Evolving Impact of PSMA PET on Localized and Locally Advanced Prostate Cancer Management

Kirsten Greene, MD, MS
Professor and Chair
UVA Department of Urology

UVA Health
SCHOOL OF MEDICINE

Disclosures

- Intuitive surgical
- Johnson & Johnson

Continuous improvement in prostate cancer imaging modalities

FDG PET

Bone scan

MRI CT

NaF PET

choline PET

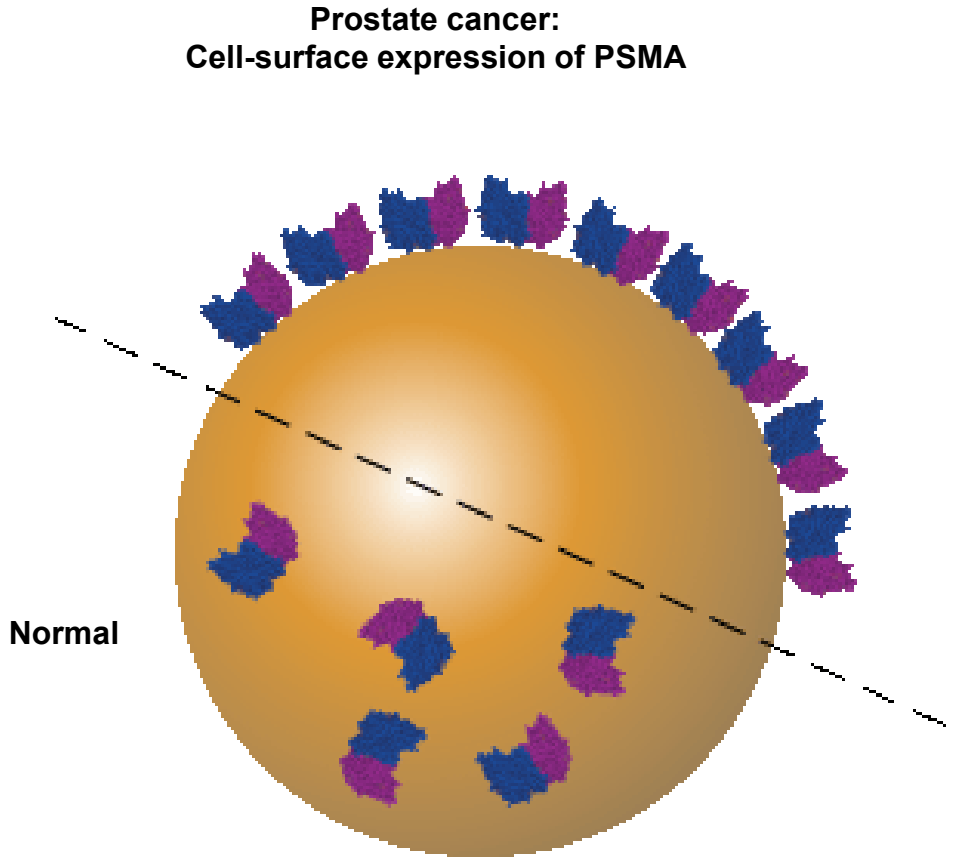
FACBC PET

PSMA PET

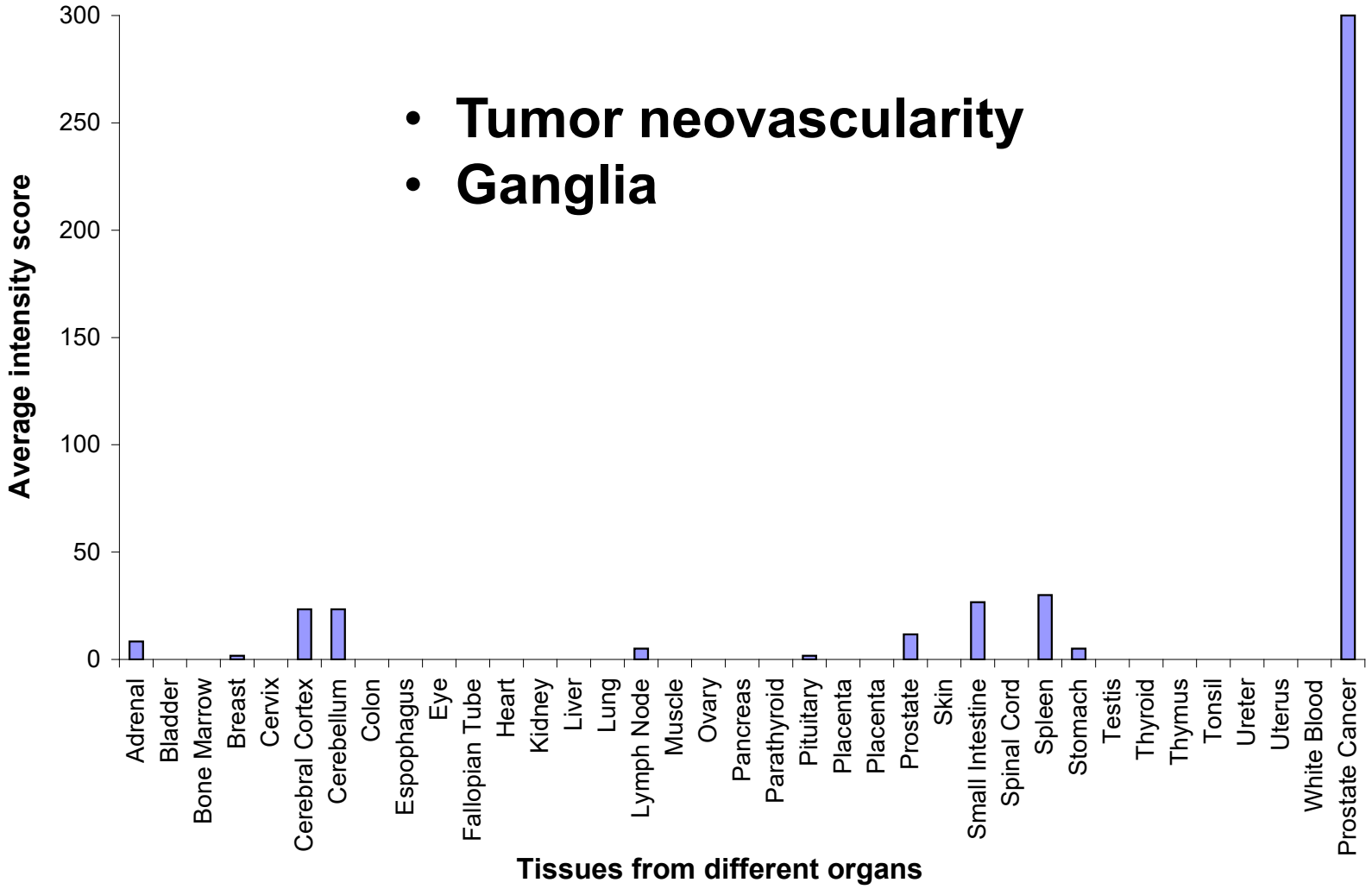
PSMA: Prostate Specific Membrane Antigen

PSMA has long been considered among the best oncology targets:

- PSMA is expressed in ~95% of prostate cancer
  - Similarly in primary and metastatic lesions
- Limited expression in normal tissues e.g., brain, intestines, parotid, salivary, lacrimal glands
- Targeting the extensive external domain of PSMA allows for efficient labeling with an imaging agent



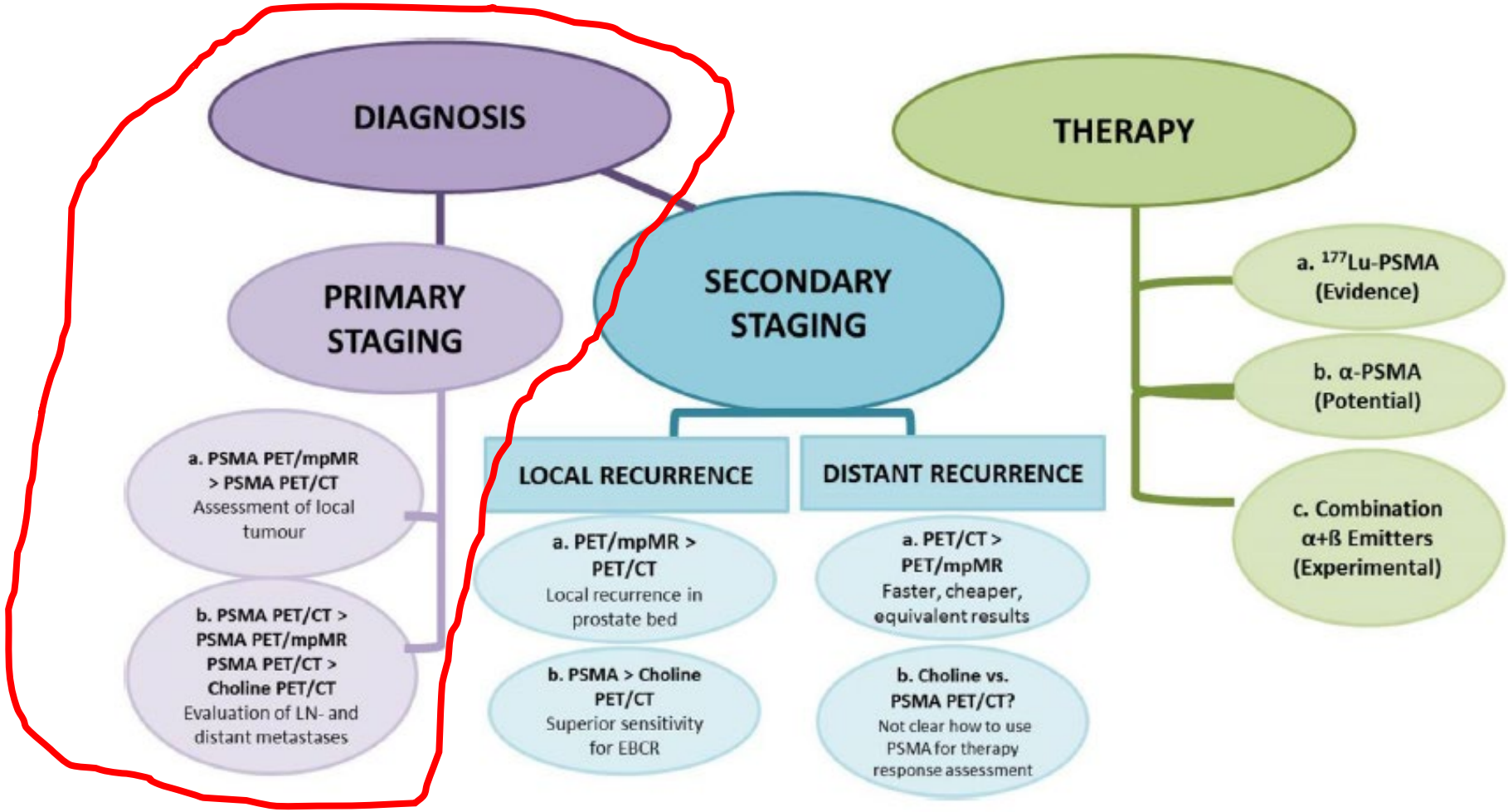
PSMA activity by organ: not just prostate



PSMA exceptions

- 5-10% do not express PSMA at all so are false negative
- Neuroendocrine prostate cancer loses PSMA expression
- After PSMA targeted treatment(lutetium) the tumor may lose PSMA expression

The role of PSMA imaging/therapy in prostate cancer



Virgolini I et al. Eur J Nucl Med Mol Imaging, 2018

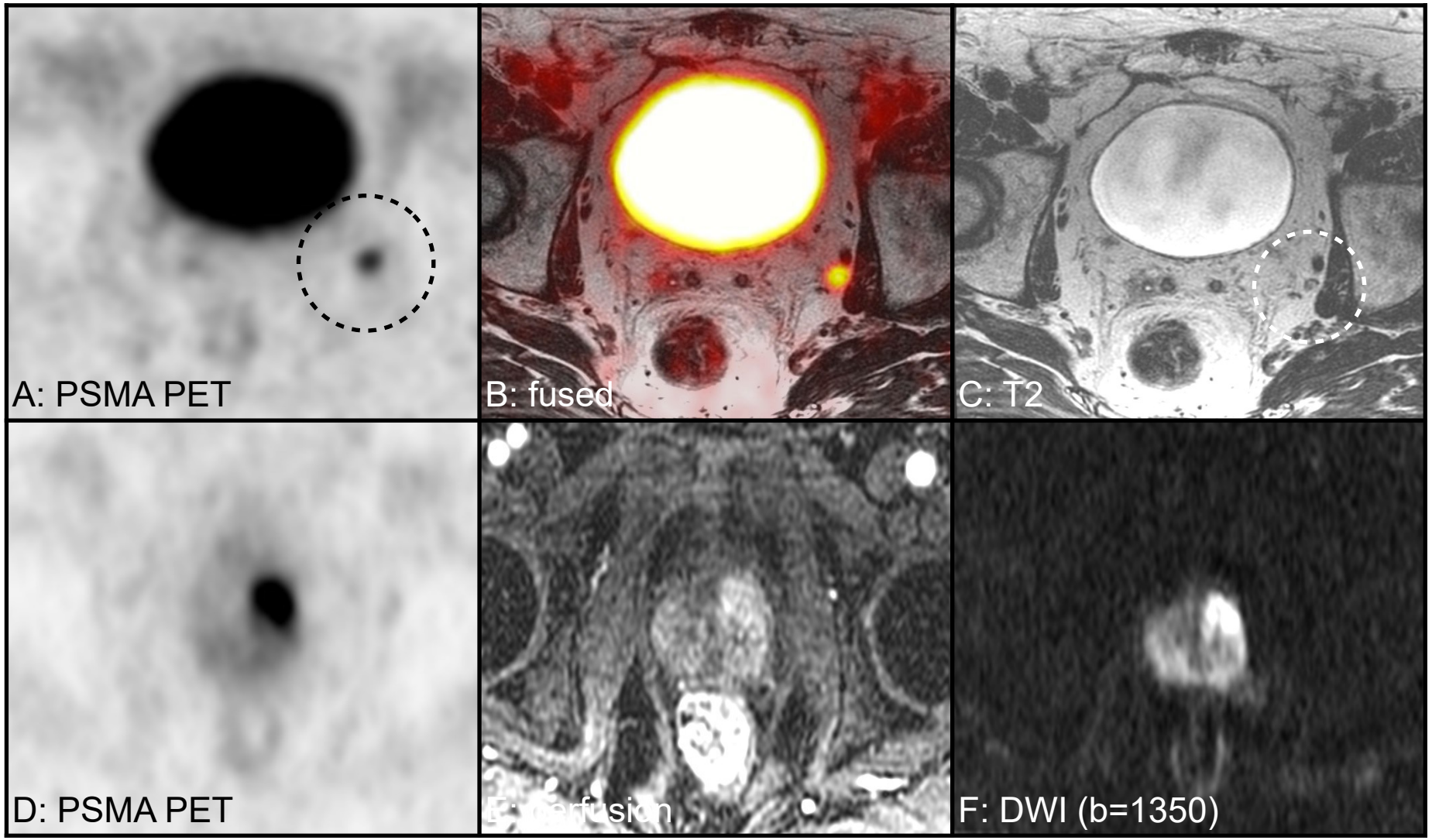


FIGURE 3: 69 year old man with Gleason 5+4 on biopsy, PSA of 18.5. PSMA PET demonstrated multiple left obturator and pelvic side wall nodes, which was confirmed at time of prostatectomy.

