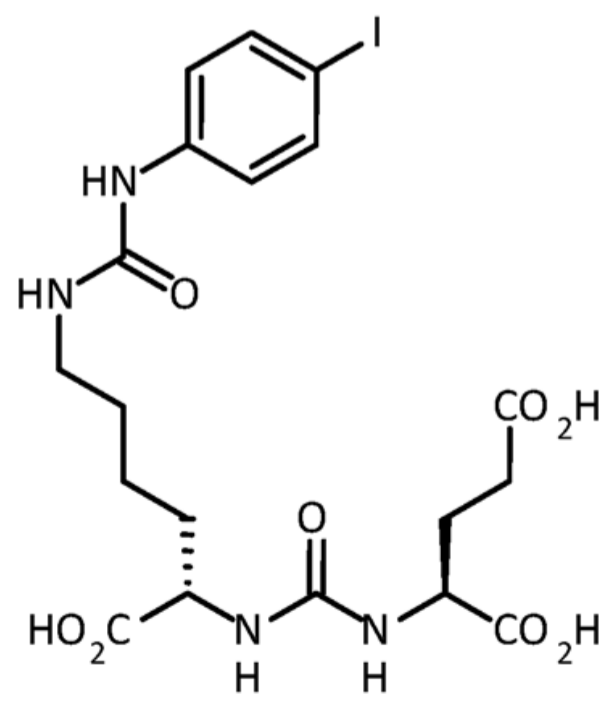
Glu-NH-CO-NH-Lys(Ahx)-HBED-CC



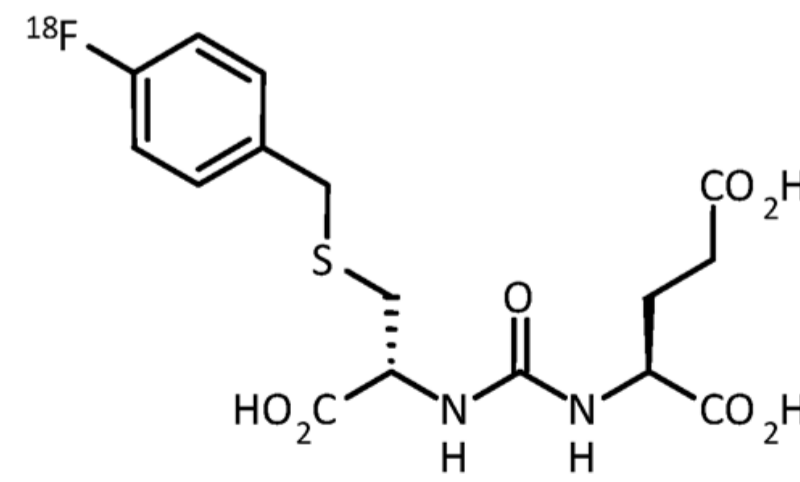
^{18}F -DCFPyl



MIP-1072



MIP-1095



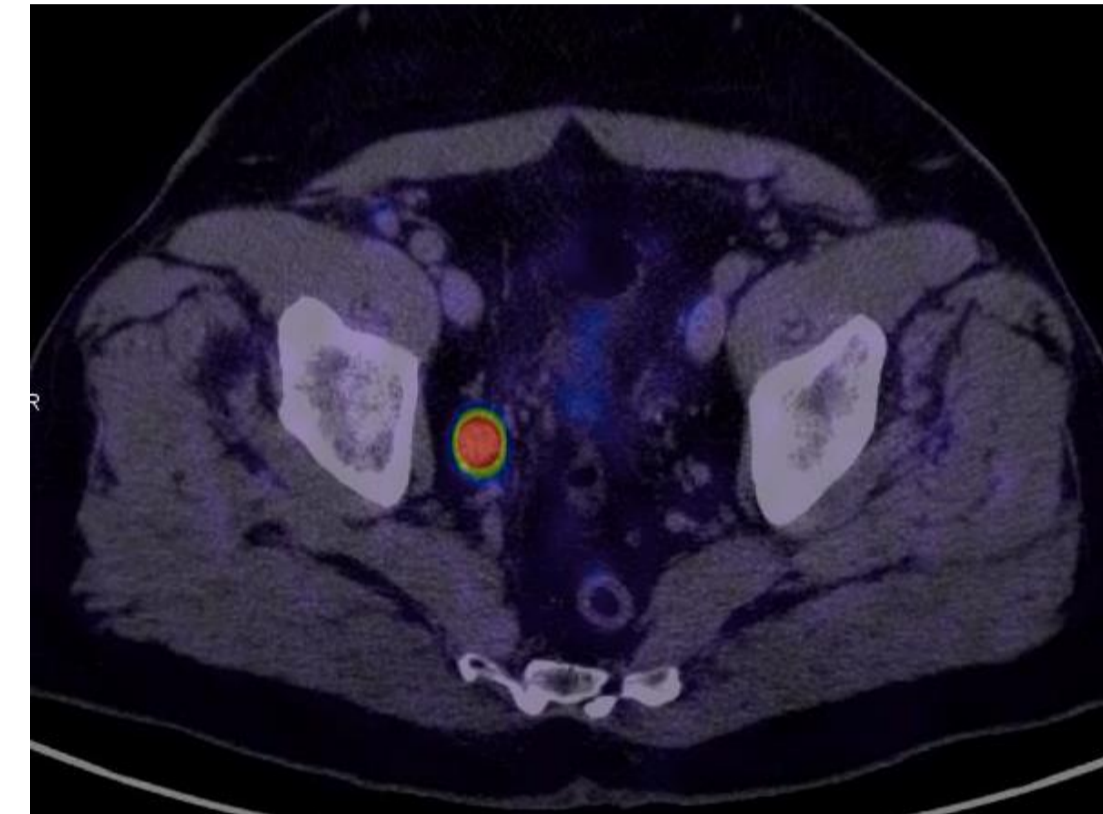
^{18}F -DCFBC

- Pomper's JHU group have been leaders in the field of radiolabeled urea based PSMA inhibitors-first to report C11, I125, Ga68, and F18 labeled ligands based on GLU-urea-LYS
- Greater stability of HBED-CC (Eder et al) has led to Ga68 PSMA PET/CT ligand being introduced into many clinical imaging facilities world wide particularly Germany and Australia following early clinical reports in 2012

F18 PSMA imaging-a viable option

Ga68 HBED PSMA imaging

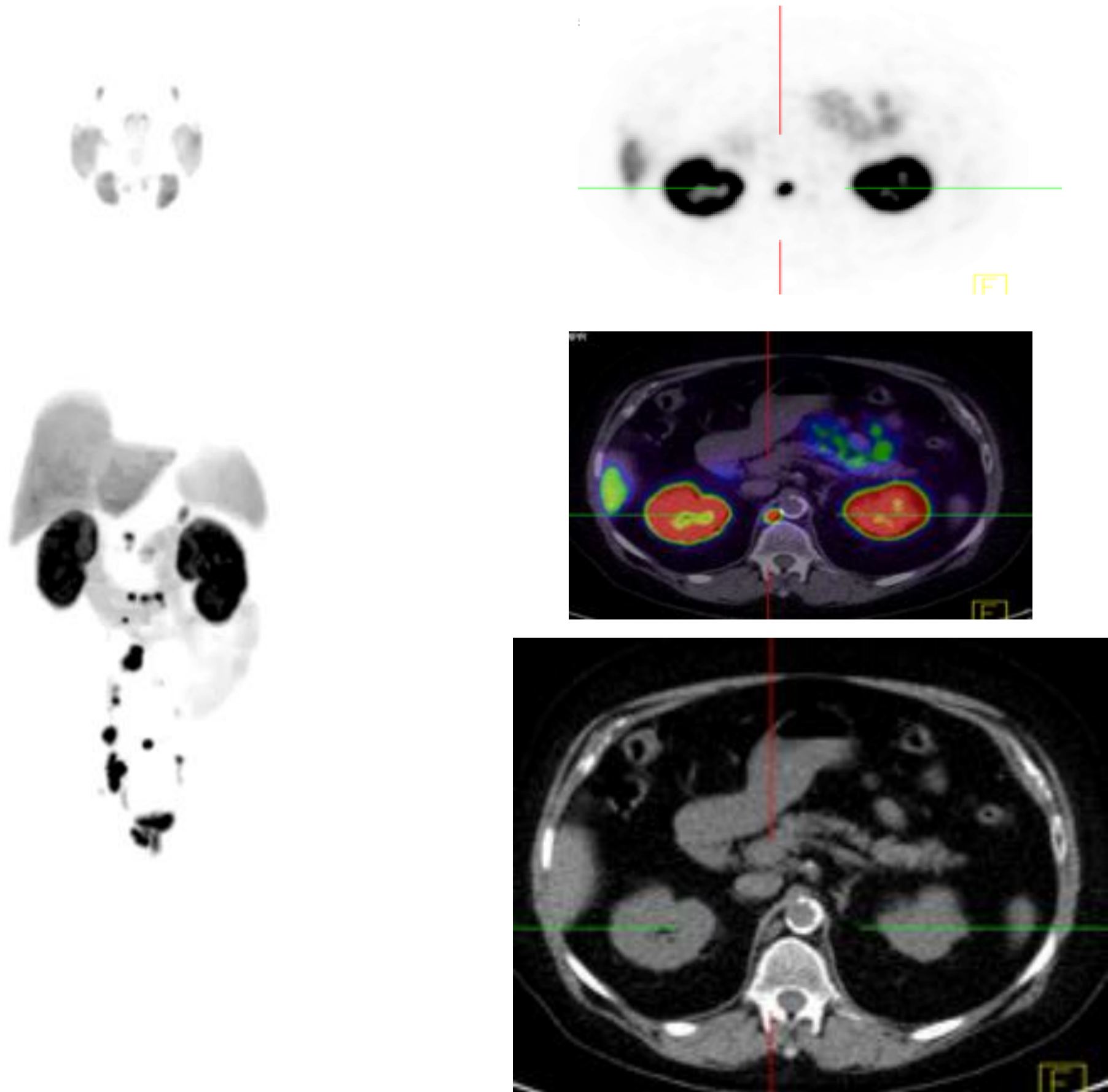
- PMCC performed over 700 studies since late 2014
- Fast elimination of tracer from background tissues
- Highly sensitive and specific



