

Beyond MRI: New Imaging Modalities and New Challenges in Prostate Cancer

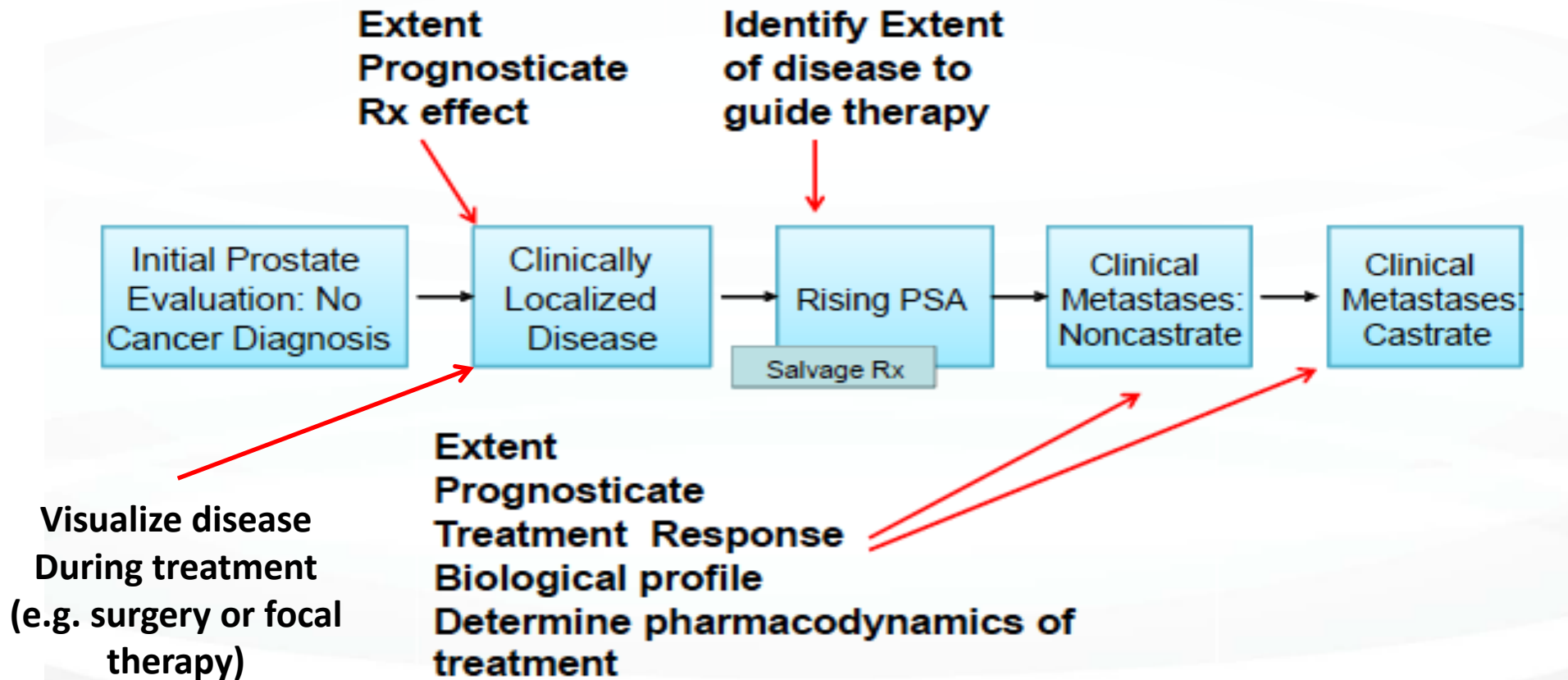
Robert E Reiter MD MBA

Bing Professor of Urologic Oncology

Chief, Division of Urologic Oncology

Geffen School of Medicine at UCLA