Current recommendations for imaging

- High risk: PSA>20ng/ml, suspected T3a or Grade group 4 or 5
- Sensitivity~30-40% for MRI and CT
- Based on shape and size of nodes

AUA Prostate Cancer Risk categories

Table 3: Risk Group Classification for Clinically Localized Prostate Cancer

Low-Risk	PSA <10 ng/mL AND Grade Group 1 AND clinical stage T1-T2a
Intermediate-Risk	PSA 10-<20 ng/mL OR Grade Group 2-3 OR clinical stage T2b-c
	• Favorable: Grade Group 1 with PSA 10-<20 ng/mL or clinical stage T2b-c and <50%* biopsy cores positive OR Grade Group 2 with PSA<10 ng/mL and clinical stage T1-2a and <50% biopsy cores positive
	• Unfavorable: Grade Group 1 with PSA 10-<20 ng/mL and clinical stage T2b-c OR Grade Group 2 with PSA 10-<20 ng/mL and/or clinical stage T2b-c and/or ≥50%* biopsy cores positive OR Grade Group 3 with PSA <20 ng/mL
High-Risk	PSA >20 ng/mL OR Grade Group 4-5 OR clinical stage T3

AUA Prostate cancer guidelines

Staging

5. Clinicians should not routinely perform abdomino-pelvic computed tomography (CT) scan or bone scan in asymptomatic patients with low- or intermediate-risk prostate cancer. (Expert Opinion)

6. Clinicians should obtain a bone scan and either pelvic multi-parametric magnetic resonance imaging (mpMRI) or CT scan for patients with high-risk prostate cancer. (Strong Recommendation; Evidence Level: Grade B)

7. In patients with prostate cancer at high risk for metastatic disease with negative conventional imaging, clinicians may obtain molecular imaging to evaluate for metastases. (Expert Opinion)

PSMA PET for Prostate Cancer: NCCN

For symptomatic patients and/or those with a life expectancy of greater than 5 years, bone and soft tissue imaging is appropriate for patients with unfavorable intermediate-risk, high-risk, and very-high-risk prostate cancer:

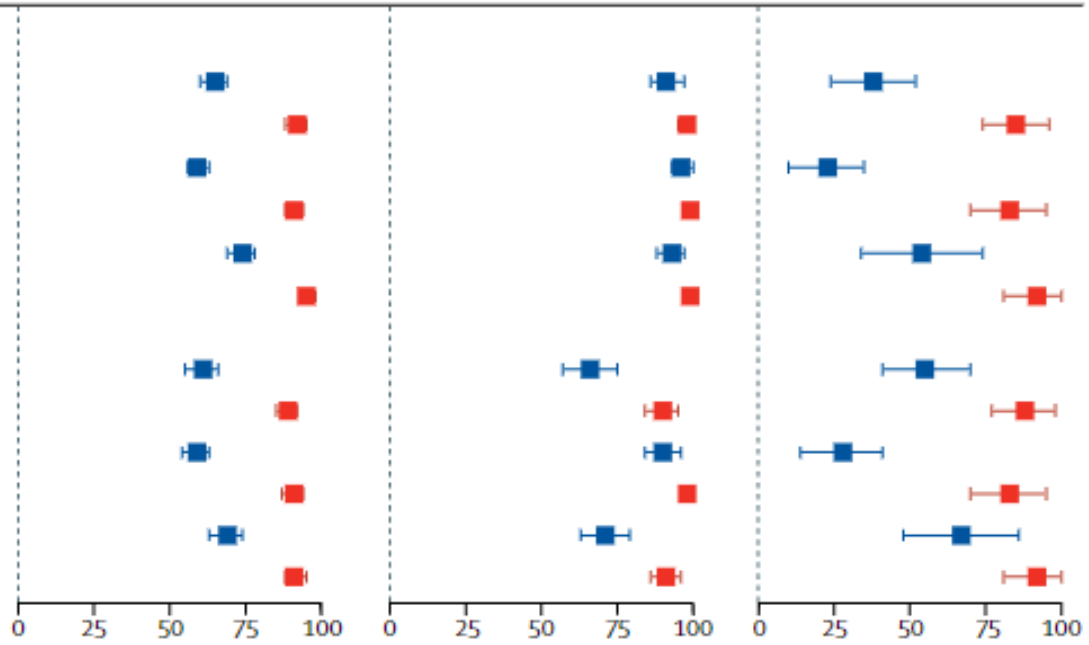
- **Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.**

Prospective randomized multicenter trial

Bone scan/CT vs PSMA PET

PSMA PET for Prostate Cancer

	N	Positive True/False	Negative True/False
Primary analysis			
Any metastatic disease	150	18/9	94/29
	145	34/2	103/6
Pelvic nodal	150	9/4	106/31
	145	29/1	109/6
Distant metasases	150	13/9	117/11
	145	22/1	120/2
Sensitivity analysis: equivocal lesions treated as positive			
Any metastatic disease	150	26/35	68/21
	145	35/11	94/5
Pelvic nodal	150	11/11	99/29
	145	29/2	108/6
Distant metasases	150	16/37	89/8
	145	22/11	110/2



Interpretation PSMA PET-CT is a suitable replacement for conventional imaging, providing superior accuracy, to the combined findings of CT and bone scanning.

Hofman MS et al, Lancet 2020

PSMA PET for Prostate Cancer

- **Histologic or radiographic confirmation of involvement detected by PET imaging is recommended whenever feasible due to the presence of false positives. Although false positives exist, literature suggests that these are outweighed by the increase in true positives detected by PET relative to conventional imaging. To reduce the false-positive rate, physicians should consider the intensity of PSMA-PET uptake and correlative CT findings in the interpretation of scans. Several reporting sytems have been proposed but will not have been validated or widely used.**

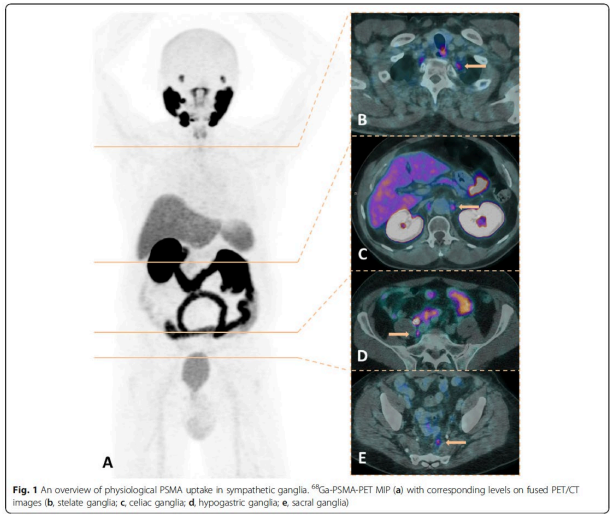


Fig. 1 An overview of physiological PSMA uptake in sympathetic ganglia. ^{68}Ga-PSMA-PET MIP (**a**) with corresponding levels on fused PET/CT images (**b**, stelate ganglia; **c**, celiac ganglia; **d**, hypogastric ganglia; **e**, sacral ganglia)

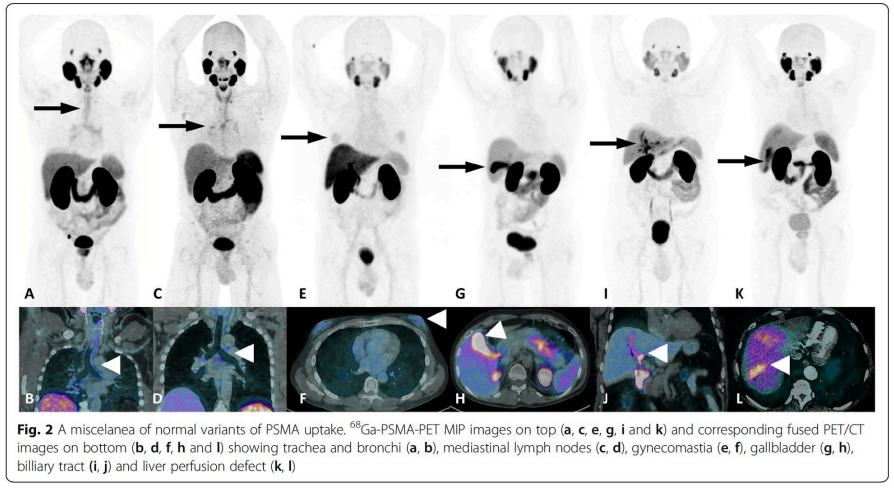


Fig. 2 A miscelanea of normal variants of PSMA uptake. ^{68}Ga-PSMA-PET MIP images on top (**a**, **c**, **e**, **g**, **i** and **k**) and corresponding fused PET/CT images on bottom (**b**, **d**, **f**, **h** and **l**) showing trachea and bronchi (**a**, **b**), mediastinal lymph nodes (**c**, **d**), gynecomastia (**e**, **f**), gallbladder (**g**, **h**), billiary tract (**i**, **j**) and liver perfusion defect (**k**, **l**)

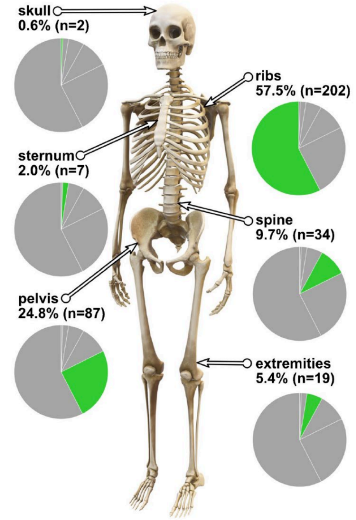


Fig. 3 Percentage and number of the three most active UBUs by anatomic region in [^{18}F]-PSMA-1007-PET

NCCN Guidelines
Version 1.2023

Negative PSMA PET and LND (what to do?)

Original Investigation

FREE

September 16, 2021

Diagnostic Accuracy of ^{68}Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection

A Multicenter Prospective Phase 3 Imaging Trial

Thomas A. Hope, MD[1,2,3]; Matthias Eiber, MD[4,5]; Wesley R. Armstrong[4]; et al

» Author Affiliations | Article Information

JAMA Oncol. 2021;7(11):1635-1642. doi:10.1001/jamaoncol.2021.3771

- **Performance characteristics of 277 men who underwent Ga-PSMA-11 PET prior to radical prostatectomy to assess staging accuracy.**

Hope TA et al, JAMA Oncology 2021

Negative PSMA PET and LND

Table 2. ^{68}Ga-PSMA-11 Test Characteristics for the Composite 3 Blinded Reads and Overall Majority Rule Read

Test characteristic	Read 1	Read 2	Read 3	Majority read
True positive	30	33	29	30
False positive	13	16	15	10
True negative	189	186	187	192
False negative	45	42	46	45
Sensitivity[a]	0.40 (0.30-0.51)	0.44 (0.33-0.55)	0.39 (0.28-0.50)	0.40 (0.30-0.51)
Specificity[a]	0.94 (0.89-0.96)	0.92 (0.88-0.95)	0.93 (0.88-0.95)	0.95 (0.91-0.97)
PPV[a]	0.70 (0.55-0.81)	0.67 (0.53-0.79)	0.66 (0.51-0.78)	0.75 (0.60-0.86)
NPV[a]	0.81 (0.75-0.85)	0.82 (0.76-0.86)	0.80 (0.75-0.85)	0.81 (0.76-0.85)

Meaning In men with intermediate- to high-risk prostate cancer, ^{68}Ga-PSMA-11 PET imaging may miss small pelvic nodal metastases, and therefore a PSMA PET scan negative for pelvic nodal metastasis does not indicate that a pelvic nodal dissection is not required; these data were the foundation of a New Drug Application for ^{68}Ga-PSMA-11.

Hope TA et al, JAMA Oncology 2021

The point? Don’t omit LND just because the PSMA is negative.

PSMA and ADT

- PSMA expression decreases rapidly with initial androgen suppression
- Order PSMA BEFORE starting ADT, not after
- In hormone resistant disease, enzalutamide may INCREASE PSMA expression
- Useful in mCRPC

What happens when PSMA PET finds mets that conventional imaging misses?

- Should we still operate?
- Is radiation better?

Recommendation	Strength rating
Any risk group staging	
Treatment should not be changed based on PSMA PET/CT findings, in view of current available data.	Strong

This is mHSPC

- Assess low vs high volume disease
- Complete staging->ideally PSMA PET
- High volume disease ≥ 4 bone mets with at least one outside of the spine/pelvis and/or visceral metastasis
- Offer genetic (germline) testing and genetic counseling

AUA guidelines for treatment

Treatment

14. Clinicians should offer ADT with either LHRH agonists or antagonists or surgical castration in patients with mHSPC. *(Strong Recommendation; Evidence Level: Grade B)*

15. In patients with mHSPC, clinicians should offer ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel). *(Strong Recommendation; Evidence Level: Grade A)*

16. In selected patients with de novo mHSPC, clinicians should offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide. *(Strong Recommendation; Evidence Level: [Abiraterone] Grade A/[Darolutamide] Grade B)*

AUA guidelines for treatment

17. In selected mHSPC patients with low-volume metastatic disease, clinicians may offer primary radiotherapy to the prostate in combination with ADT. *(Conditional Recommendation; Evidence Level: Grade C)*

18. Clinicians should not offer first generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with LHRH agonists in patients with mHSPC, except to block testosterone flare. *(Strong Recommendation; Evidence Level: Grade A)*

19. Clinicians should not offer oral androgen pathway directed therapy (e.g., abiraterone acetate plus prednisone, apalutamide, bicalutamide, darolutomide, enzalutamide, flutamide, nilutamide) without ADT for patients with mHSPC. *(Expert Opinion)*

Out of template node prior to surgery

60yo man Gleason 4+3 PSA 10, bone scan and CT negative
PMH significant for depression requiring ECT, hesitant to accept ADT

Pathology:

Gleason 4+3, pT3bN1

½ PSMA nodes positive

2/9 right pelvic nodes positive

0/8 left pelvic nodes positive

- Patient declining adjuvant radiation and ADT due to history of severe depression requiring ECT.
- Radiation without ADT not an option given to the patient

PSA 7/20/16 0.01
PSA 10/26/16 0.01

Is there a role for surgery in this case?