Ga68 PSMA-rising PSA after EBRT

F18 PSMA imaging-a viable option

Ga68 HBED PSMA imaging

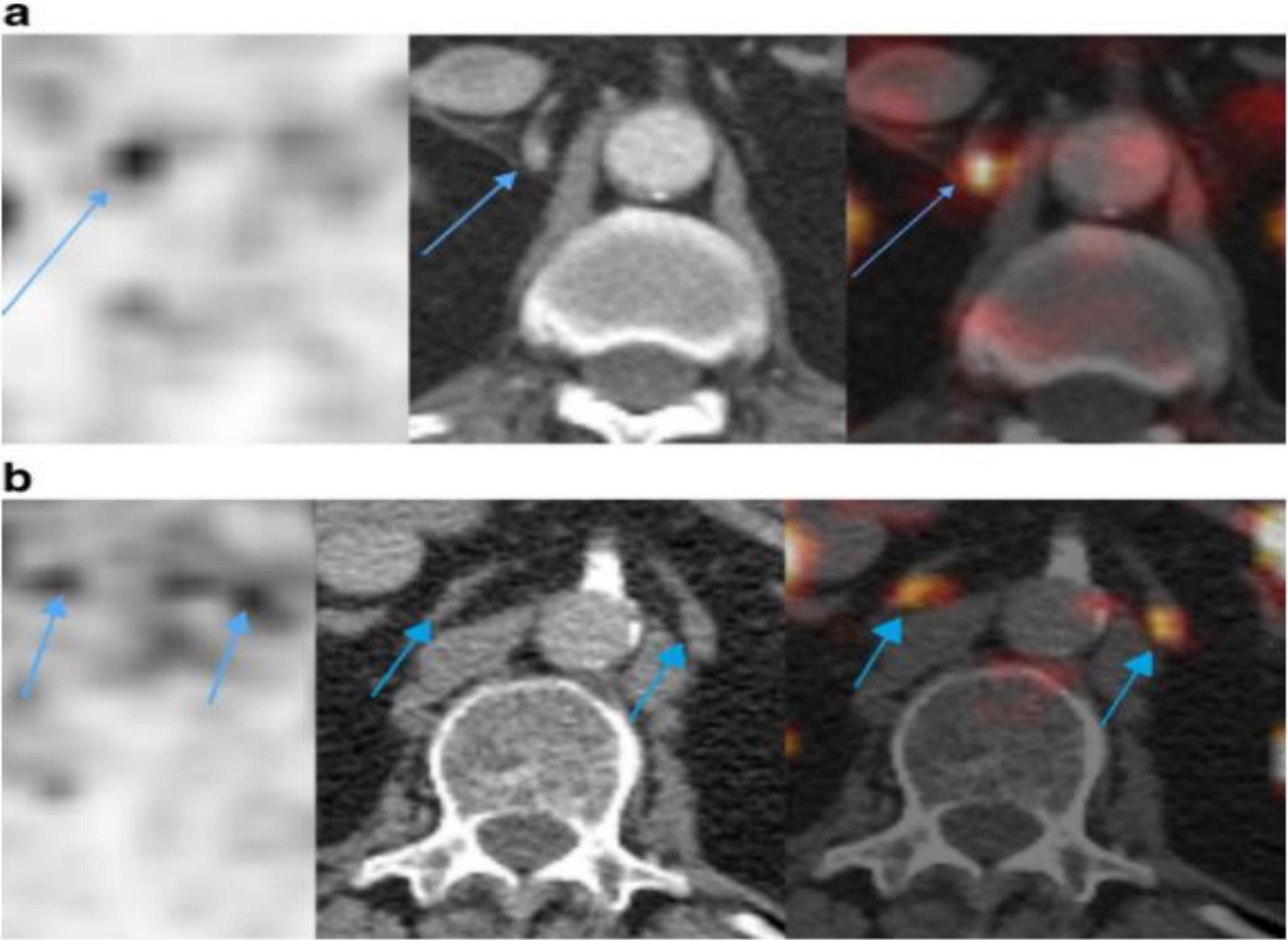
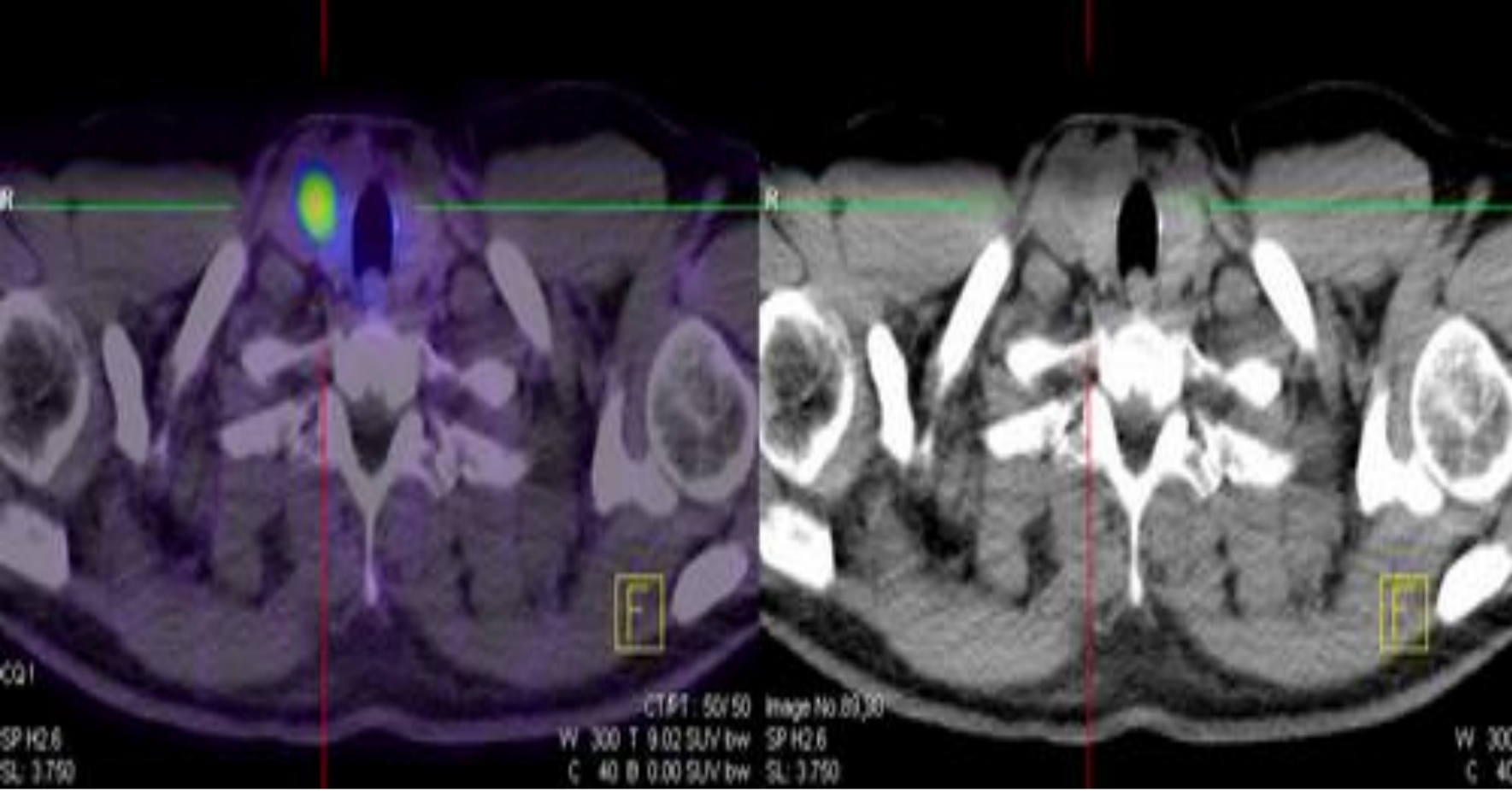


Site	Analysed	T/B mean	T/B range
Prostate	26	41	10-166
Soft tissue	55	50	10-290
Bone	36	49	5-242