Imaging in Prostate Cancer By Clinical Stage



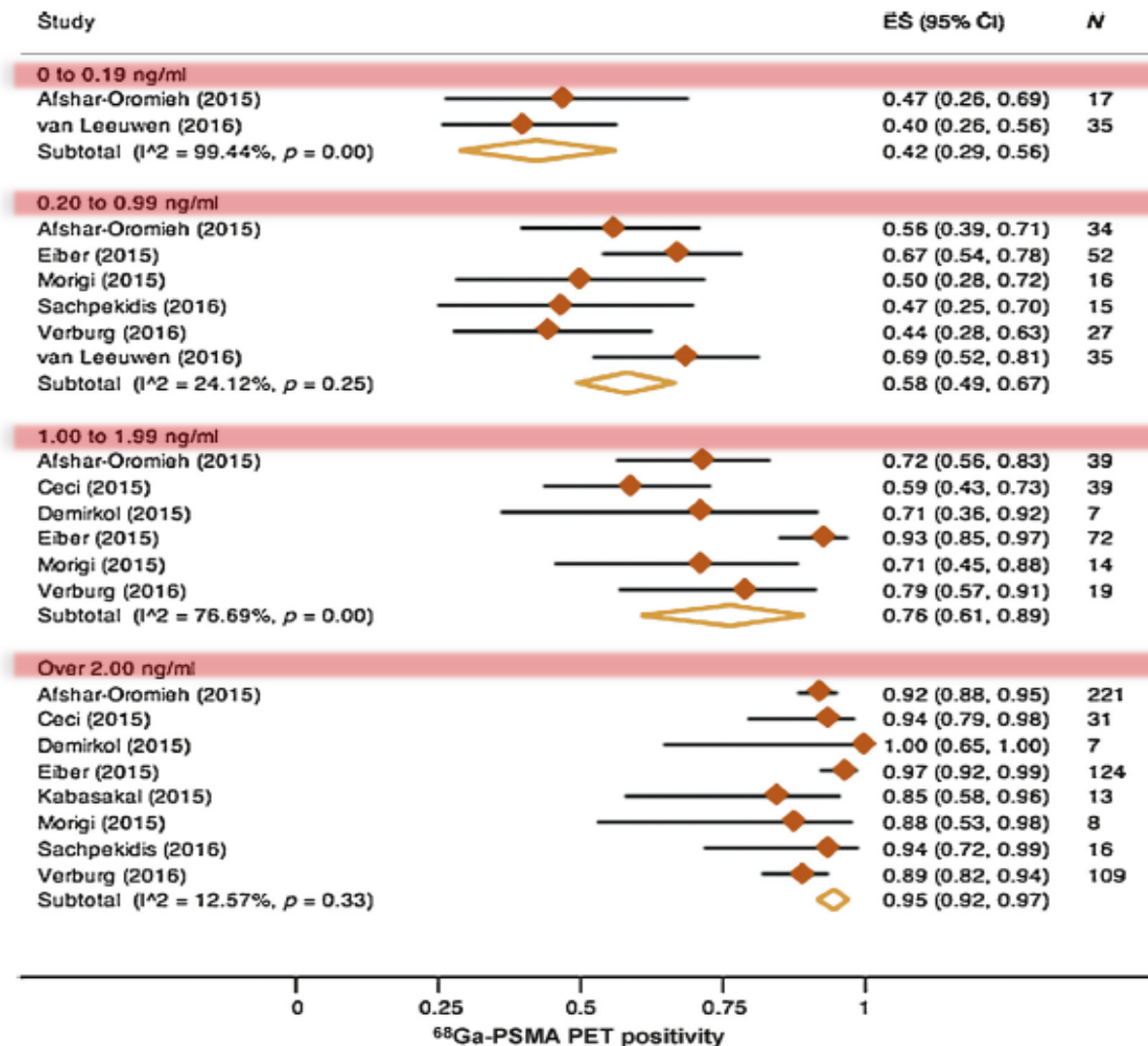
Adapted from Scher et al.

Molecular Imaging Tracers 2018

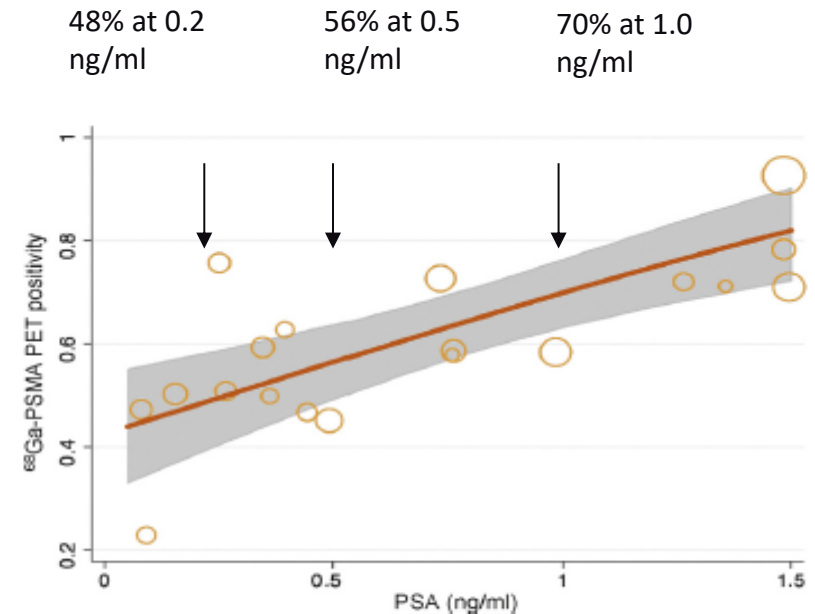
- Sodium Fluoride
- FDG
- Choline
- Acetate
- **PSMA**
 - Ga-PSMA
 - DyPCL
- FACBC (Axumin)