- In 2016, yes
- Radiation without ADT was not an option offered

- 2018 STAMPEDE trial
  - Survival advantage to radiation and ADT

- 2022 PEACE-1
  - Survival advantane to radiation, ADT, docetaxel and abiraterone/prednisone

What do guidelines say?

- **N** ... ate data to ... fa...

REGIONAL RISK GROUP (ANY T, N1, M0)

EXPECTED PATIENT SURVIVAL[l]	INITIAL THERAPY	ADJUVANT THERAPY

EBRT[p] + ADT[u] + abiraterone[ee,ii] (preferred)

jj There is limited evidence that RP + PLND is beneficial in the setting of node-positive disease. Use of this approach should be limited to patients with >10-year life expectancy and resectable disease and should be used in the context of a clinical trial or planned multimodality approach.

RP[q] + PLND in select patients[jj]

→ Monitoring, with consideration of early RT for a detectable and rising PSA or PSA >0.1 ng/mL (See PROS-9)

→ No adverse features or lymph node metastases

→ Lymph node metastases:[bb]
ADT[u,cc] (category 1) ± EBRT[p] (category 2B)
or
Monitoring, with consideration of early treatment for a detectable and rising PSA or PSA >0.1 ng/mL (See PROS-9)

Observation[r]

What do guidelines say?

- **AUA guidelines:** pelvic lymph node dissection provides staging information but does not consistently improve metastasis free, cancer specific or overall survival

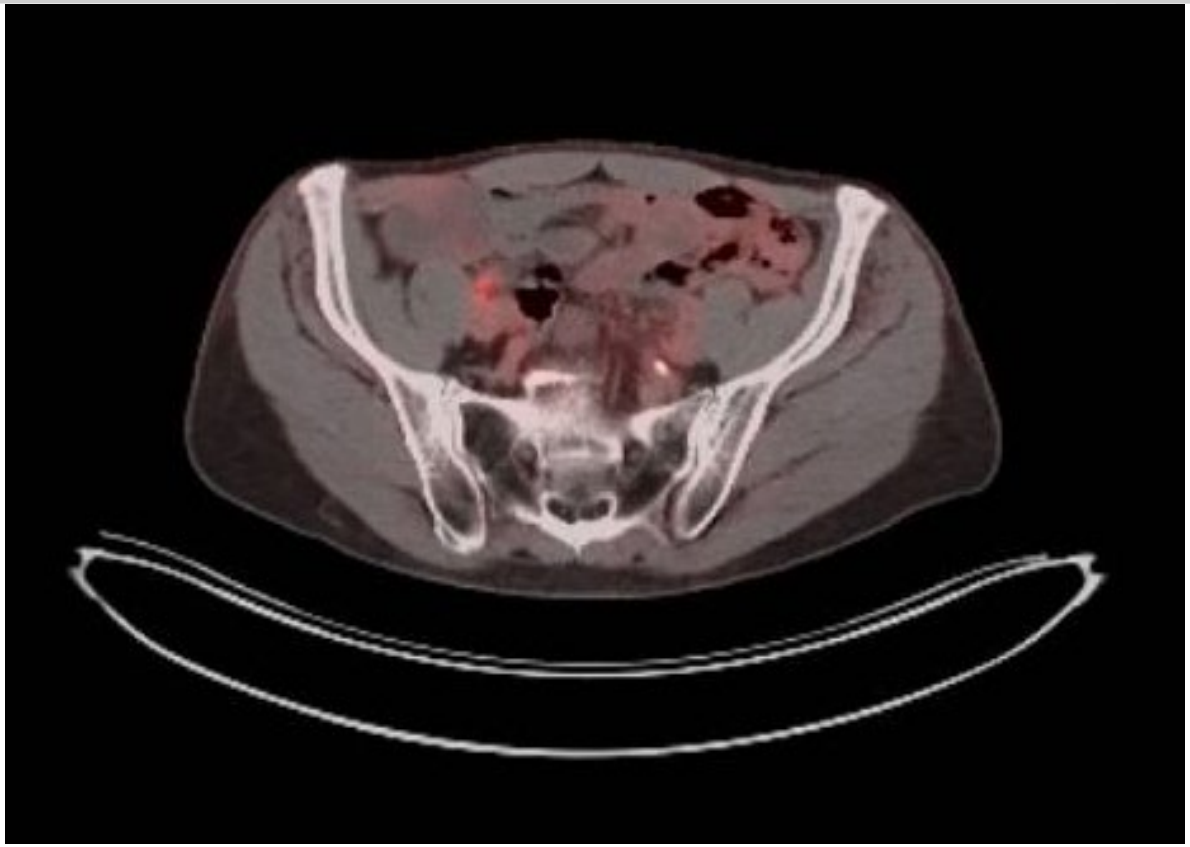
- If a node dissection is performed, it should be an extended node dissection

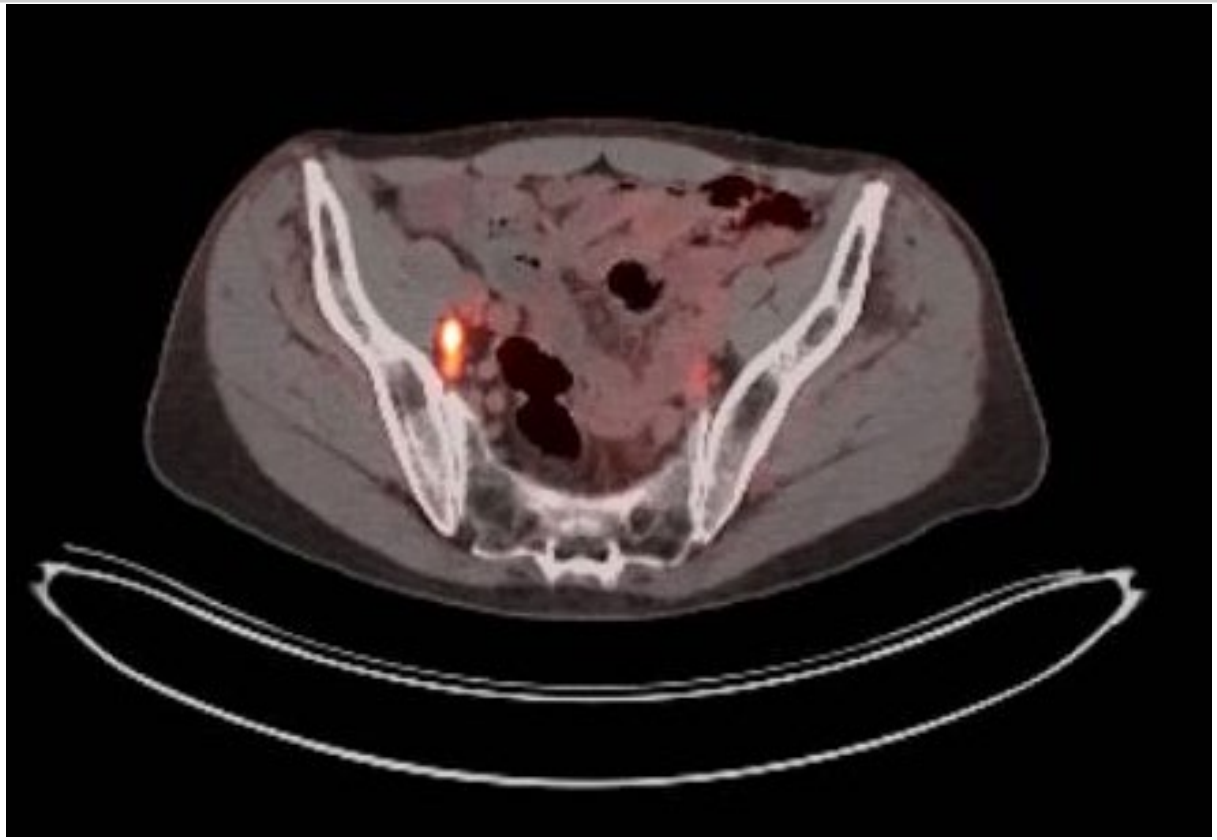
66yo man PSA 27

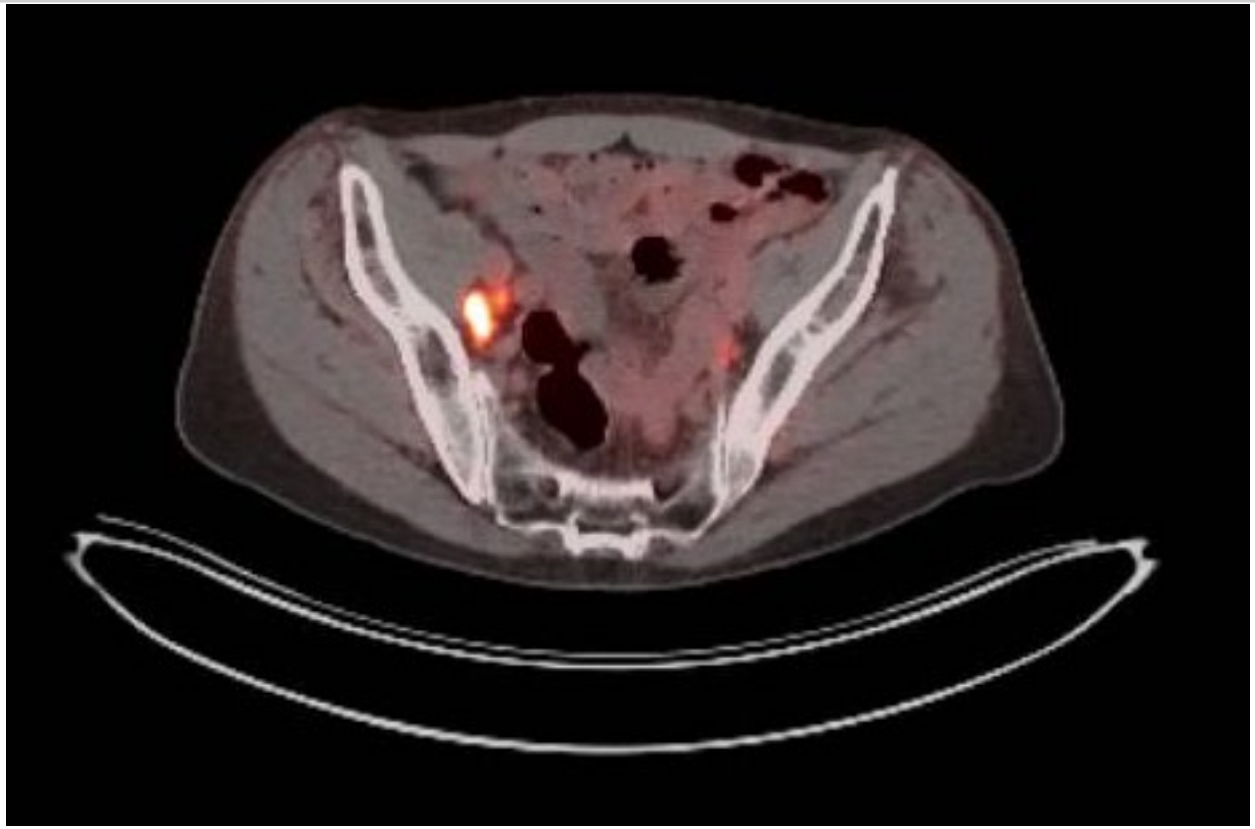
MRI prostate PIRADS 5
With ECE, NVI, suspicious nodes