Ga68 PSMA-increasing PSA on ADT post RP

F18 PSMA imaging-a viable option

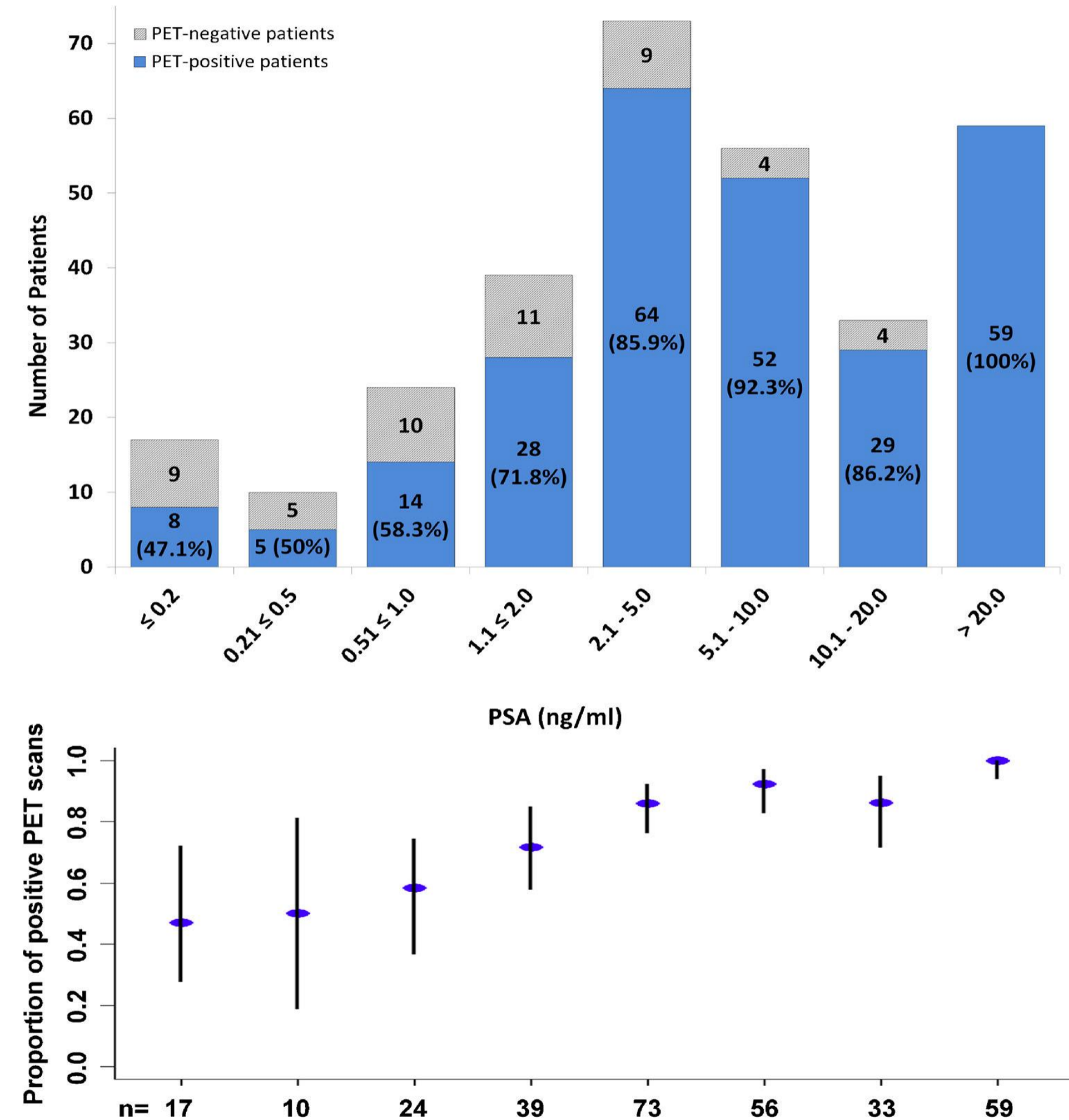
Ga68 HBED PSMA imaging



F18 PSMA imaging-a viable option

Ga68 HBED PSMA imaging

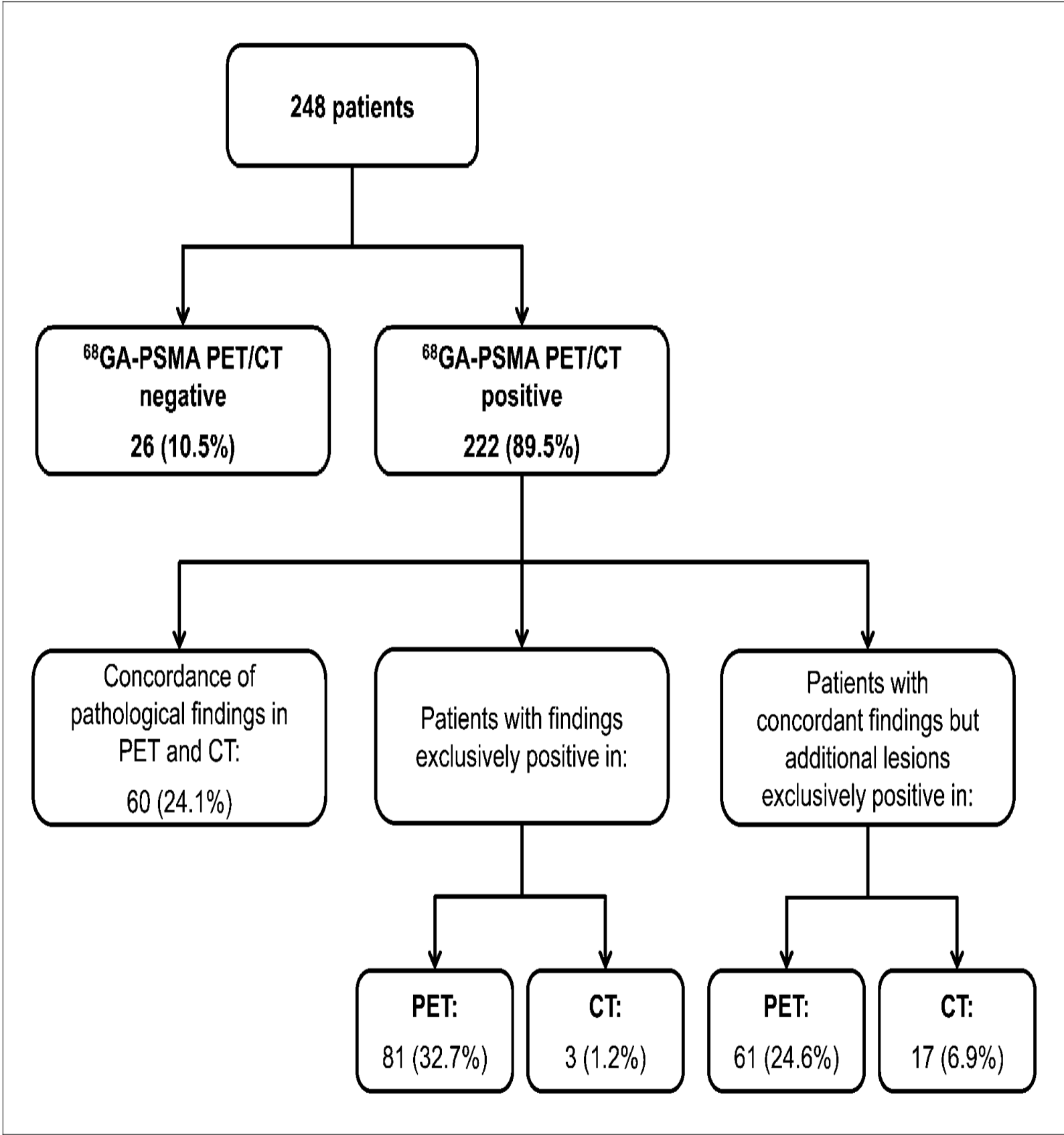
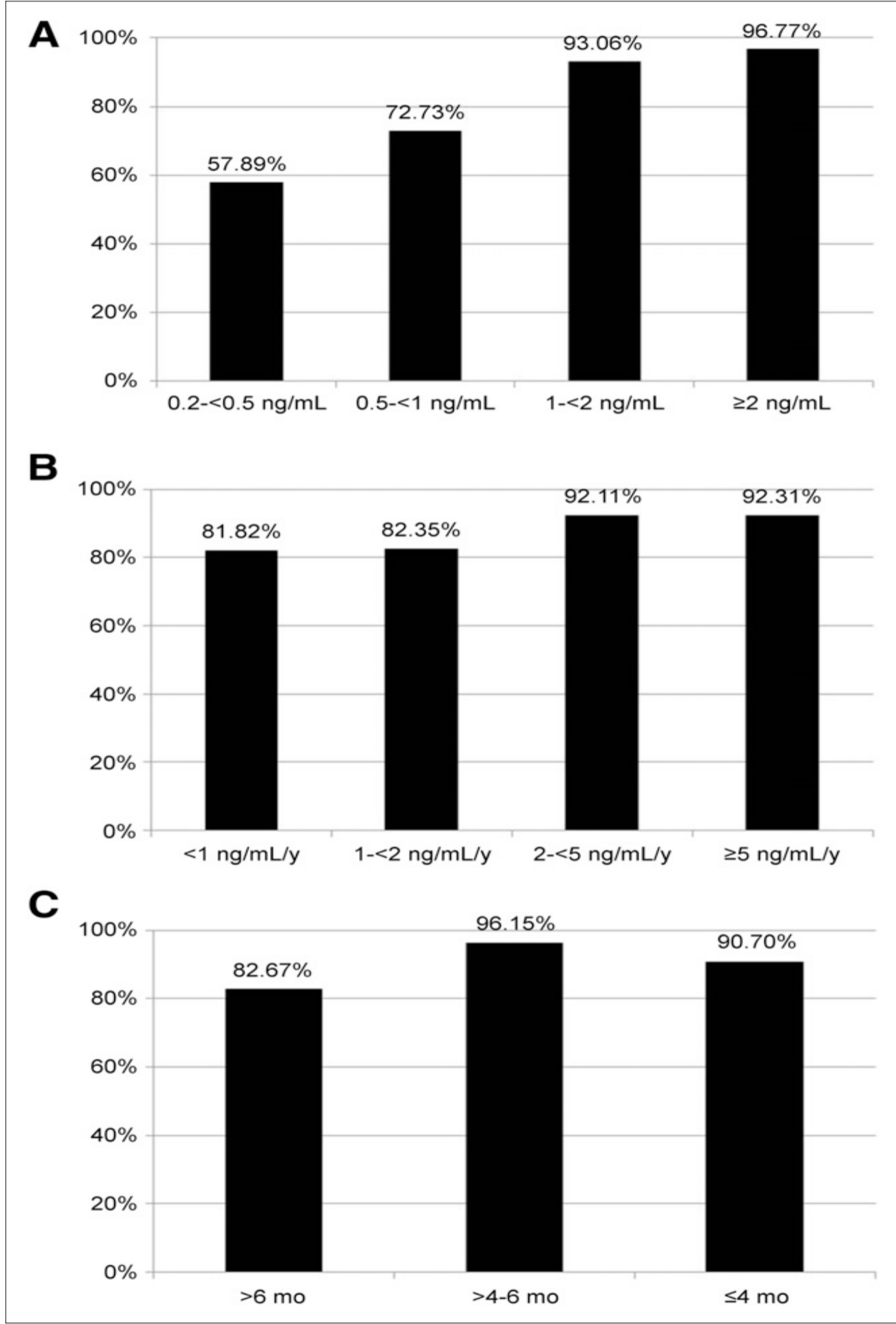
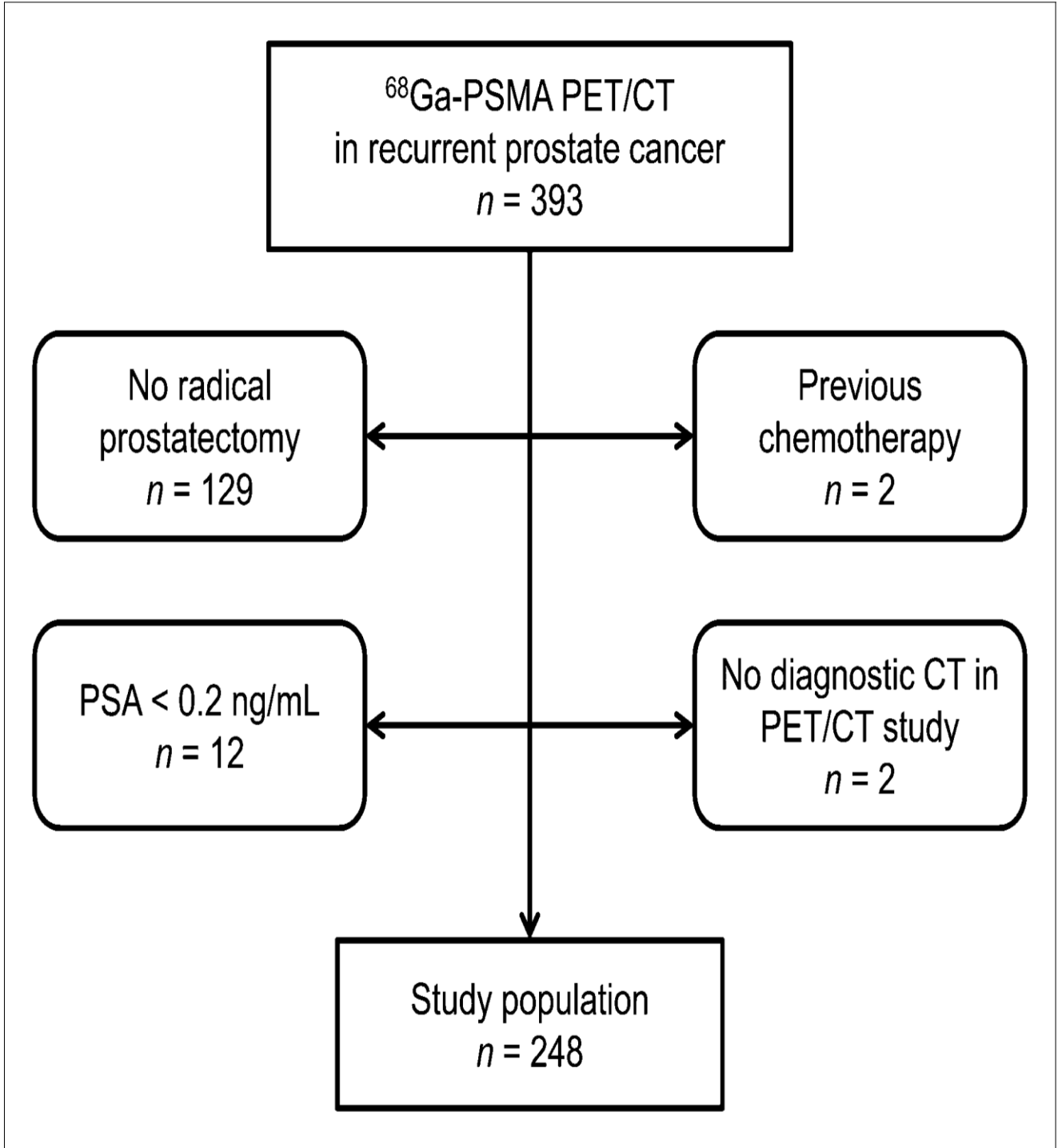
- Afshar-Oromieh et al. retrospectively investigated the diagnostic value of 68 Ga-HBED-PSMA-PET/CT in 319 patients with recurrent prostatic carcinoma
 - PET/CT at 1 h p.i. detected PCa in 83% of the patients (264 of 319 patients)
 - No false positive examinations