Performance of ^{68}Ga -PSMA PET for BCR

Detection efficacy stratified by PSA-values



Predicted positivity in meta-regression analysis



Choline labelled agents:

16% for PSA <1 ng/ml, 26% for PSA <2 ng/ml

Treglia et al, Clin Chem Lab Med 2013

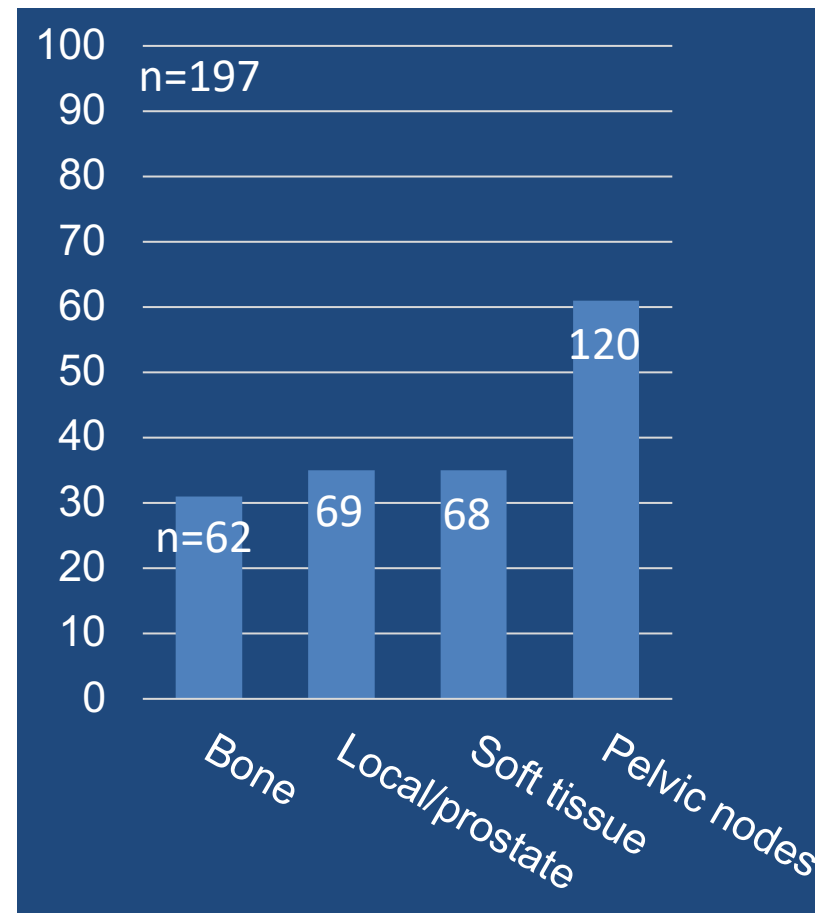
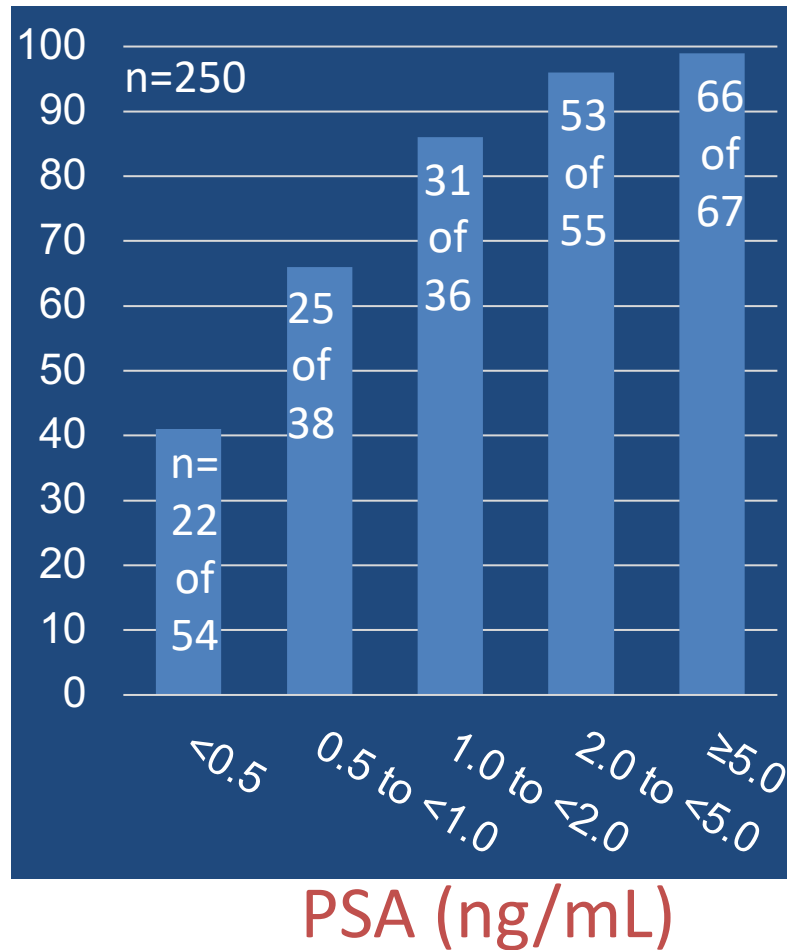
Perrera et al Eur Uro. 2016