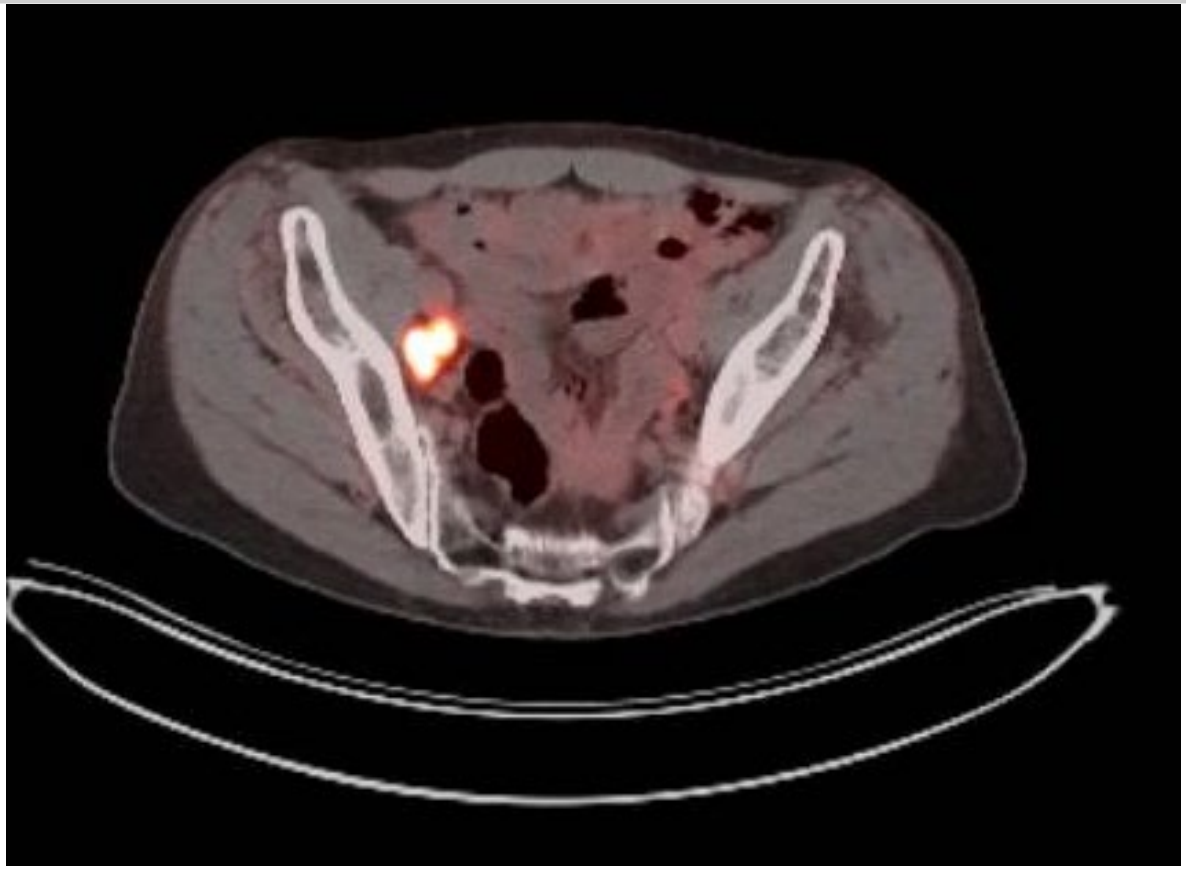
Gleason 4+5 6/17 cores
pT3aN1

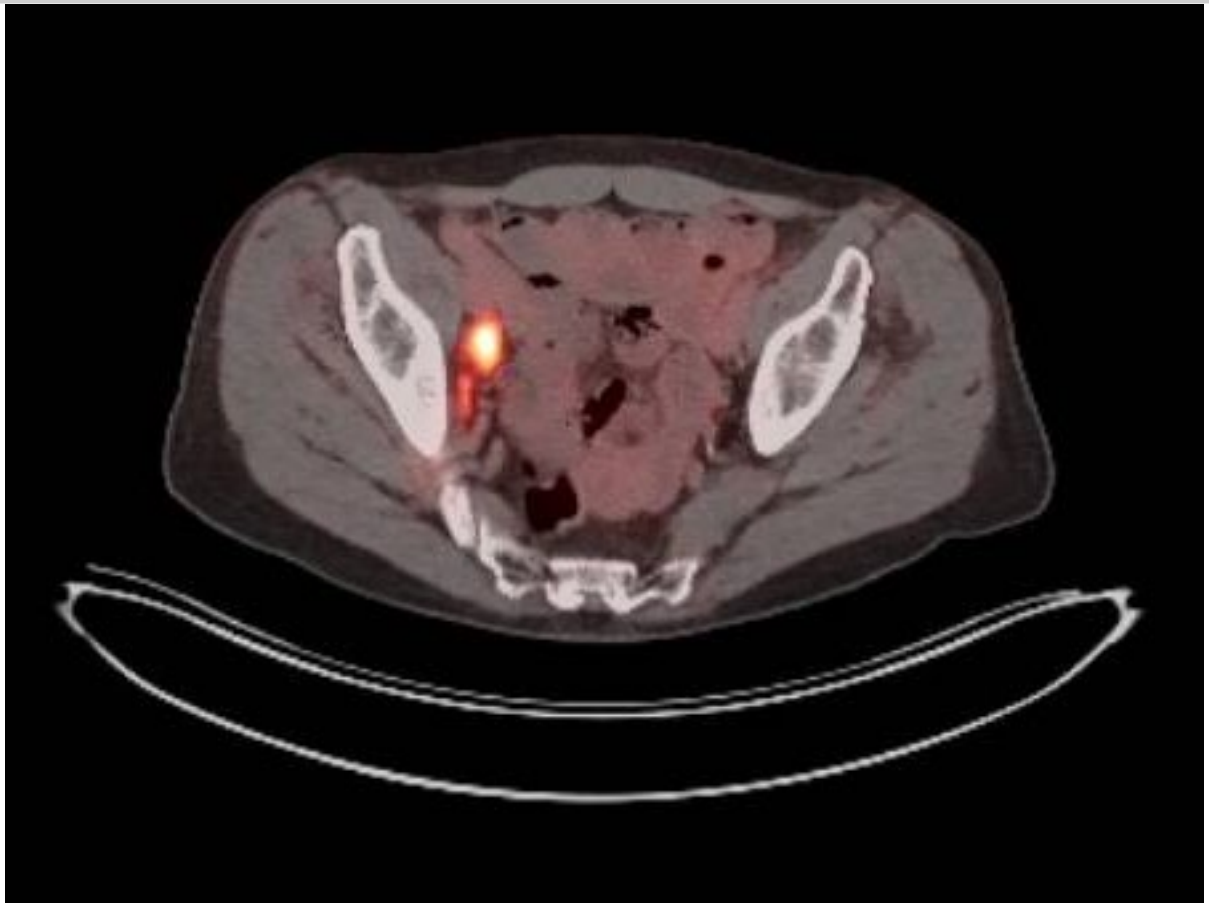
PMH:
Hodgkins lymphoma
Testis cancer
Both treated with radiation