Afshar-Oromieh et al. EJNMMI 2015

F18 PSMA imaging-a viable option

Ga68 HBED PSMA imaging

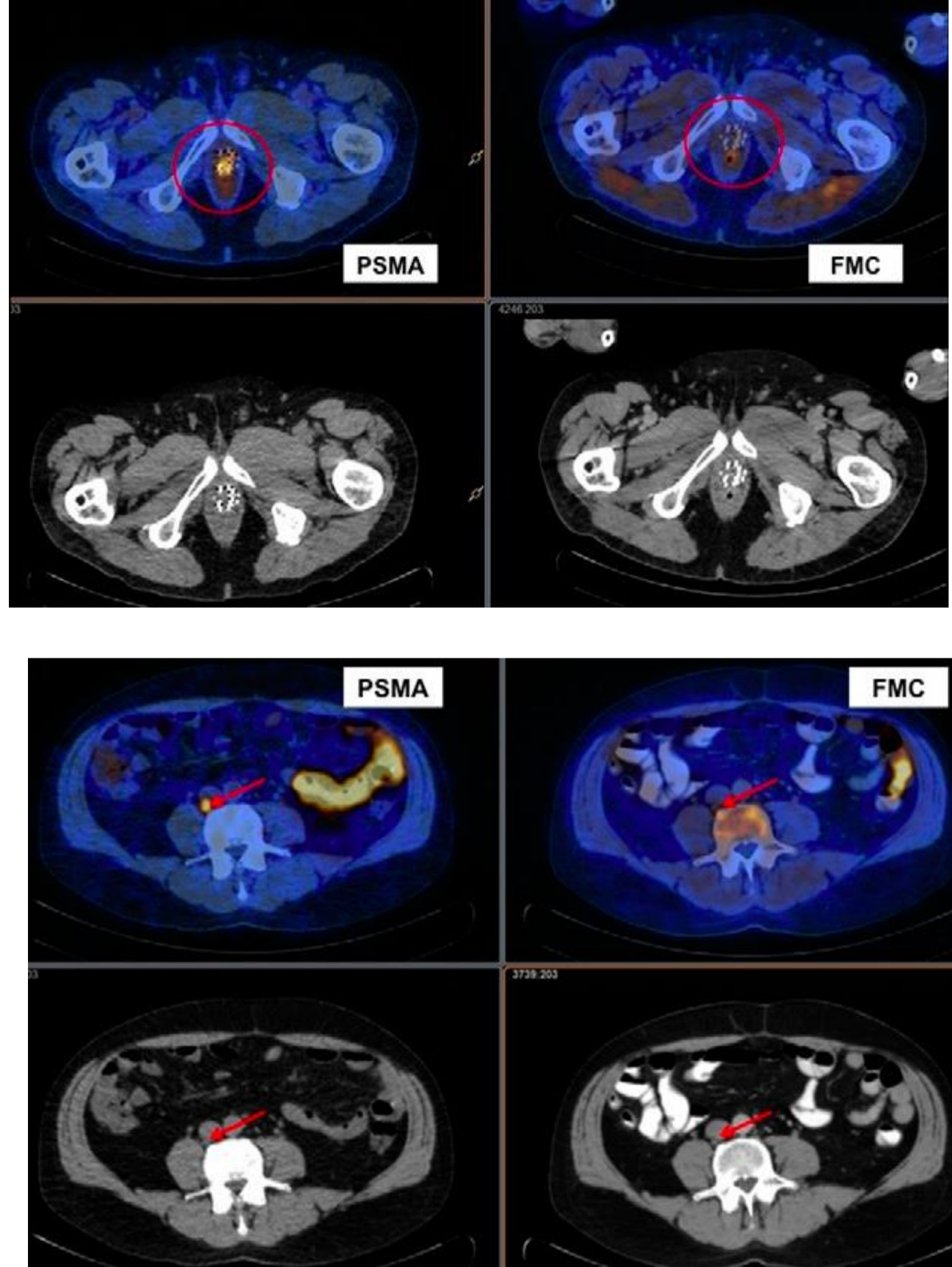
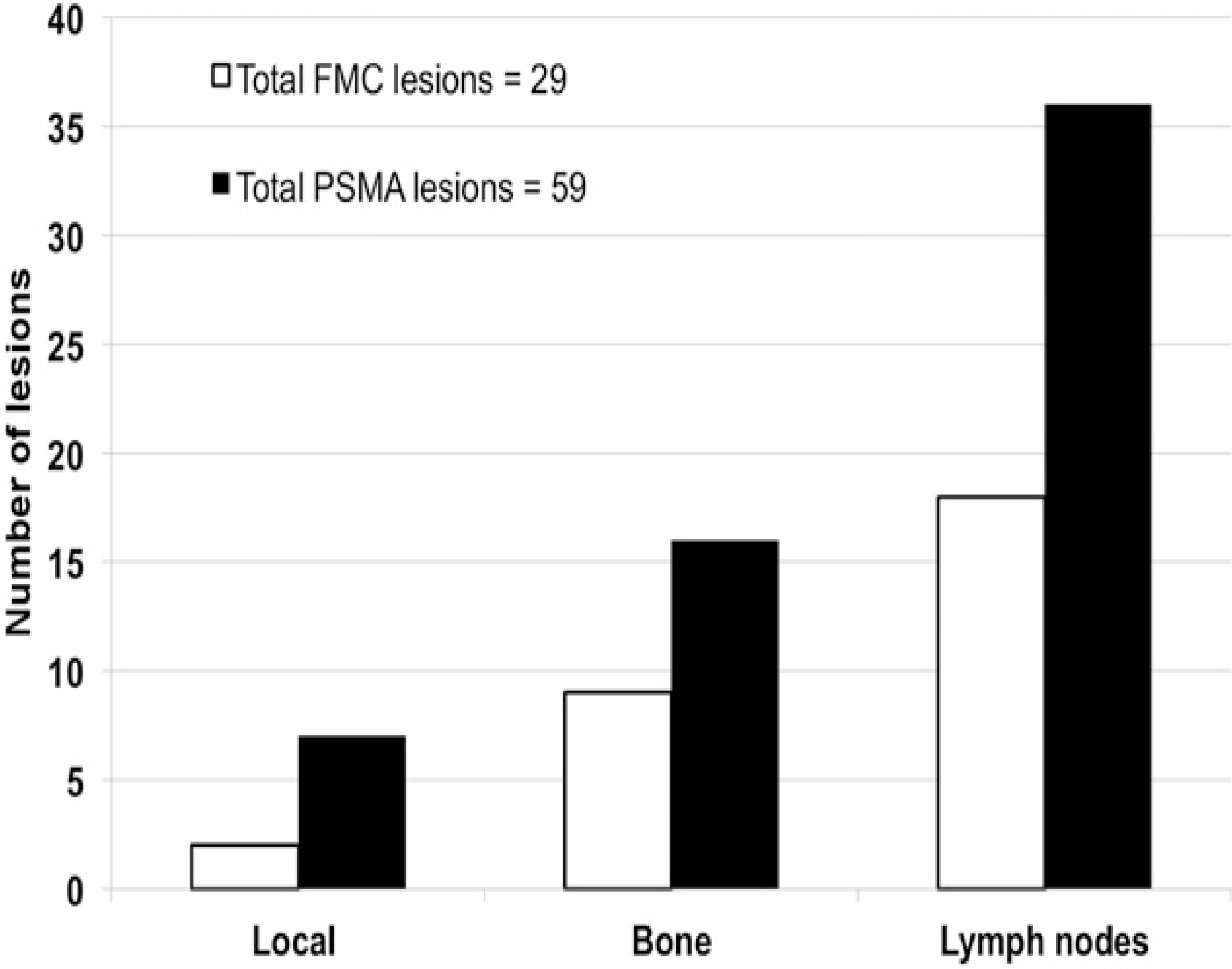


Eiber et al. JNM 2015



F18 PSMA imaging-a viable option

Ga68 HBED PSMA vs FCHOL imaging



Emmett et al. JNM 2016



F18 PSMA imaging-a viable option

Ga68 HBED PSMA vs FCHOL imaging

Sensitivity	PSA > 2ng/ml	PSA .5- 2ng/ml	PSA < .5ng/ml
PSMA	88%	71%	50%
FCHOL	63%	36%	12%

- Total management impact 24/38.
- Major management impact in 13/38 patients due to Ga68 PSMA alone
- No additional management impact due to accurate discordant FCHOL findings

F18 PSMA imaging-a viable option

Ga68 HBED PSMA imaging

- **Undoubtedly an excellent tracer for staging and restaging prostate cancer!**
- Guide for planning and monitoring PSMA based radionuclide therapy
- On-site on demand production from a Ge/Ga generator

Who could wish for more?



F18 PSMA imaging-a viable option

Ga68 HBED PSMA-some limitations?