UCLA Patient characteristics

- n=250 patients enrolled
- Median age (range): 68 (44-88) years
- Median PSA 1.9 ng/ml, n=95 (38%) with PSA<1 ng/mL
- 82% s/p prostatectomy, 18% s/p radiotherapy
- n=86 (34%) with Gleason Score ≥ 8
- PSA response after PET-guided therapy (surgery/radiotherapy):
Recorded in 23 of 25 patients (8% drop out)

PSMA PET detection rate and location

Lesions detected in 197 of 250 (79%) patients



Primary Endpoint (pos. predictive value, PPV)

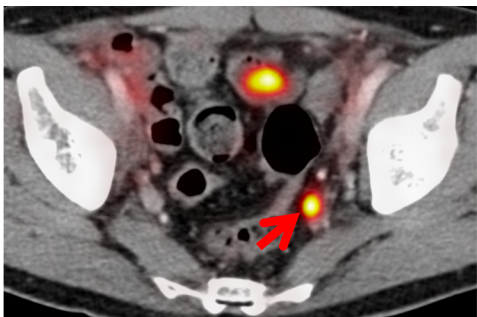
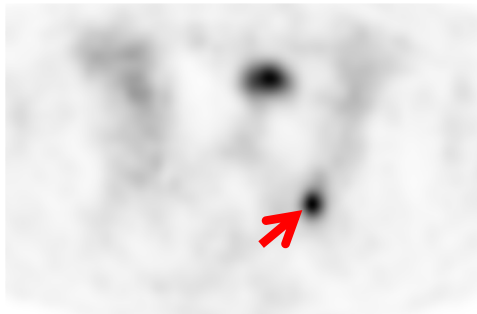
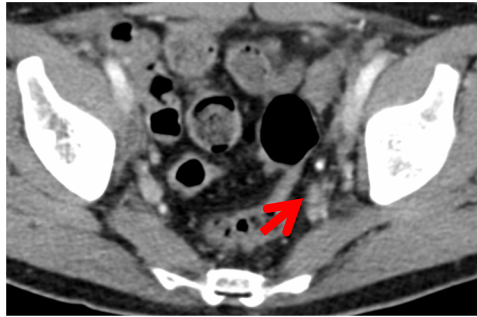
- Validation by histopathology

	PCa confirmed	PCa ruled out	PPV
PET positive (Patient basis, n=33)	28	5	85%
PET positive (Region basis, n=35)	30	5	86%