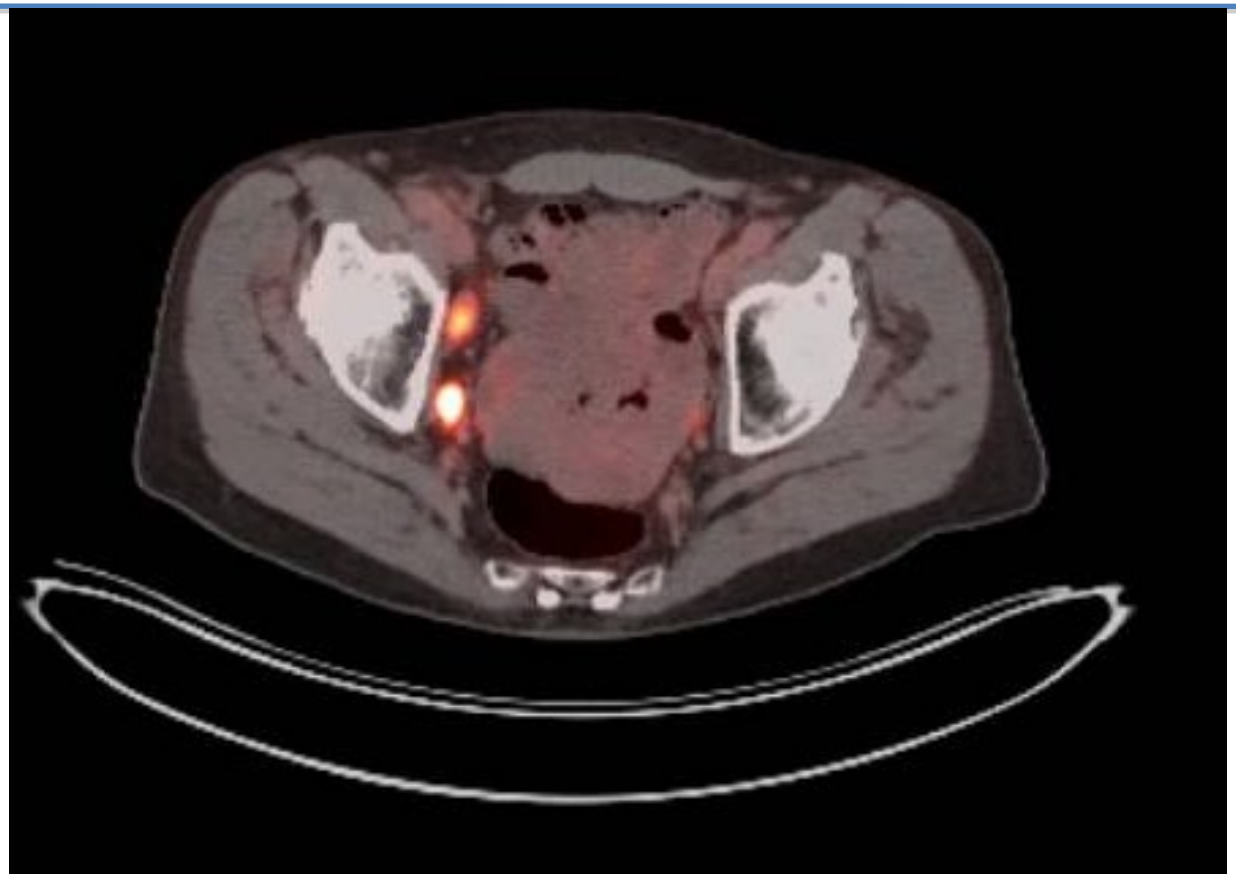


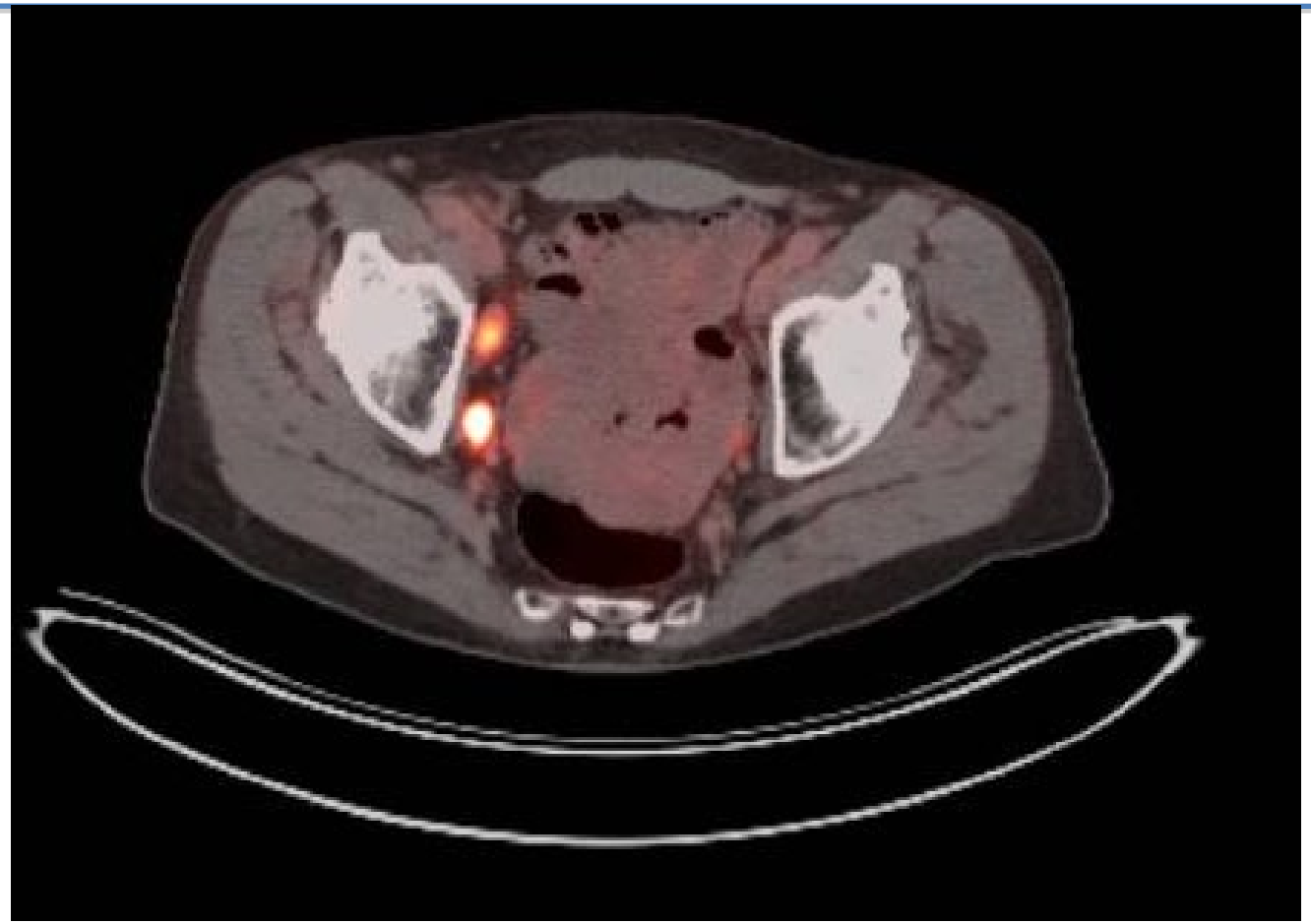


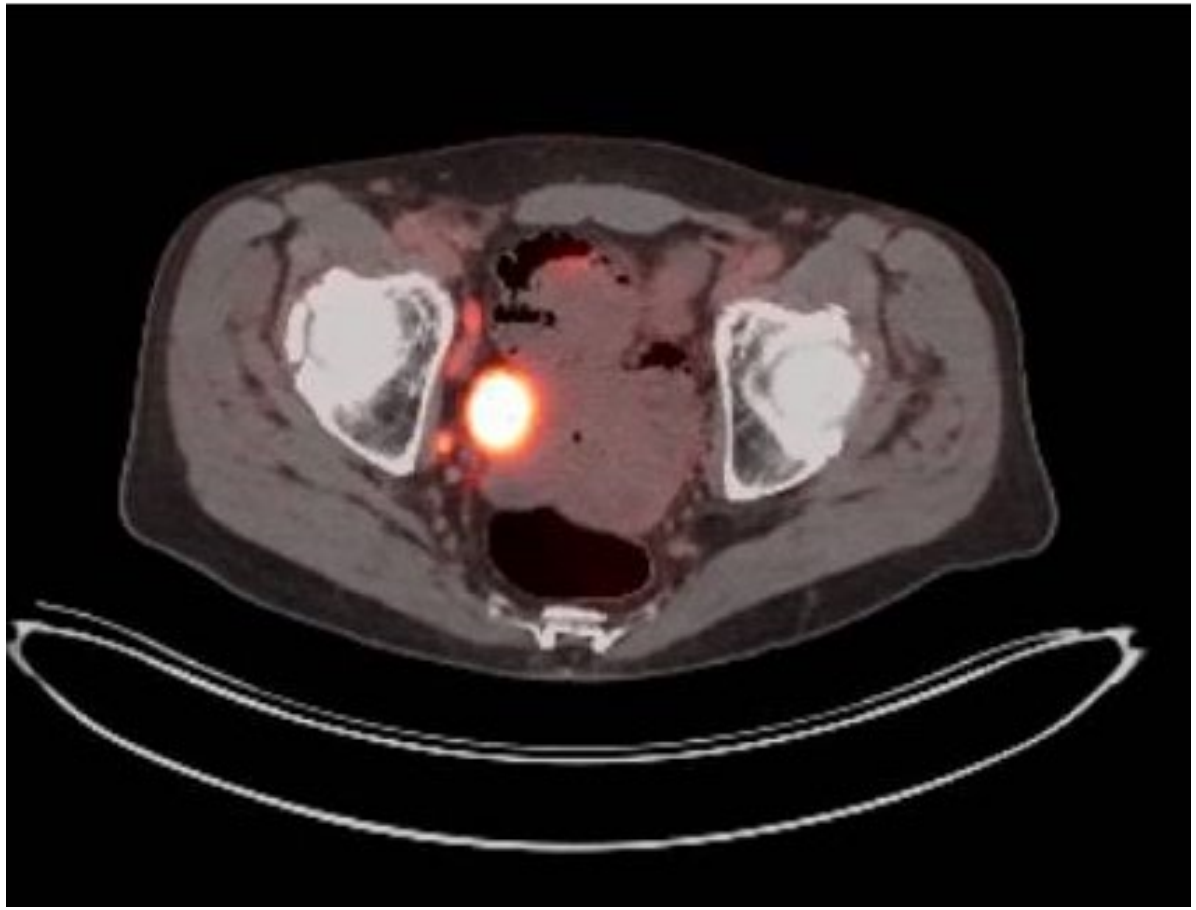


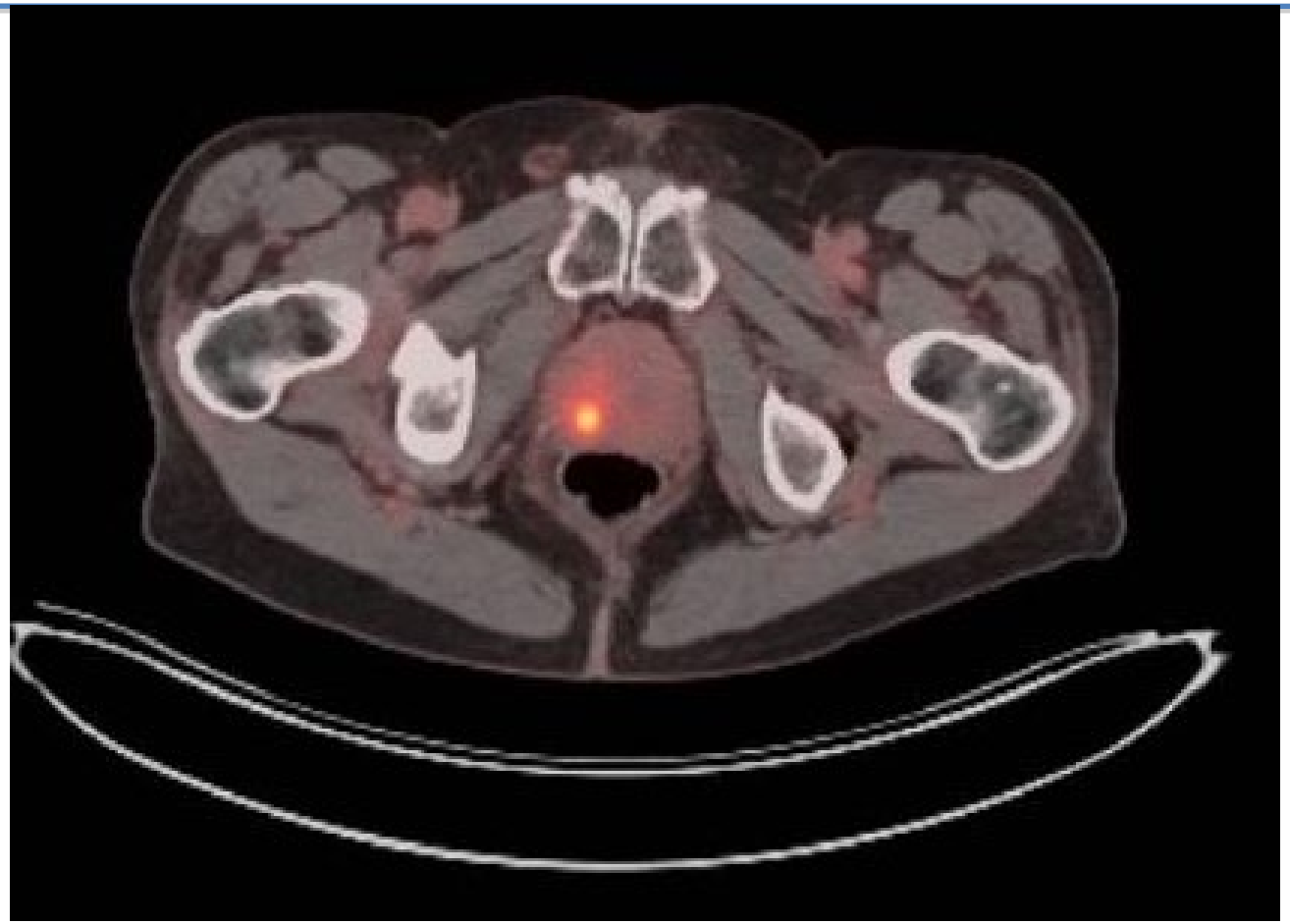


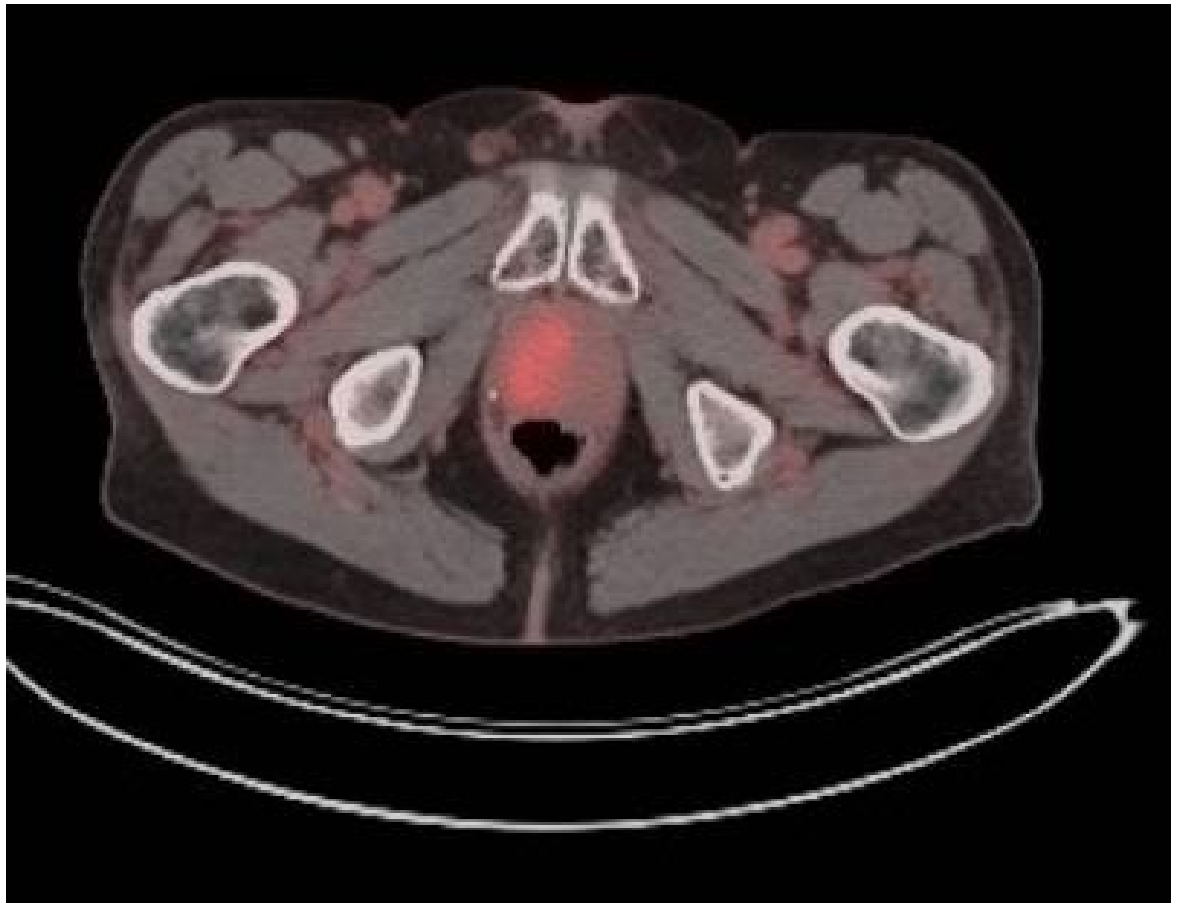


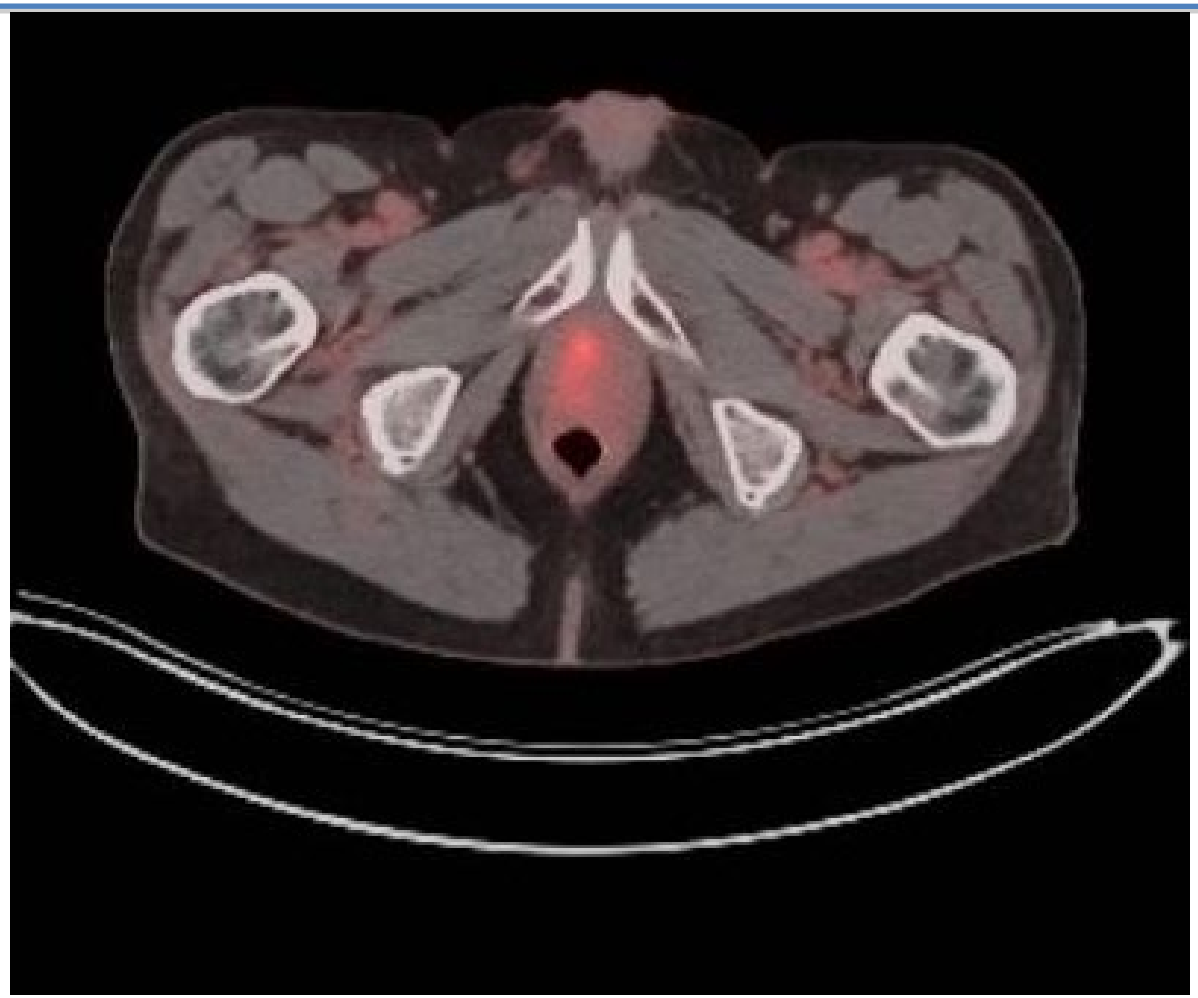


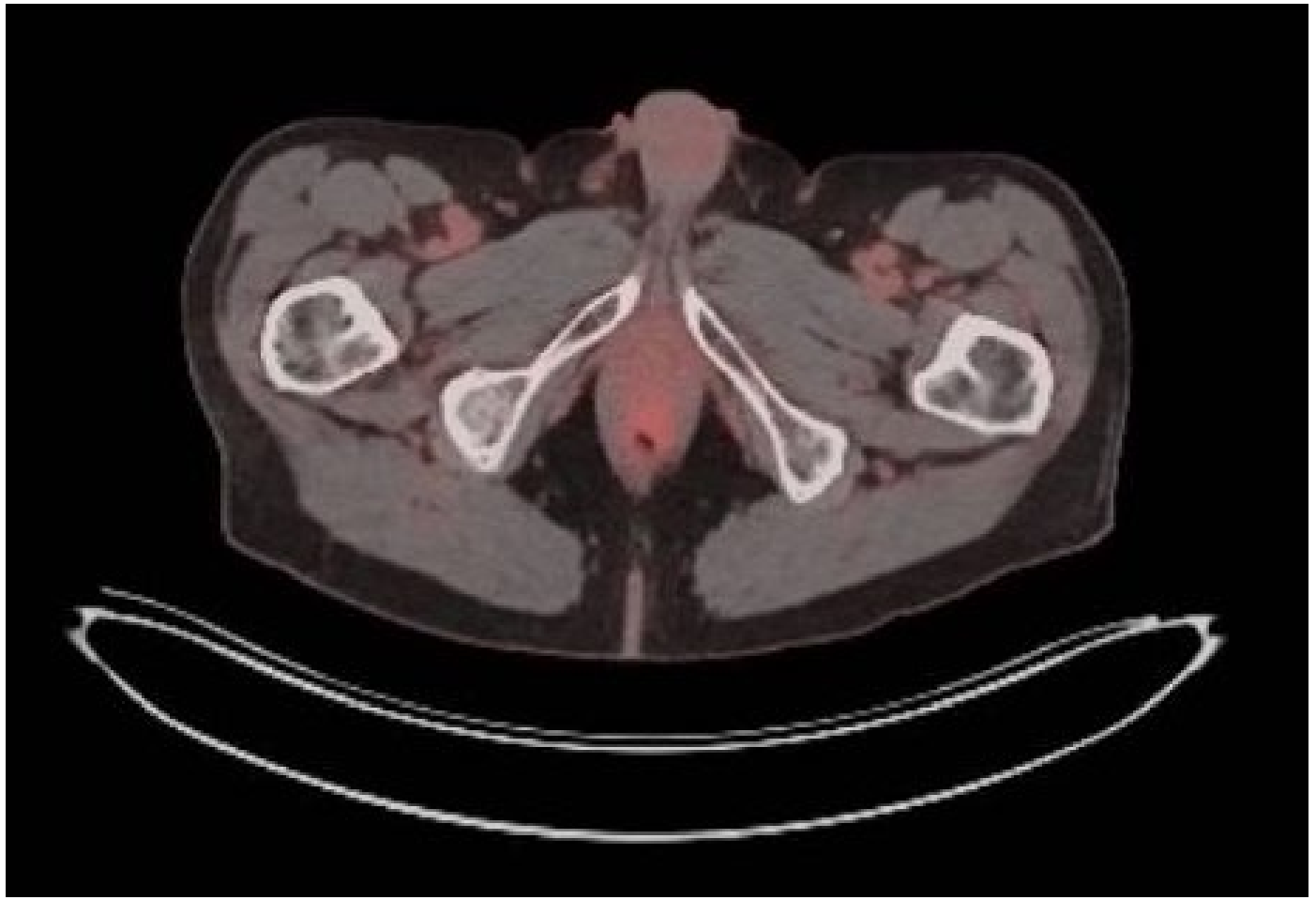












- This patient clearly will not benefit from surgery and node dissection
- Surgery may be complex due to prior radiation