- **Logistical**

- Staff resources for synthesis and quality control
- Variable generator synthesis yields
- Occasional generator failure
- Waste

- **Low injected activity**

- Limited image statistics/image noise

- **Short half-life**

- Late imaging difficult

- **Cost**

- staff
- Generator
- Kits
- Synthesis units
- Microbiology/endotoxin
- Compliant manufacturing environment

- **Quality/Regulatory Milieu**

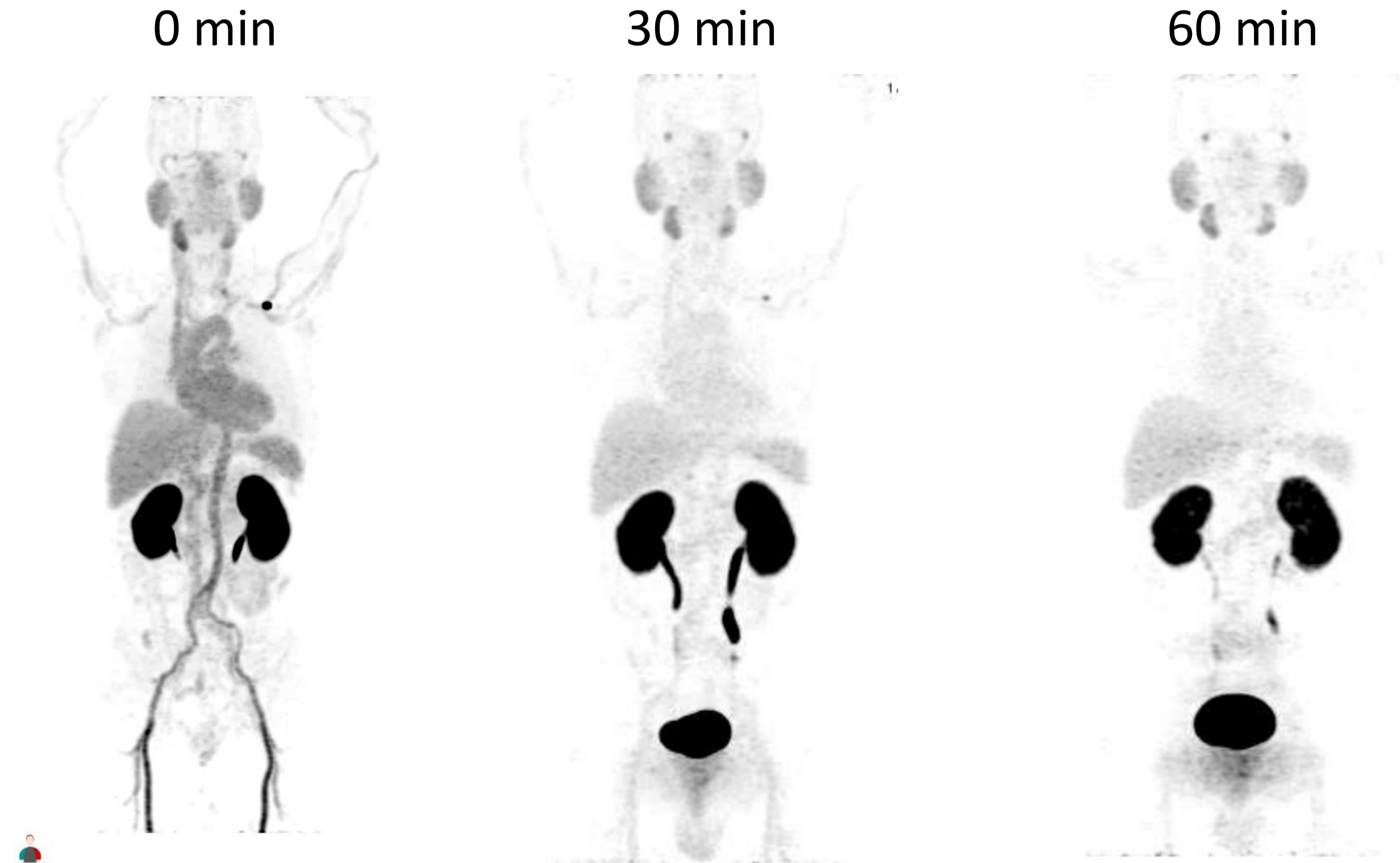
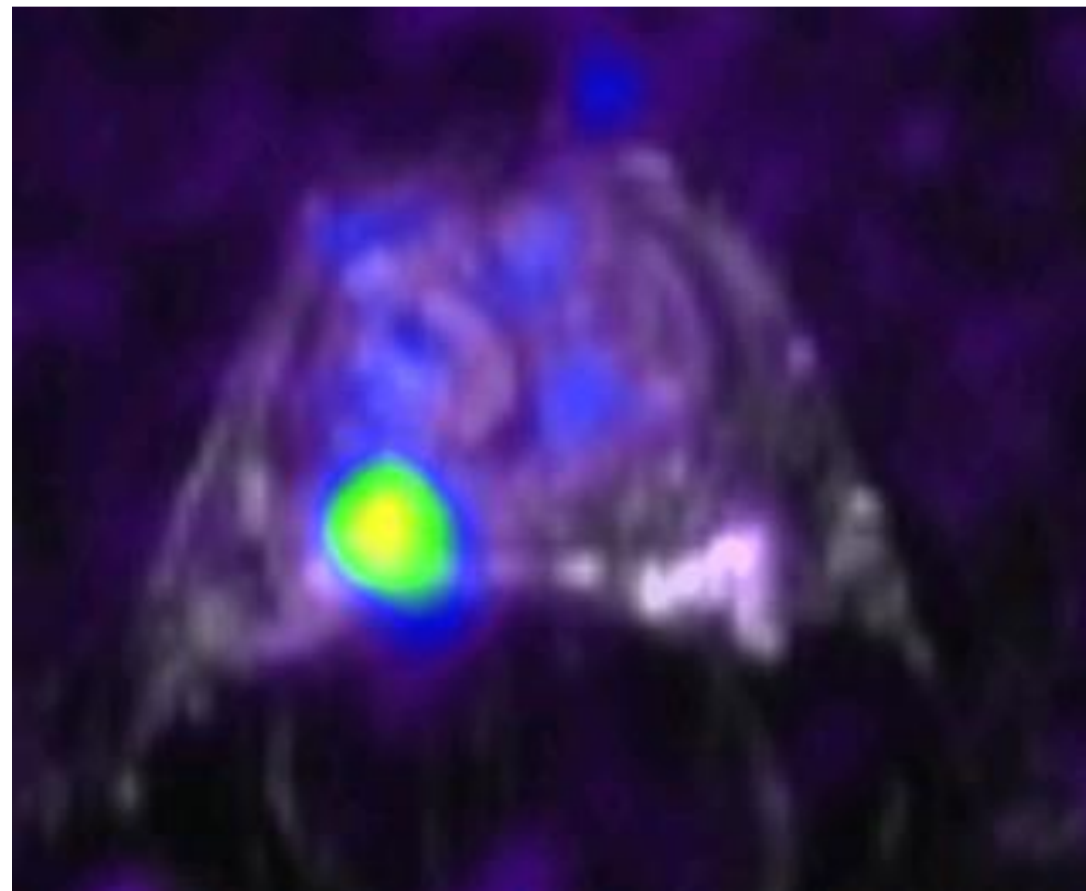
- Generators not ARTG registered
- Complex synthesis -who is qualified to perform?

F18 PSMA imaging-a viable option

Ga68 PSMA alternatives

- Simpler synthesis
- Kit based formulation
- Ga68-THP-PSMA
- Phase 0/1 Trial PMCC

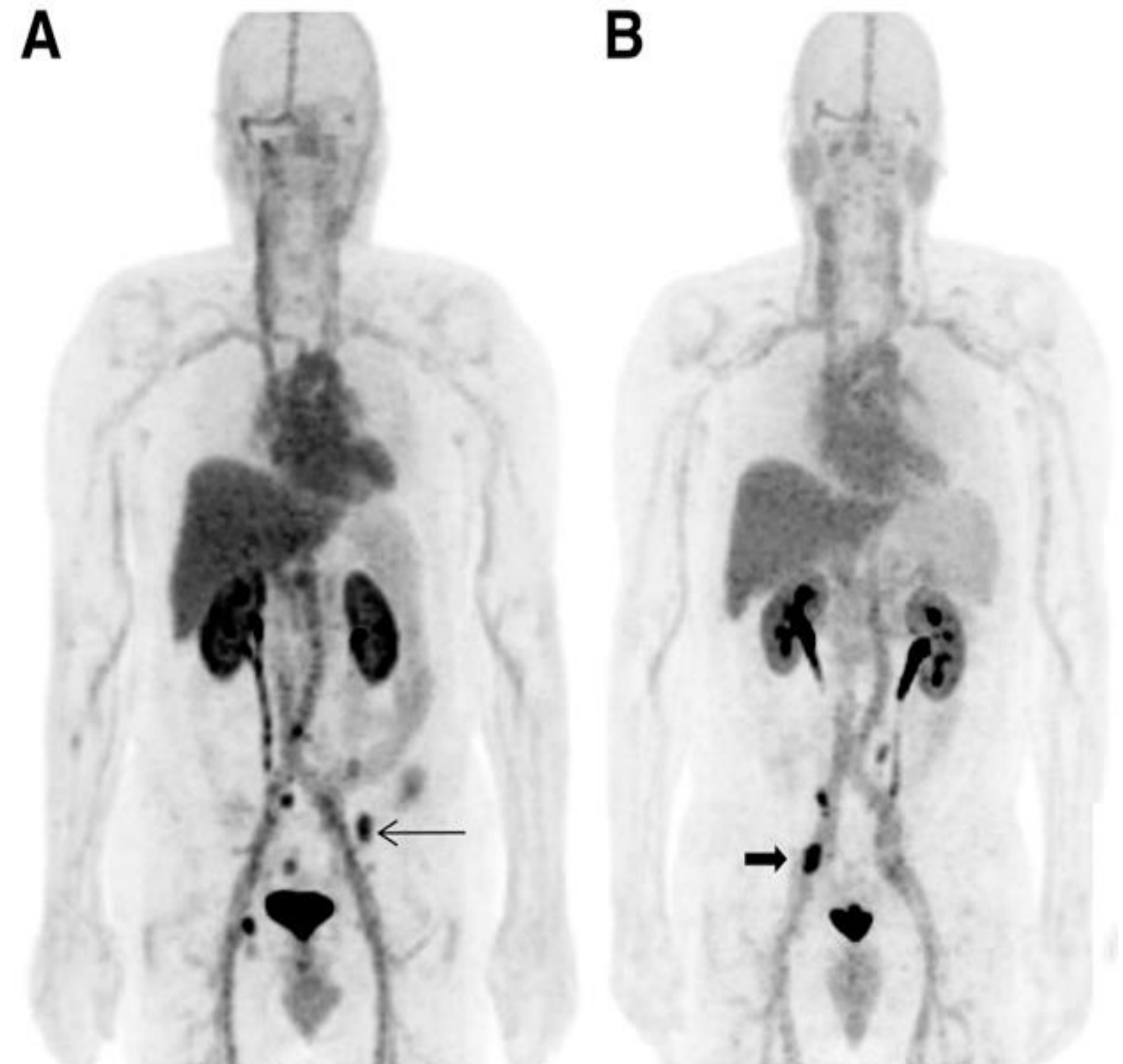
THE^RAGNOSTICS



F18 PSMA imaging-a viable option

F18 PSMA development- F18 DCFBC

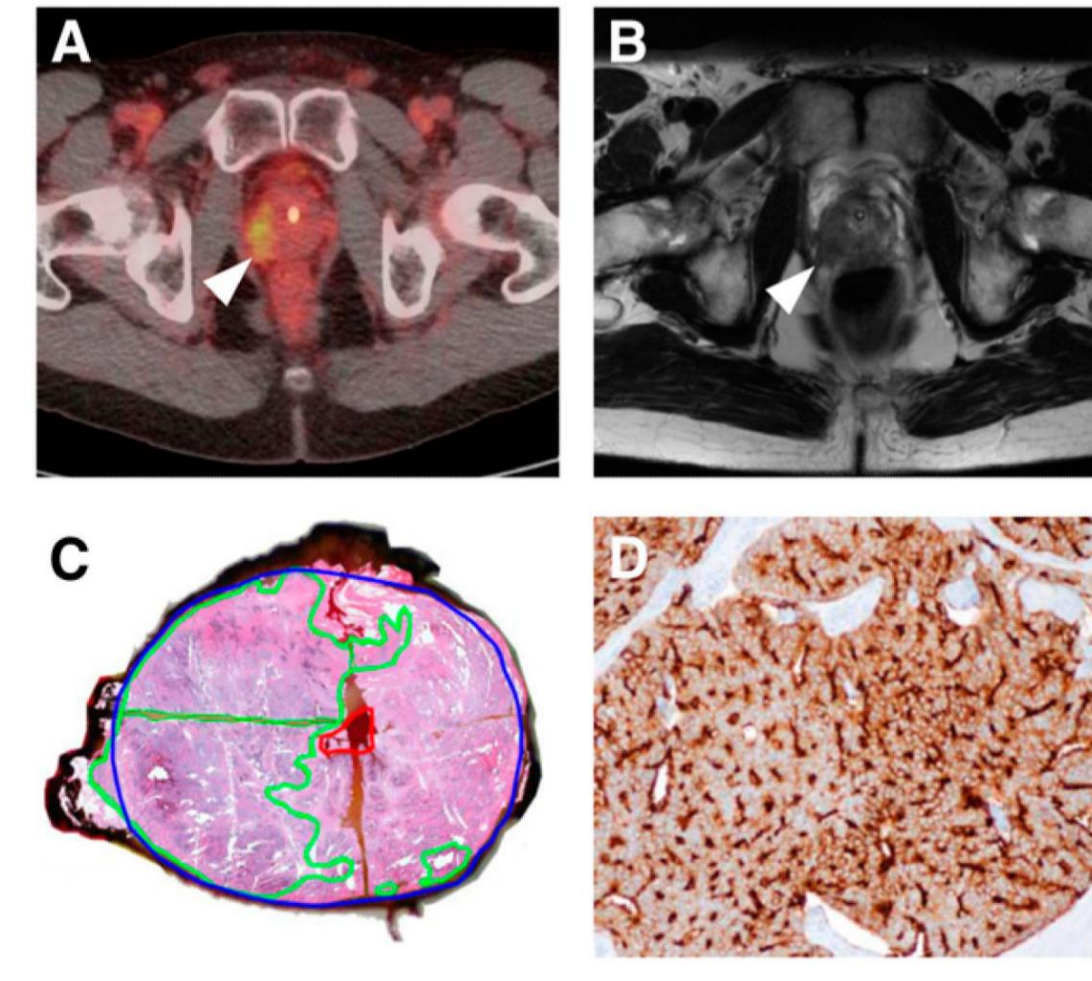
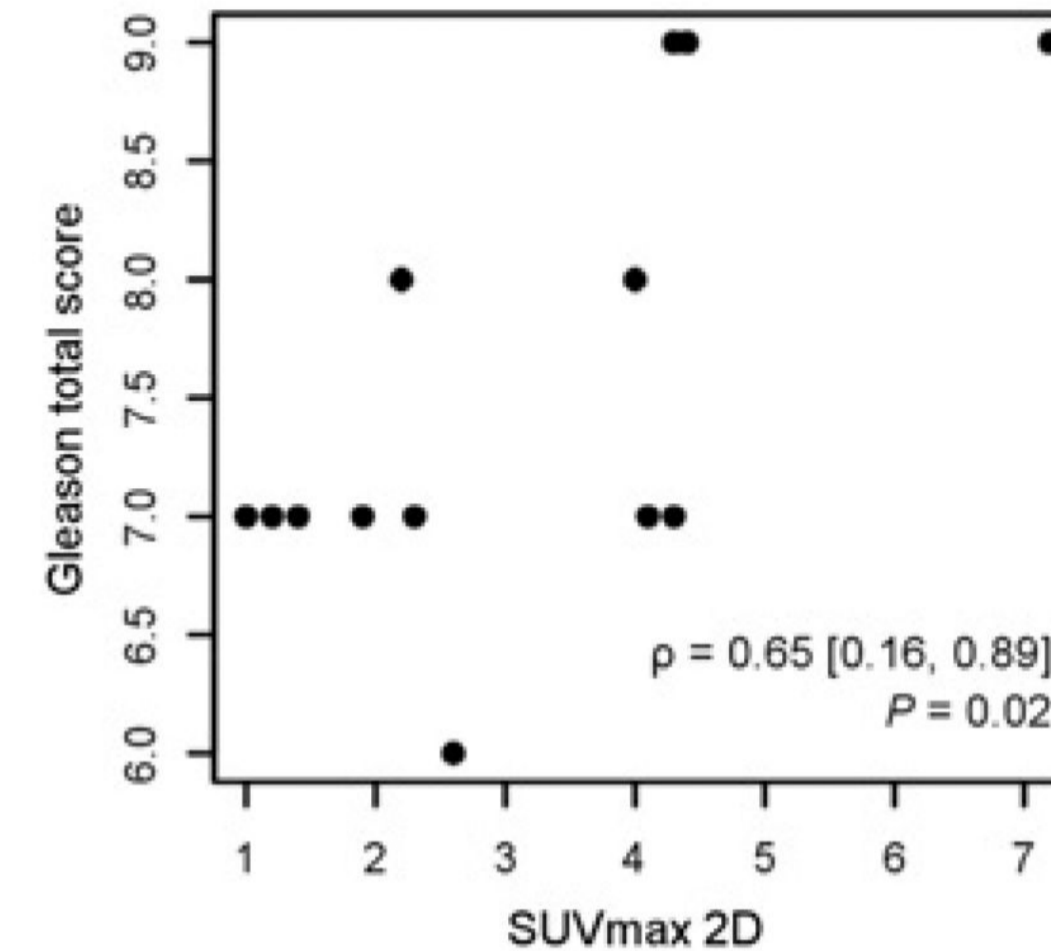
- 5 patients with prostate cancer studied (PSA 9-46)
 - No adverse effects
 - Radiation dose similar to FDG
 - Slow blood clearance
 - 21 known metastatic lesions visualised
 - 11 sites (bone>soft tissue) visualised, presumed metastases
 - Lesion contrast less than typically seen with Ga68HBED



F18 PSMA imaging-a viable option

F18 PSMA development- F18 DCFBC

- 13 patients with primary prostate cancer studied
- Compared PET/CT, MRI and surgical pathology on a dominant lesion basis
 - Sensitivity PET .46 vs MRI .92
 - All Gleason 8 and 9 score lesions >1cc volume detected by PET
 - Low contrast apparent