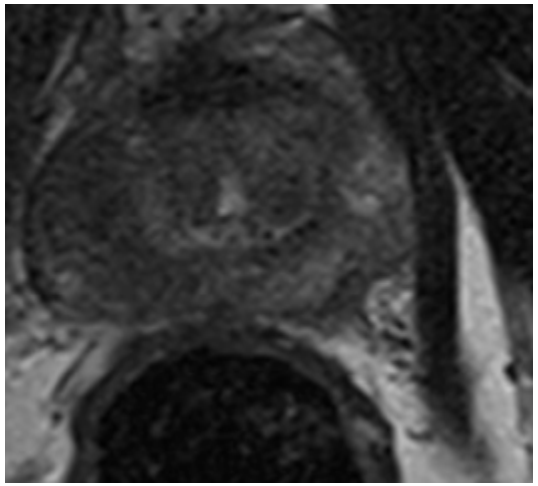
- Complications will delay the treatments with proven survival benefit

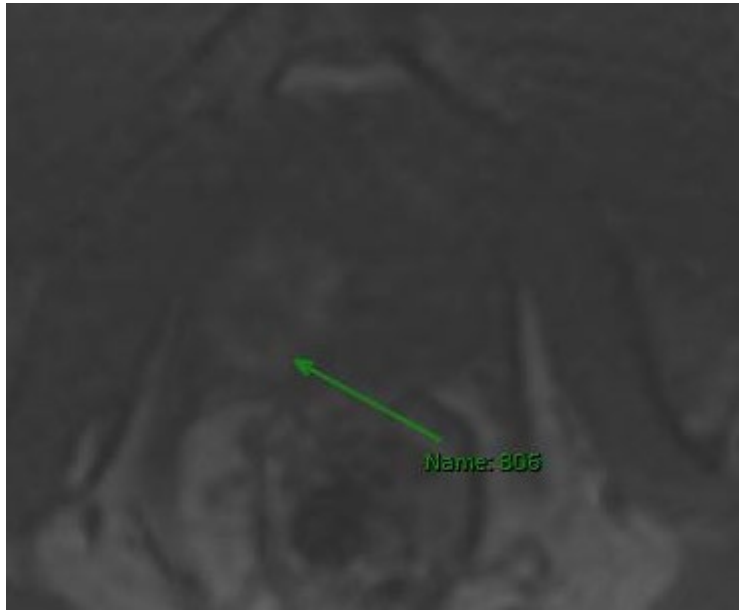
73yo man PSA GI 4+3 cT2a

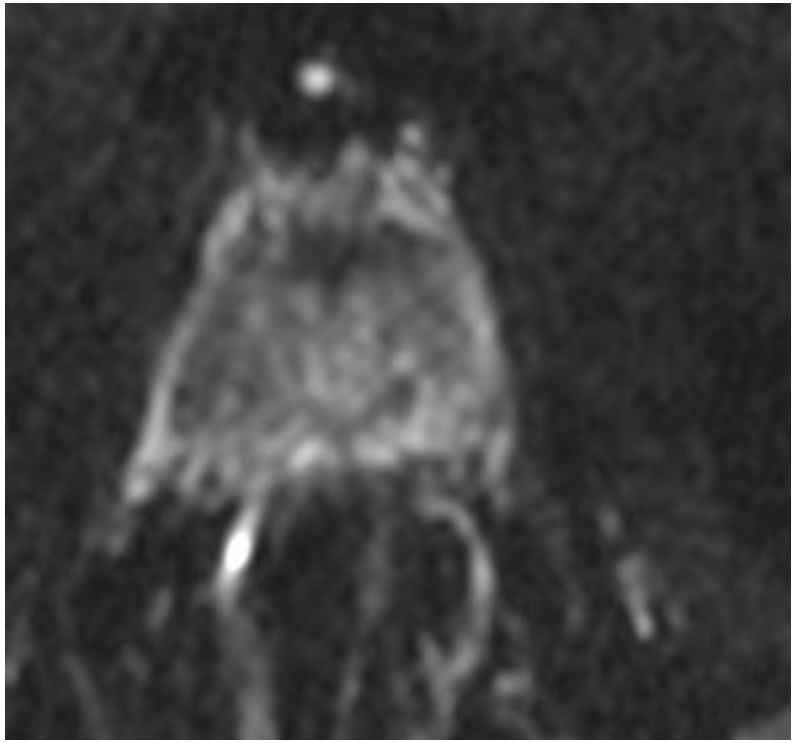
- 4+3 5/6
- 3+4 6/6
- 3+3 ½

- MRI PIRADS 5 right likely ECE, no nodes or mets

PSMA PET not available







That one case everyone remembers…

- Gleason 4+3 pT3b N1 1/8
- 0.5mm largest deposit left(likely would have seen this on PSMA)

Lab Results

Component	Value	Date
PSAULTRA	0.02 (H)	08/03/2023
PSAULTRA	0.02 (H)	02/07/2023
PSAULTRA	<0.01	10/07/2022
PSAULTRA	<0.01	05/19/2022
PSAULTRA	<0.01	12/14/2021
PSAULTRA	<0.01	09/30/2021
PSAULTRA	<0.01	06/21/2021
PSAULTRA	<0.01	03/18/2021

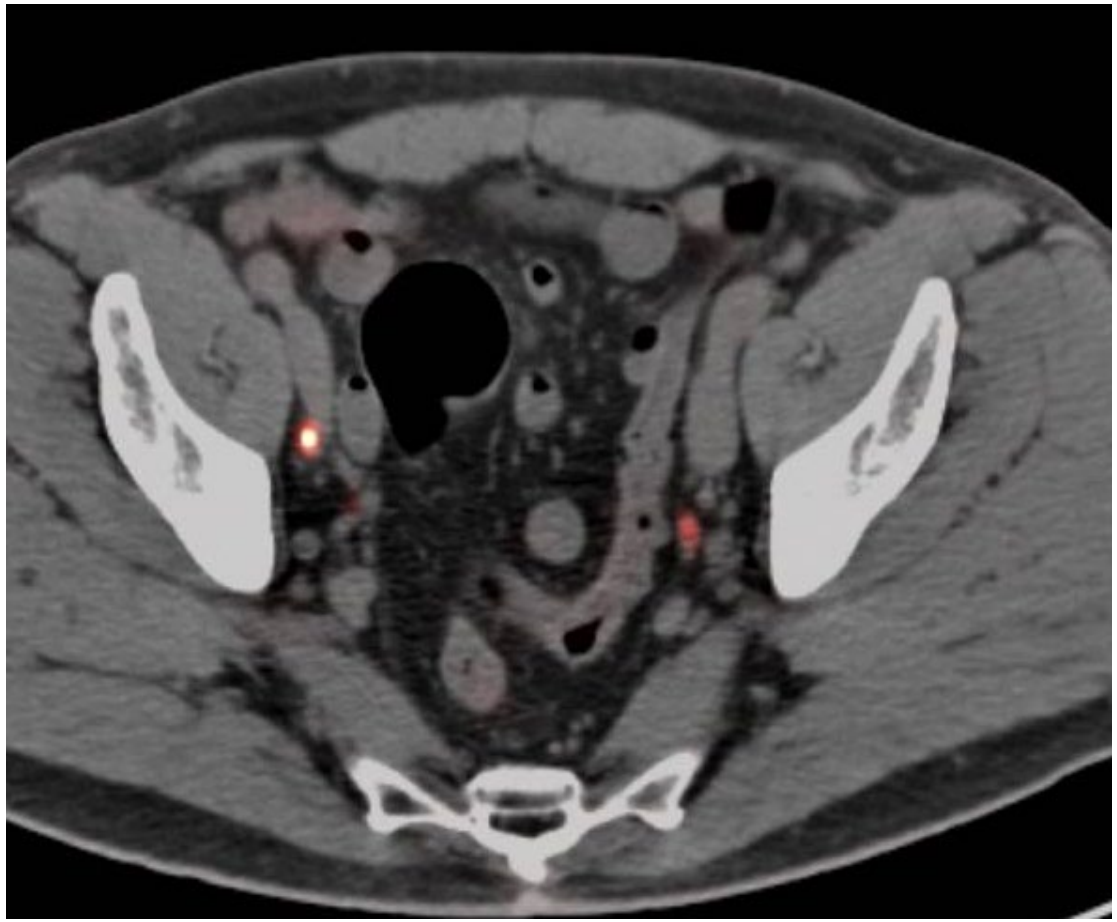
What is the best management strategy?

- Multidisciplinary team of Urologic Surgery, Medical Oncology and Radiation Oncology
- Consider other patient factors which may limit your team's overall options: ADT risk, radiation exposure
- Consider voiding symptoms and local control as well as quality of life goals

How do I manage these patients?

- Clarify what is and what is not possible(surgery will not be a solo cure)
- Have them repeat back the steps in multidisciplinary care that will occur
- Consider surgery for patients who
  - **have serious LUTS/are in retention**
  - have a very strong MEDICAL contraindication to radiation
  - Need to **delay** ADT as long as possible
  - Have limited positive nodes

64yo man PSA 8.5 Gleason 4+3 4/14 MRI PIRADS 4 lesion apex right and mid



Bottom line

Surgery should be the exception for clinical N1 disease based on current data

This is mHSPC and there are other treatments with proven benefit

Conclusions

- The recommendations for initial staging of high-risk prostate cancer are evolving
  - MRI is superior to CT with respect to characterizing local tumor anatomy.
  - Both CT and MRI are suboptimal for LNs
  - PSMA PET is more sensitive than either for metastasis
  - Need 5mm of cancer in one location

Conclusions

- **Value in both primary staging and recurrent disease following therapy**
- **Remember the variable impact of ADT and order the scan BEFORE you start initial ADT**
- **The patient must have a PSMA PET showing activity greater than the liver**

The dilemma

Stage Migration/"Will Rogers Phenomenon: Improved imaging increases the detection of metastatic disease but also the number of patients with oligometastatic disease.
It has been there all along. The difference is now we know and can change treatment.

Recommendation	Strength rating
Any risk group staging	
Treatment should not be changed based on PSMA PET/CT findings, in view of current available data.	Strong

technique?"

How do patients pay for these tests?
This is the biggest obstacle now. Elimination of the "standard" imaging will help decrease overall cost and radiation exposure.

Future directions

Intraoperative visualization

PSMA linked fluorescence

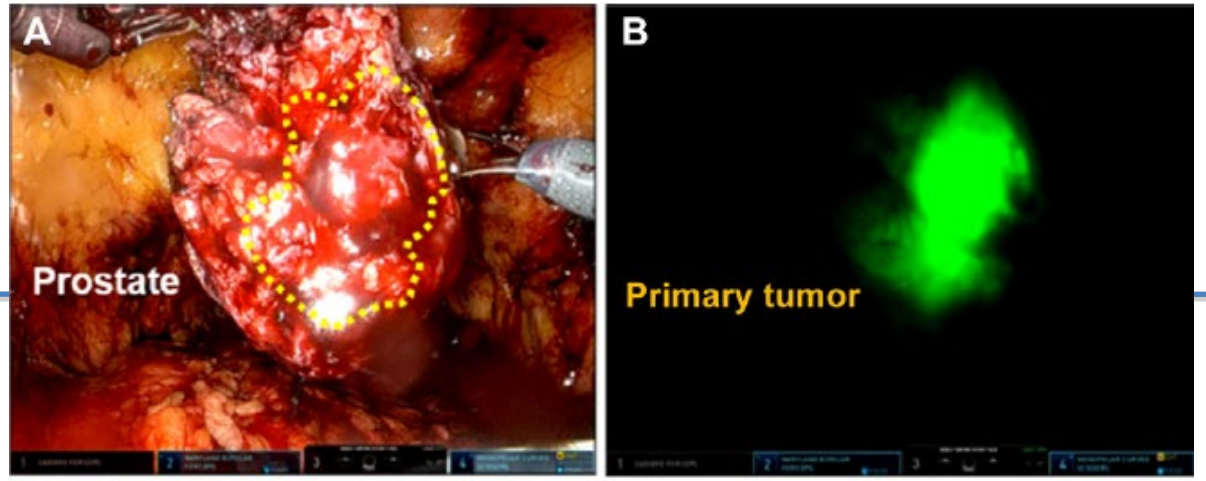
- Stibbe and van der Poel OTL78
- Nguyen and Carroll IS-002

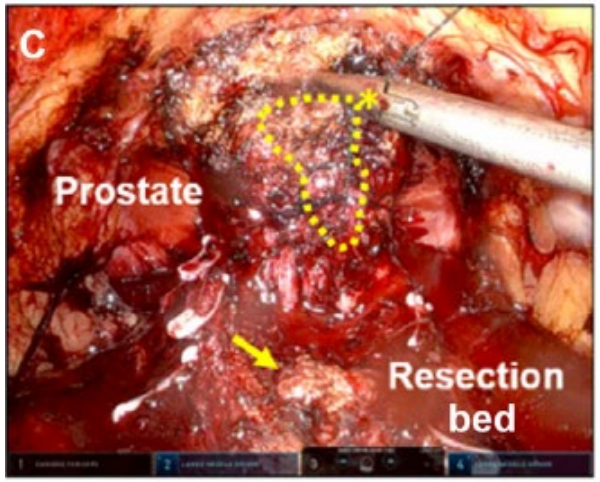
European Association of Urology

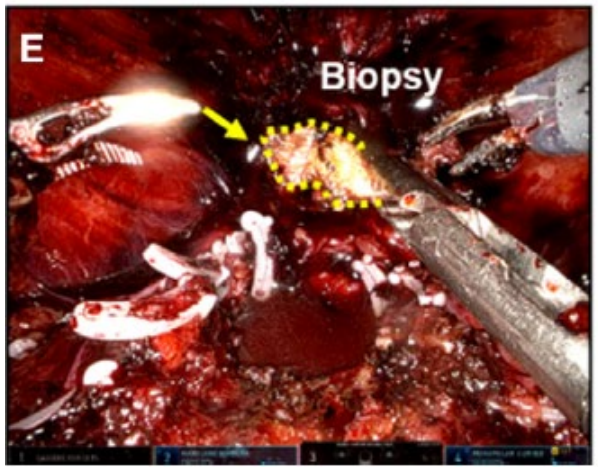
First-in-human Evaluation of a Prostate-specific Membrane Antigen–targeted Near-infrared Fluorescent Small Molecule for Fluorescence-based Identification of Prostate Cancer in Patients with High-risk Prostate Cancer Undergoing Robotic-assisted Prostatectomy

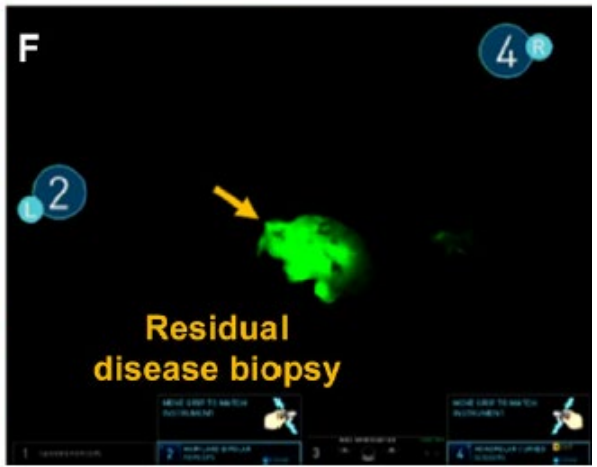
Hao G. Nguyen [a,†], *Nynke S. van den Berg* [b,†], *Alexander L. Antaris* [b,†], *Lingru Xue* [a], *Scott Greenberg* [a], *J. Walker Rosenthal* [b], *Anna Muchnik* [b], *Alwin Klaassen* [b], *Jeffry P. Simko* [c], *Sanjeev Dutta* [b], *Jonathan M. Sorger* [b], *Pamela Munster* [d], *Peter R. Carroll* [a,*]

Nodes	PPV 97%	NPV 45%
Residual disease	PPV 100%	NPV 80%

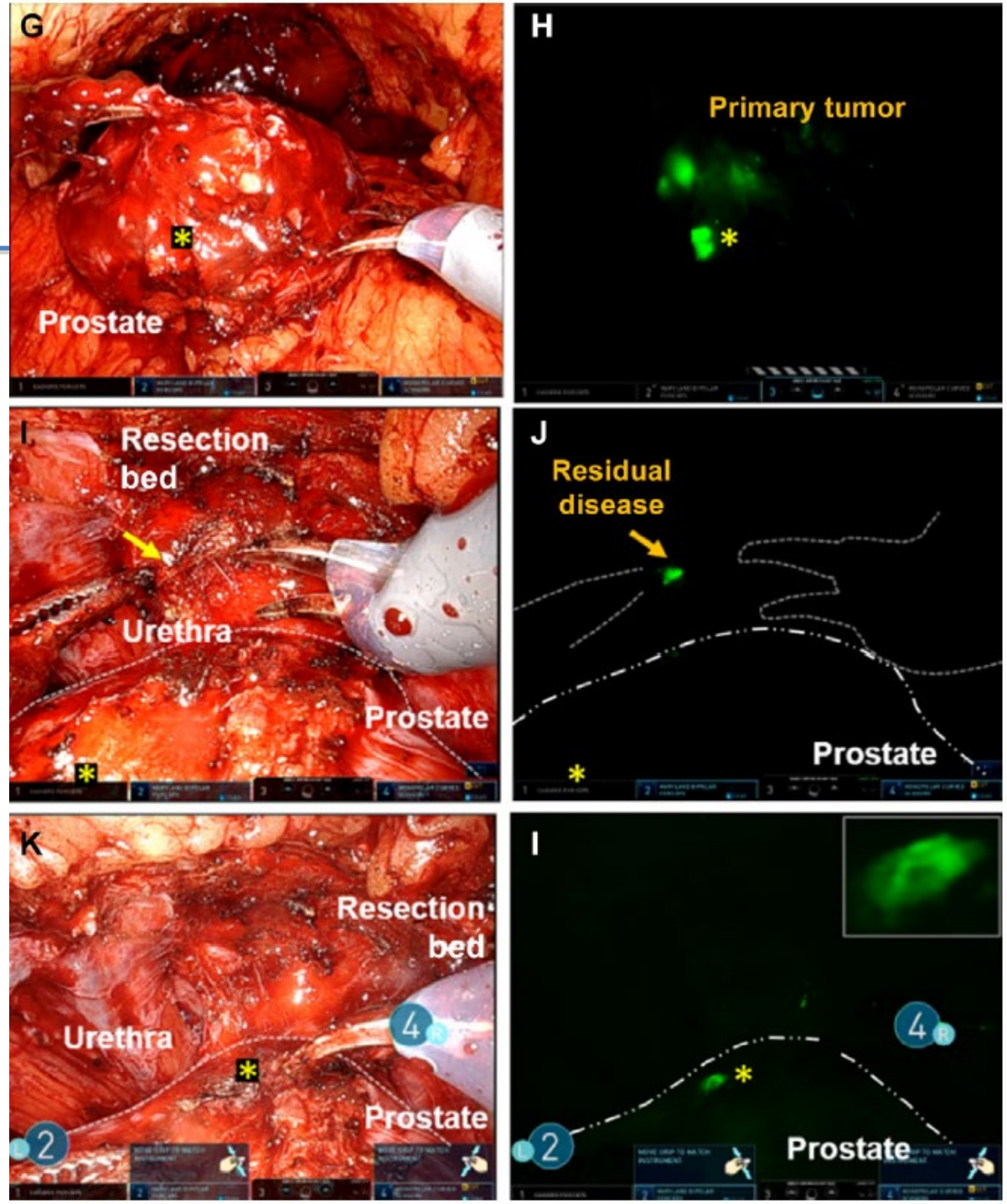






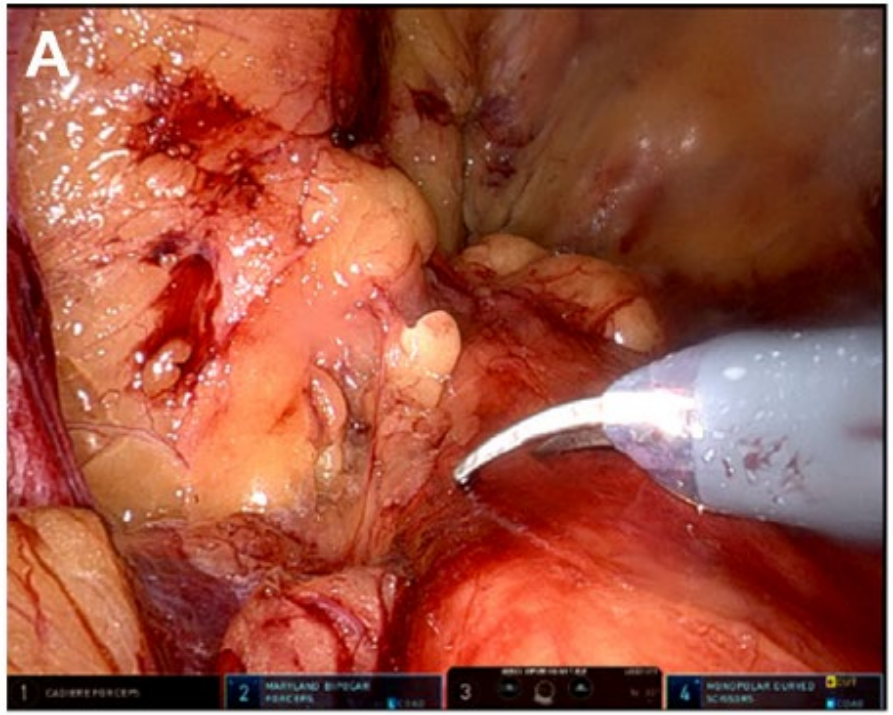


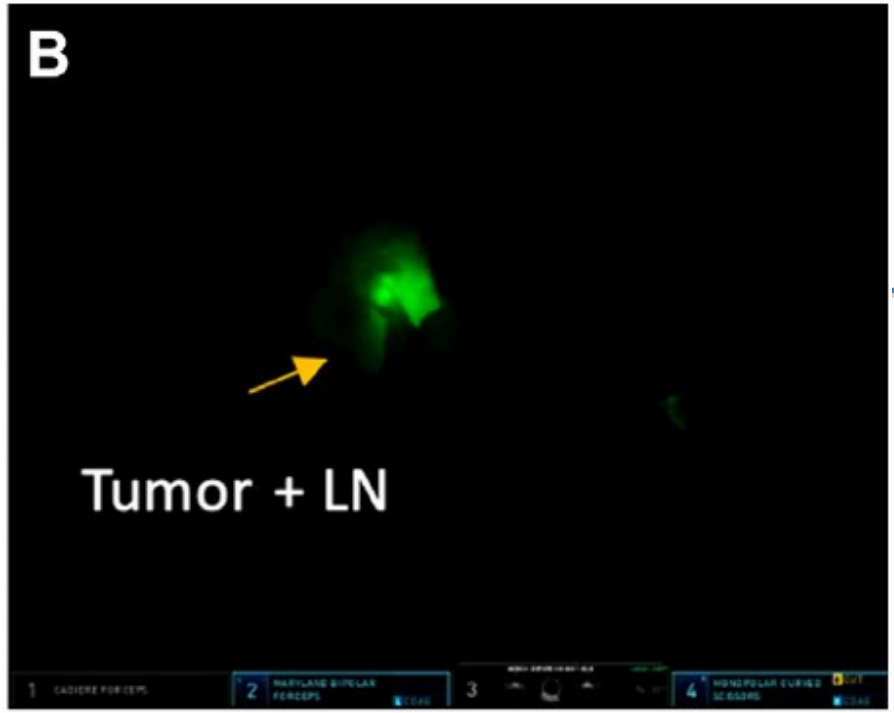
25 µg/kg dose
Dose administered 24 hours prior to surgery

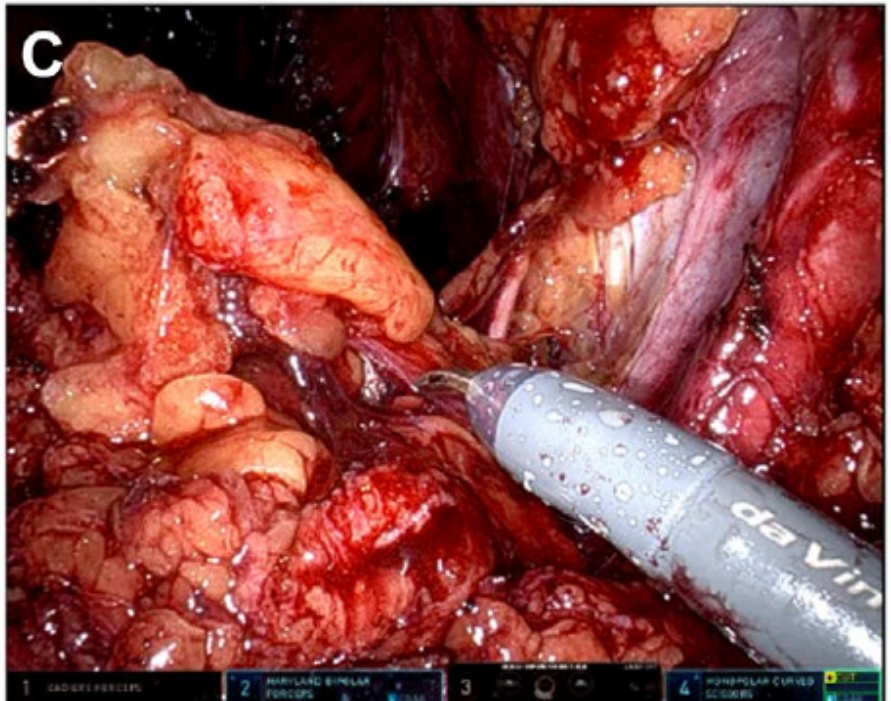


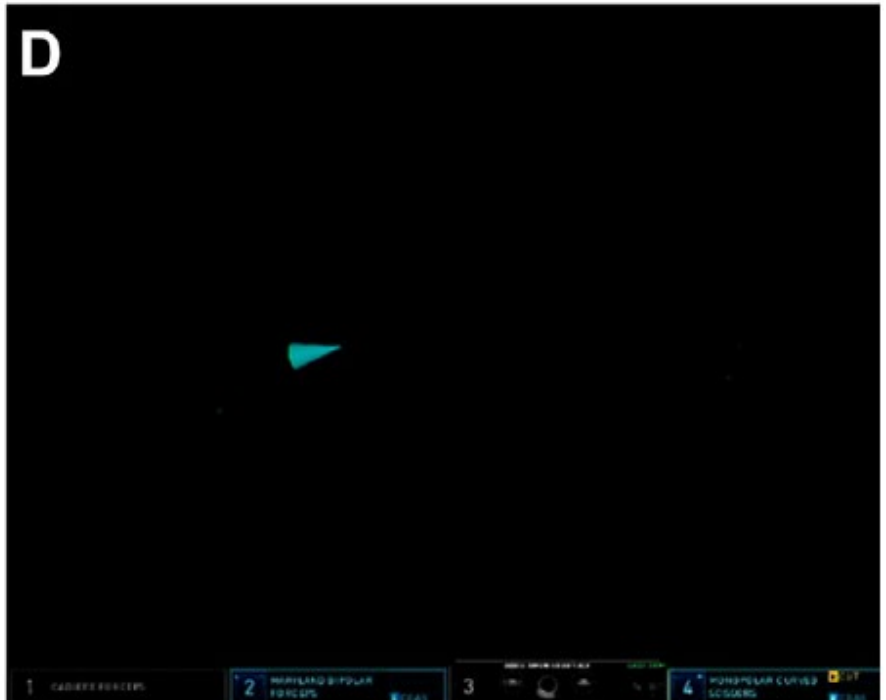
29% of patient had disease seen only on sensitive Firefly fluorescence.