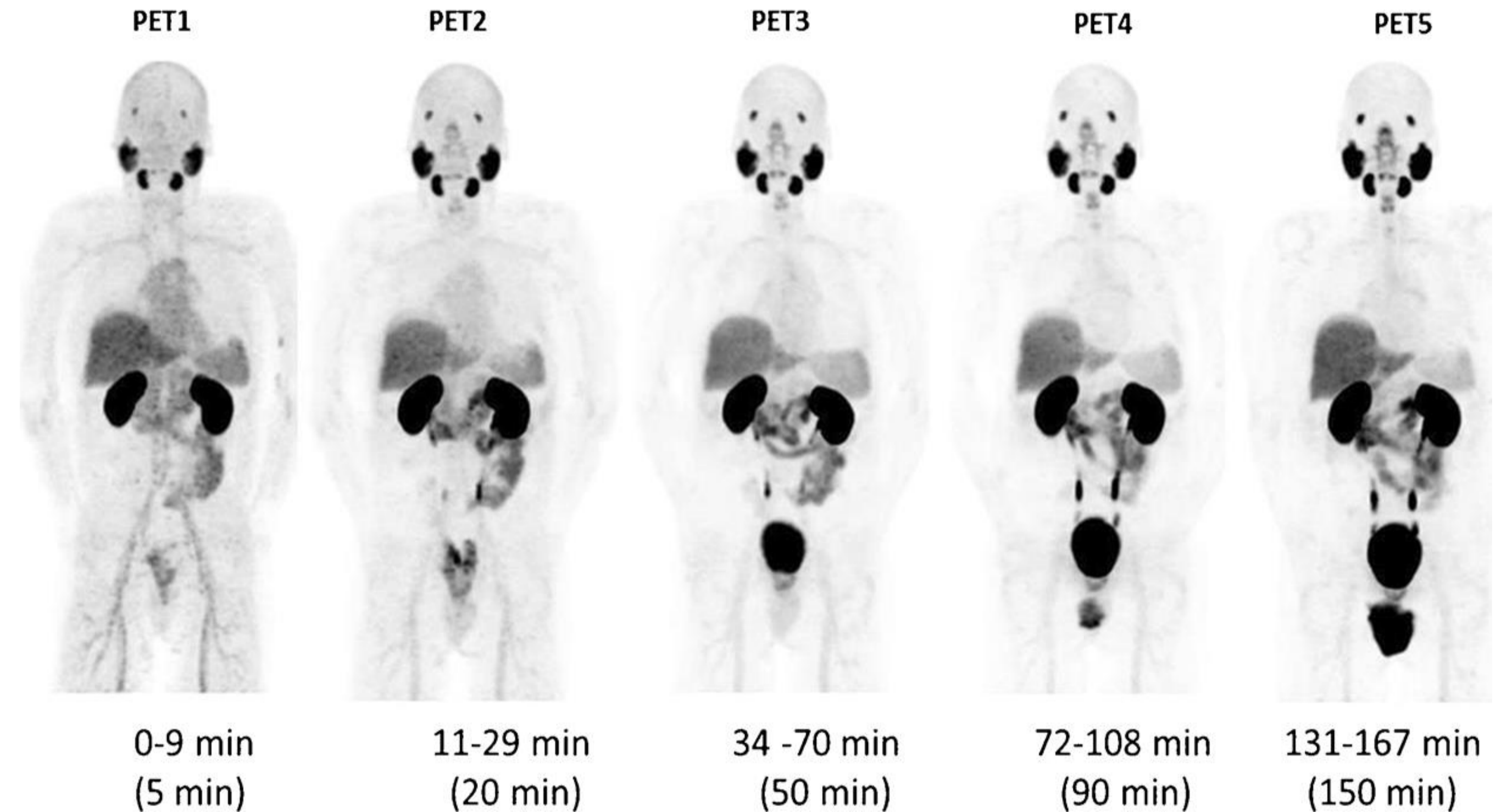


Cho et al. JNM 2015

F18 PSMA imaging-a viable option

F18 PSMA development- F18 DCFPyL

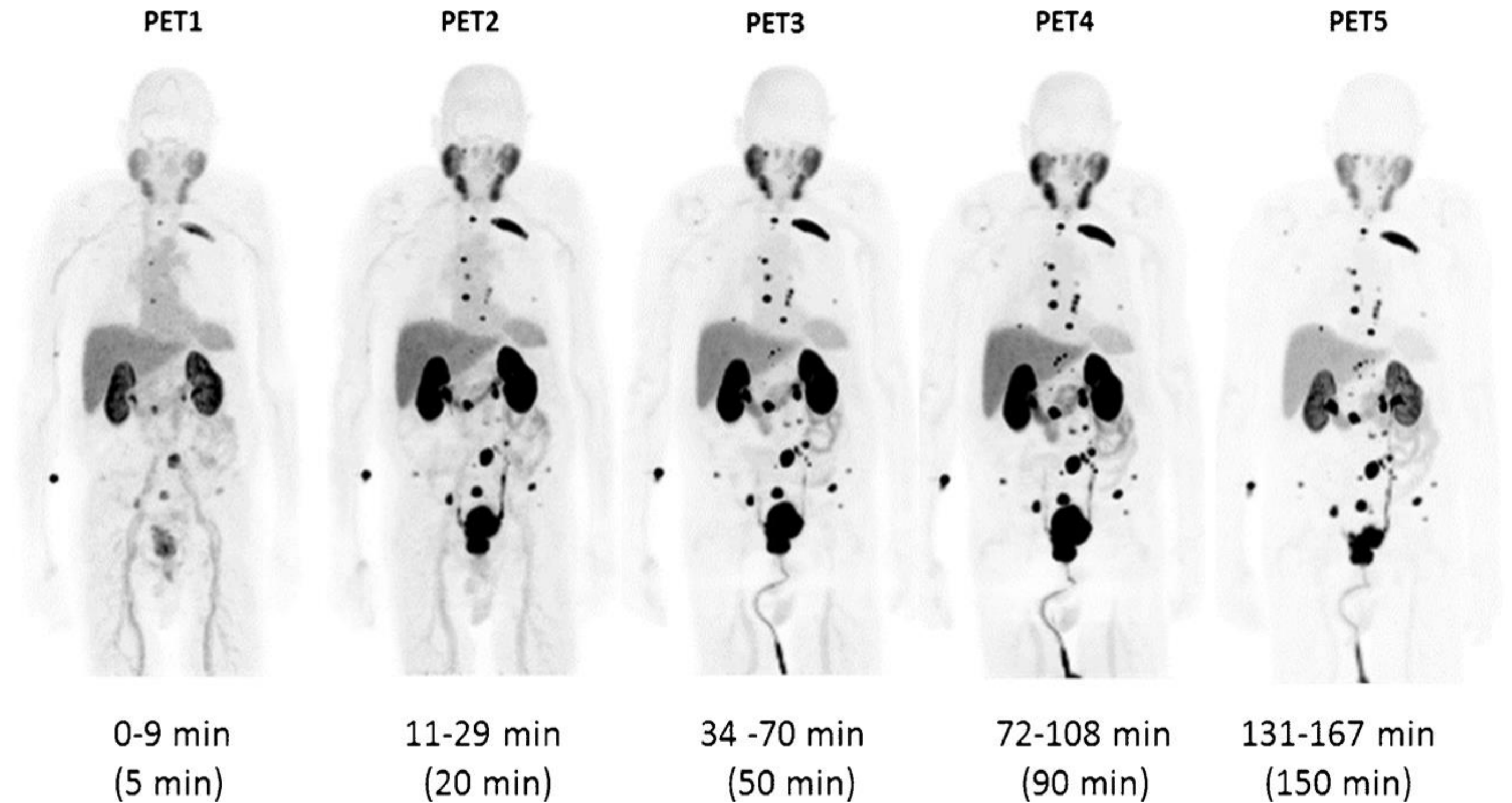
- Phase 0/1 Trial data
 - Safe
 - favorable biodistribution
 - favorable dosimetry



F18 PSMA imaging-a viable option

F18 PSMA development- F18 DCFPyL

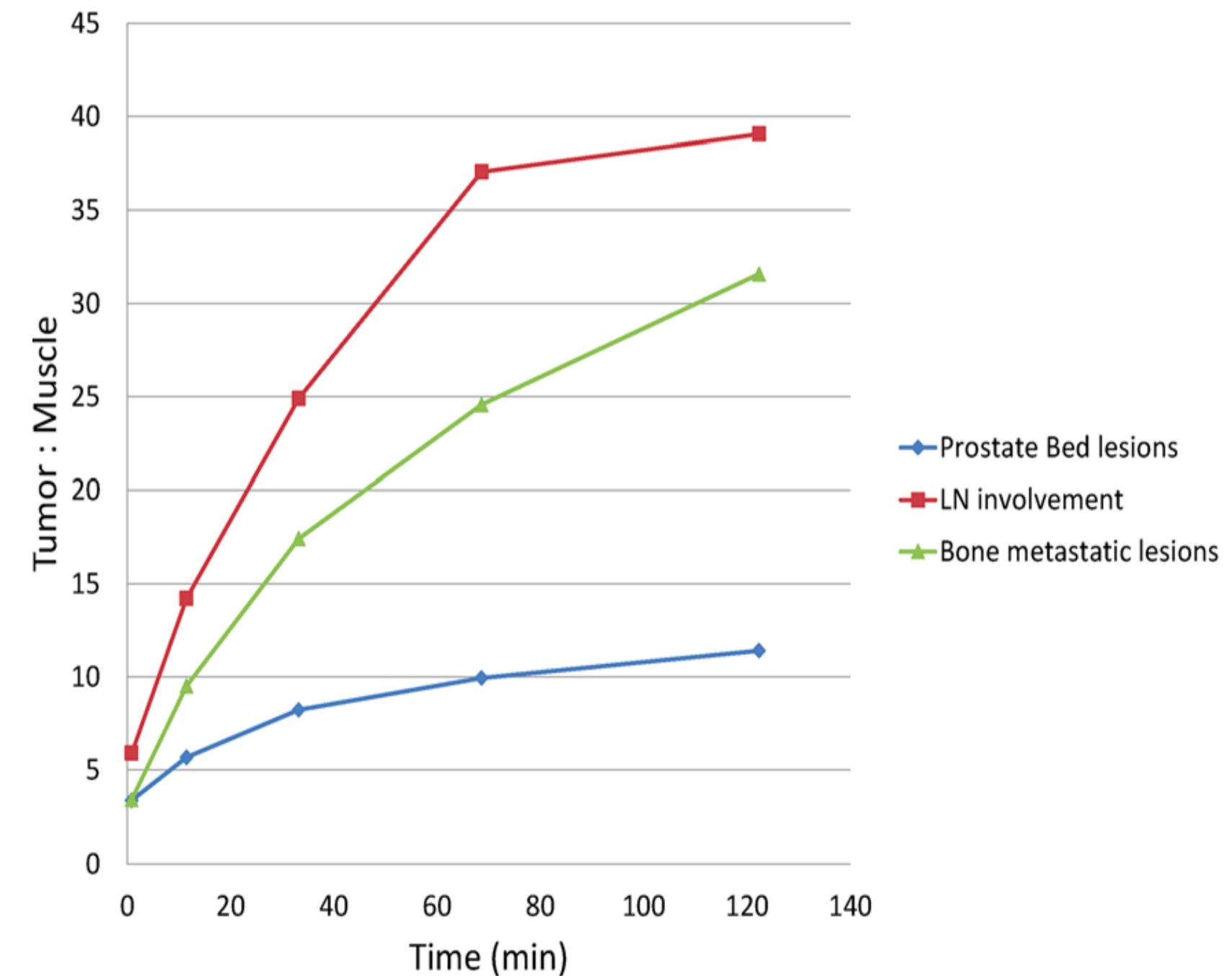
- Phase 0/1 Trial data
 - High uptake in prostate carcinoma lesions
 - More lesions apparent with time
 - Excellent image quality



F18 PSMA imaging-a viable option

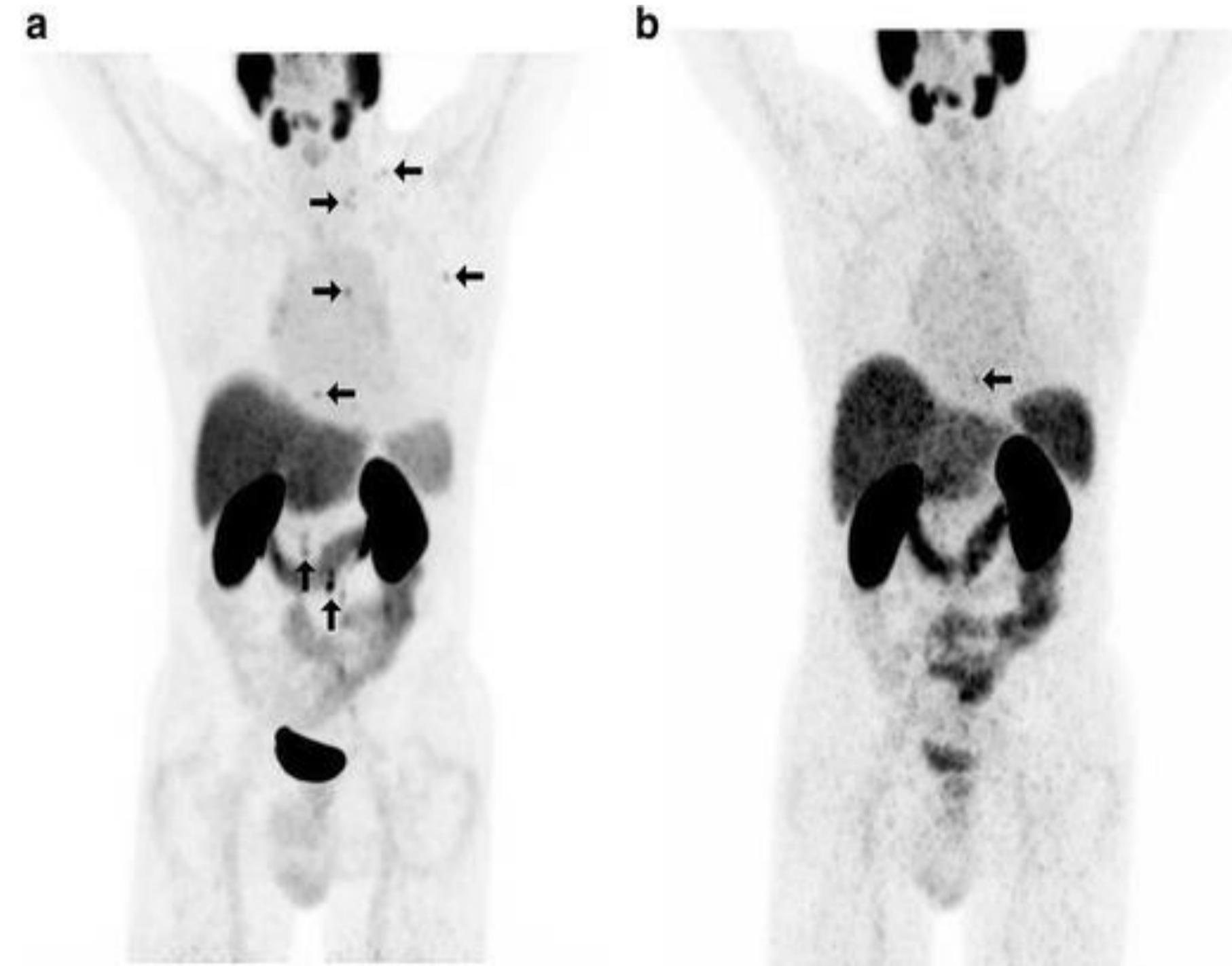
F18 PSMA development- F18 DCFPyL

- Phase 0/1 Trial data
 - Different time course of uptake in primary, node and bone metastases
 - Possibility of greater sensitivity at later time points than feasible with Ga68 PSMA