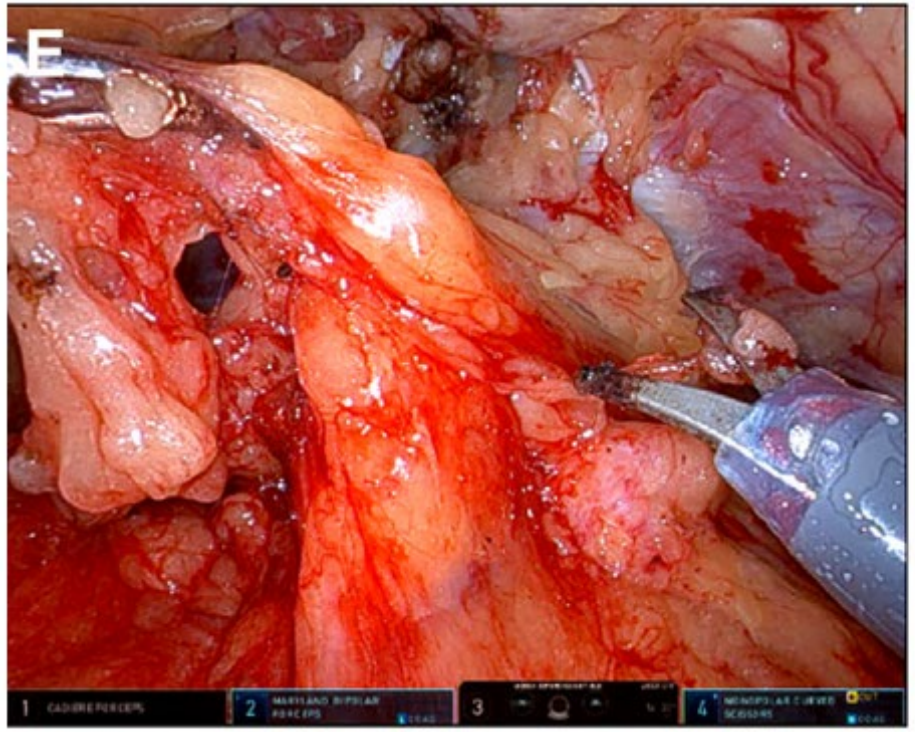
Corcordance with pathology 63%

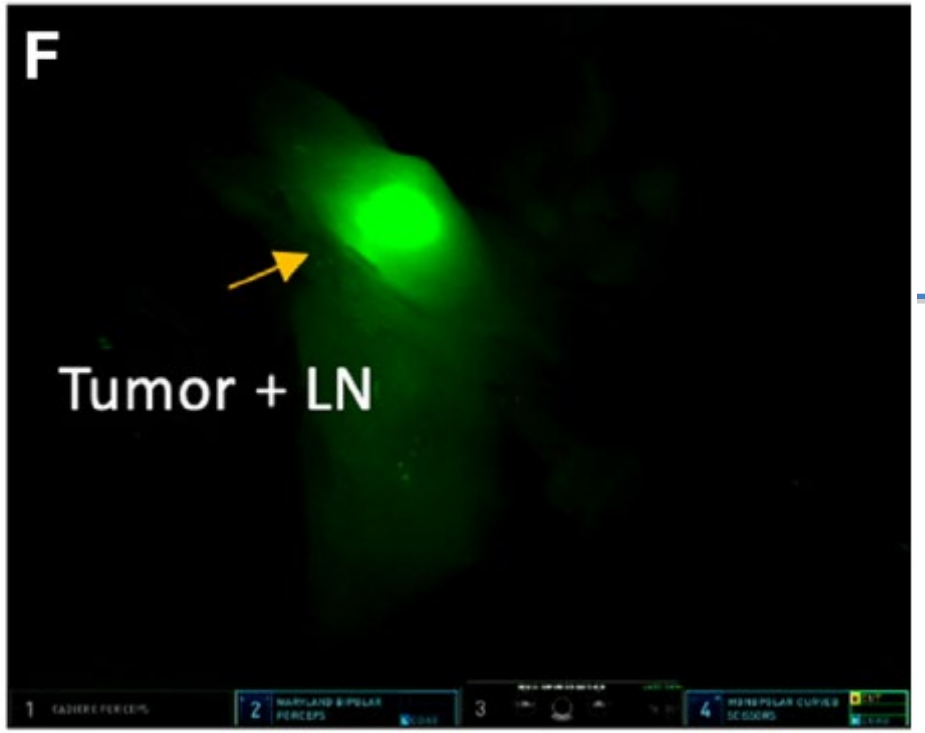

A


B
Tumor + LN

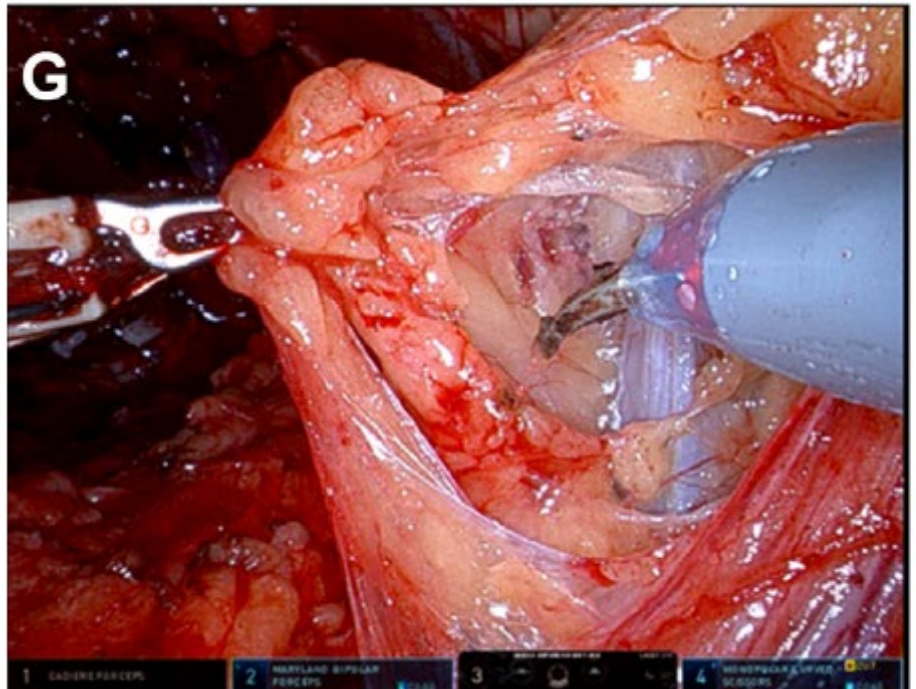

C

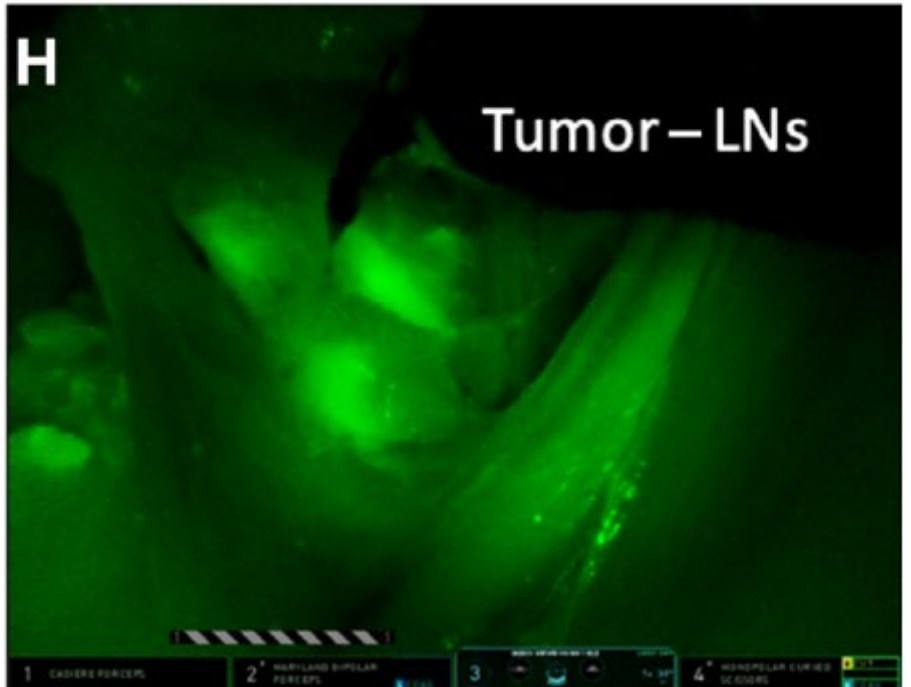

D





True positive nodes



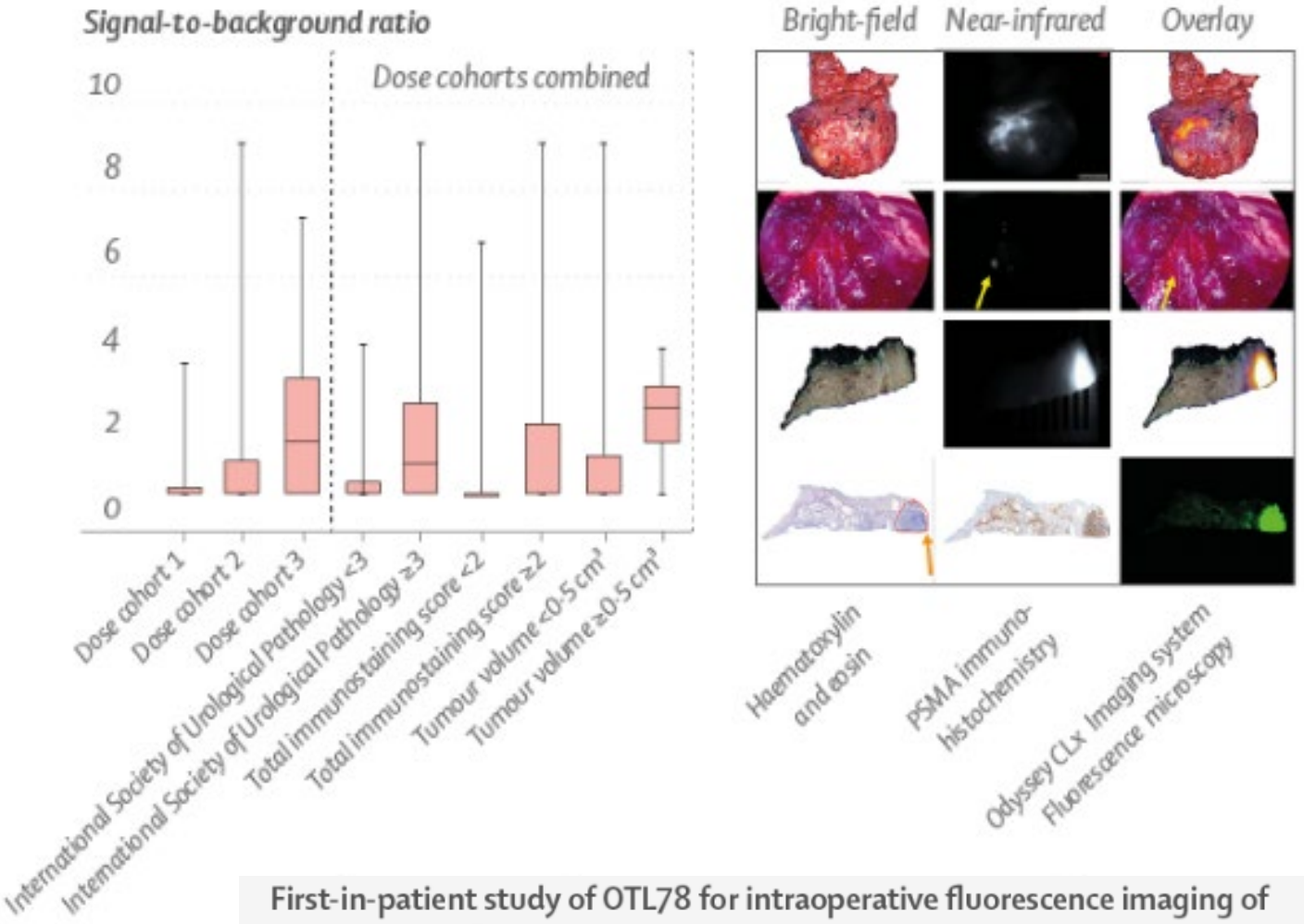


False positive nodes

First-in-patient study of OTL78 for intraoperative fluorescence imaging of prostate-specific membrane antigen-positive prostate cancer: a single-arm, phase 2a, feasibility trial

Judith A Stibbe [1], Hilda A de Barros [2], Daan G J Linders [1], Shadhvi S Bhairosingh [1], Elise M Bekers [3], Pim J van Leeuwen [2], Philip S Low [4], Sumith A Kularatne [4], Alexander L Vahrmeijer [1], Jacobus Burggraaf [5], Henk G van der Poel [6]

OTL78 was safe, well-tolerated, and allowed VisionSense* real-time visualisation of prostate cancer.



First-in-patient study of OTL78 for intraoperative fluorescence imaging of prostate-specific membrane antigen-positive prostate cancer: a single-arm, phase 2a, feasibility trial

Judith A Stibbe, Hilda A de Barros, et al.

Dose 0.03 mg/kg

24 hours prior to surgery

82% sensitivity for margins

Dose dependent false positive for nodes

Conclusions

- PSMA PET/CT is showing us metastatic disease and causing a stage migration.
- US guidelines don’t tell us what to do with this. EAU says do not change practice(which is hard to do).
- PSMA is currently used as not only an imaging agent but also a therapy(PSMA Lu) and will have many more applications in the future.