F18 PSMA imaging-a viable option F18 DCFPyL vs Ga68HBED PET/CT

- Direct comparison F18DCFPyL and Ga68HBED
 - 14 patients relapsed prostatic carcinoma (PSA .4-50 ng/ml)
 - Administered activity of F18 at least 1.5 x Ga68



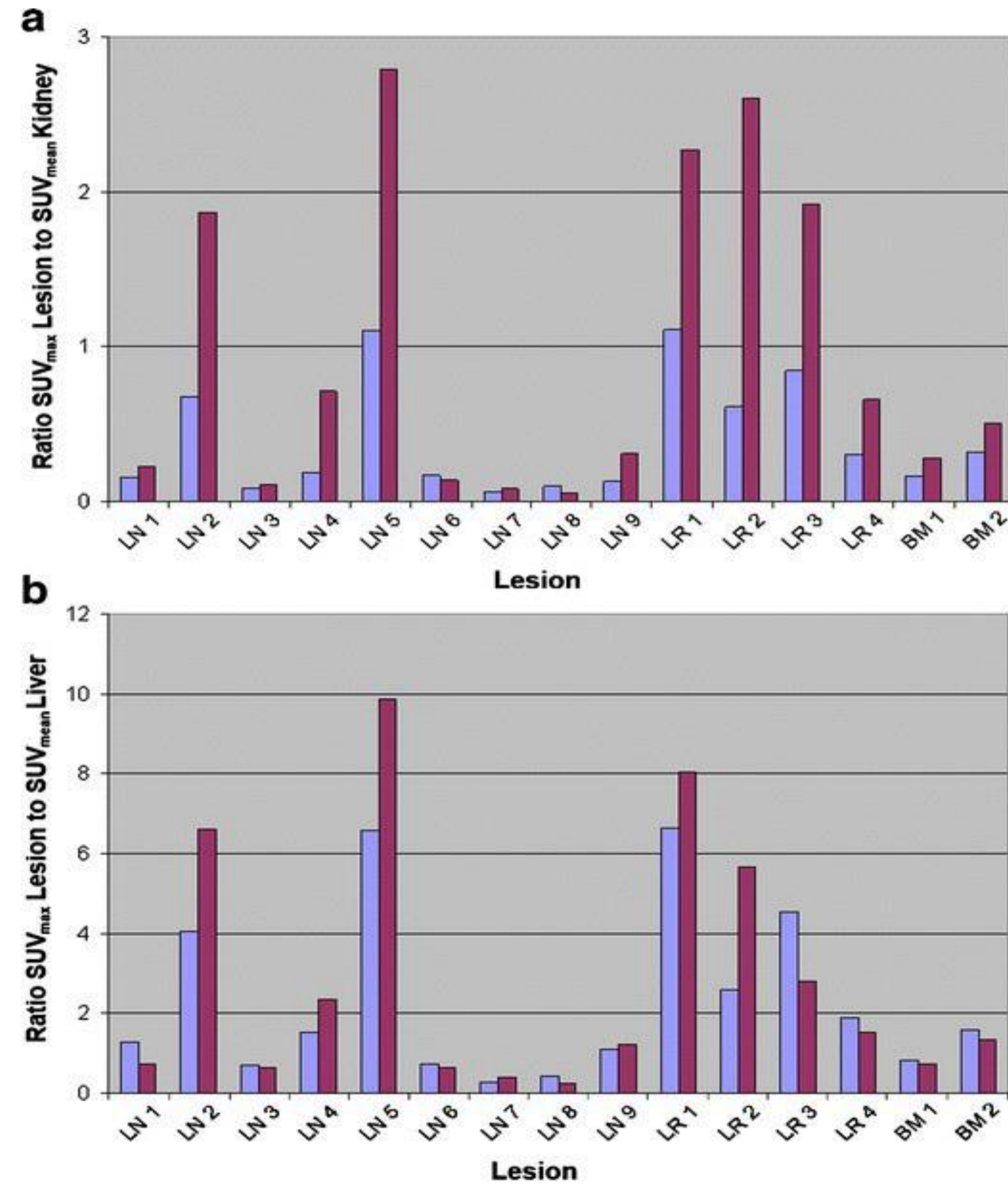
F18DCFPyL

Ga68HBED

F18 PSMA imaging-a viable option

F18 DCFPyL vs Ga68HBED PET/CT

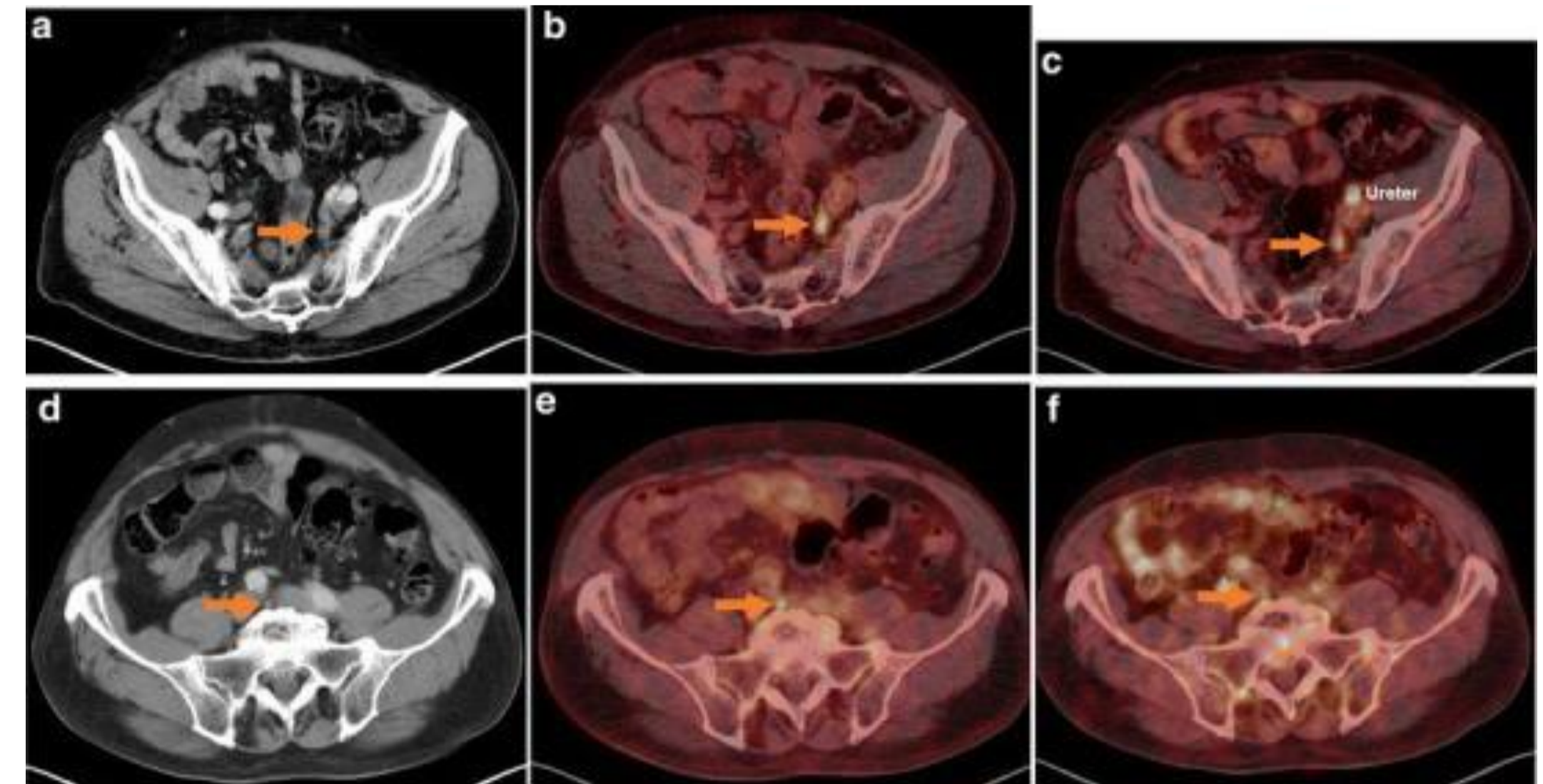
- SUV values higher for F18 DCFPyL
-14.5 vs 12.2, $p=.028$
- T/B F18 DCFPyL
 - Higher kidney, spleen, parotid
 - Same liver, mediastinum



F18 PSMA imaging-a viable option

F18 DCFPyL vs Ga68HBED PET/CT

- All Ga68HBED lesions visualised on F18DFFPyL
- 3 patients additional lesions F18DCFPyL had potential management indications



F18DCFPyL

Ga68HBED

F18 PSMA imaging-a viable option

F18 DCFPyL vs Ga68HBED PET/CT

- Both excellent tracers
- F18DCFPyL appears to provide
 - better image quality
 - Higher injected dose
 - Later imaging time
 - Less energetic positron emission
 - diagnostic performance appears non inferior

F18 DCFPyL synthesis

- High radiochemical purity (>95%)
- High specific activity (mean 72-158 GBq/micromole)
- Low yield (3–12 % non decay corrected)
- Complex two reactor synthesis
- Long synthesis of 90 minutes or more
- **Synthesis characteristics make commercial distribution problematic**

F18 PSMA imaging-a viable option

Recent improvements to F18 DCFPyL production

- Bouvet et al reported (SNM 2015) a simplified F18 DCFPyL synthesis
 - Radiochemical yield after HPLC of 27% decay corrected
 - 45 minute synthesis duration
 - Automated
- Similar results achieved at Johns Hopkins and by ABX
- Good basis for cost effective centralised production and distribution of F18PSMA ligand

F18 PSMA imaging-a viable option

CYCLOTEK development path

- Begin production validation for GMP compliance
- Do local non inferiority trial and Peter Mac
- Facilitate multi-centre trials to establish improved clinical and economic outcomes
- Make available for individual patient use in Australia and New Zealand

F18 PSMA imaging-a viable option

CONCLUSION

- PSMA imaging with PET/CT is a huge advance for diagnostic assessment of patients with primary and recurrent prostatic cancer
- F18 PSMA imaging appears viable with DCFPyL, a GuL small molecule inhibitor developed at John's Hopkins and which has been licensed to CYCLOTEK for clinical trial and clinical use in Australia and New Zealand
- Non inferior diagnostic performance to Ga68 HBED demonstrated
- Logistic improvements appear likely with development of improved and automated synthesis
- Cost efficiencies should be achievable
- GMP production will impact potential quality and regulatory issues associated with Ga68 HDEB, and may impact reimbursement potential



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The 4th Theranostics World Congress (4TWC)
November 7 – 9, 2016 |
<http://theranostics2016.org>