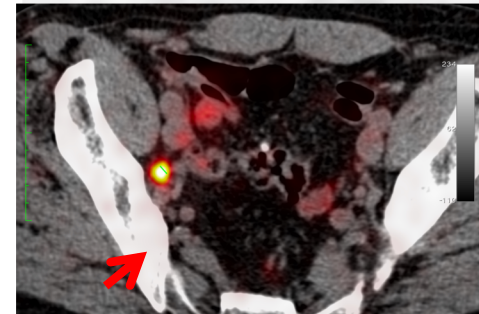
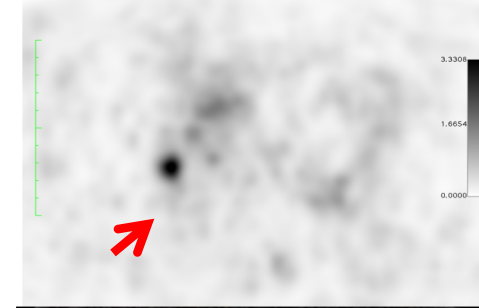
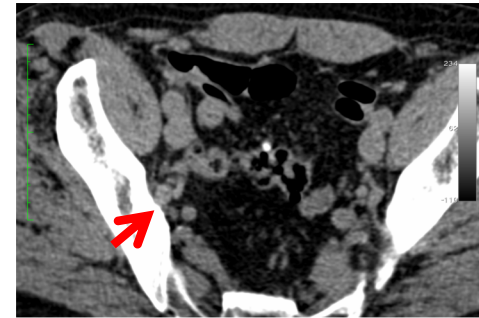
- Four regions: prostate bed, pelvis, extrapelvic, bone
- Primary Endpoint (PPV>50%) is met

^{68}Ga -PSMA PET/CT in biochemical recurrence – UCLA experience

60y/o patient, s/p. RPE, PSA: 0.9 ng/ml



77y/o patient, s/p. RPE, PSA: 0.6 ng/ml



PSMA PET

FDG PET

Na-F PET

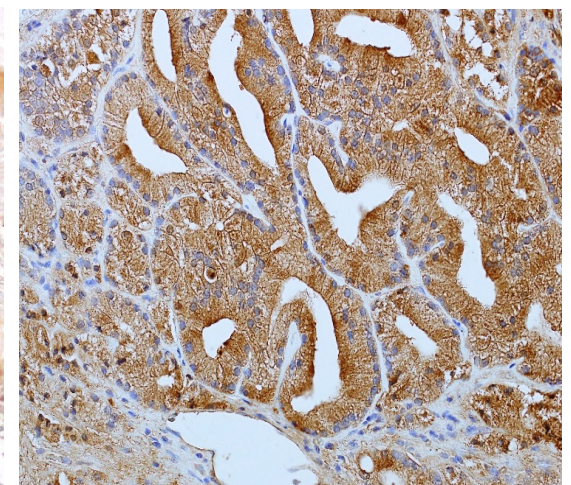
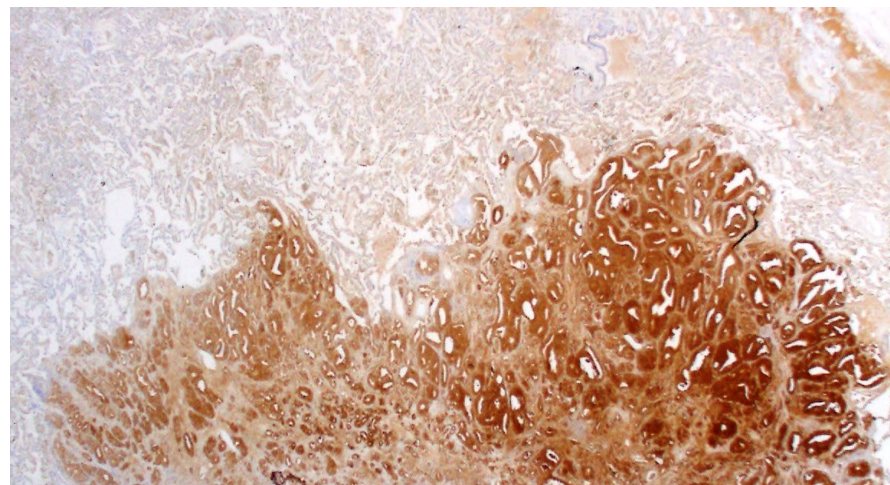
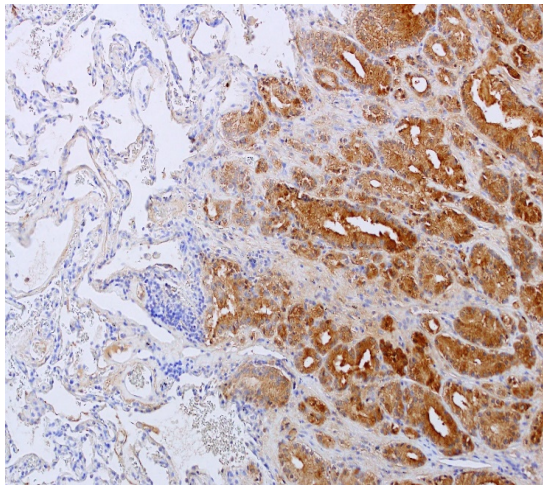
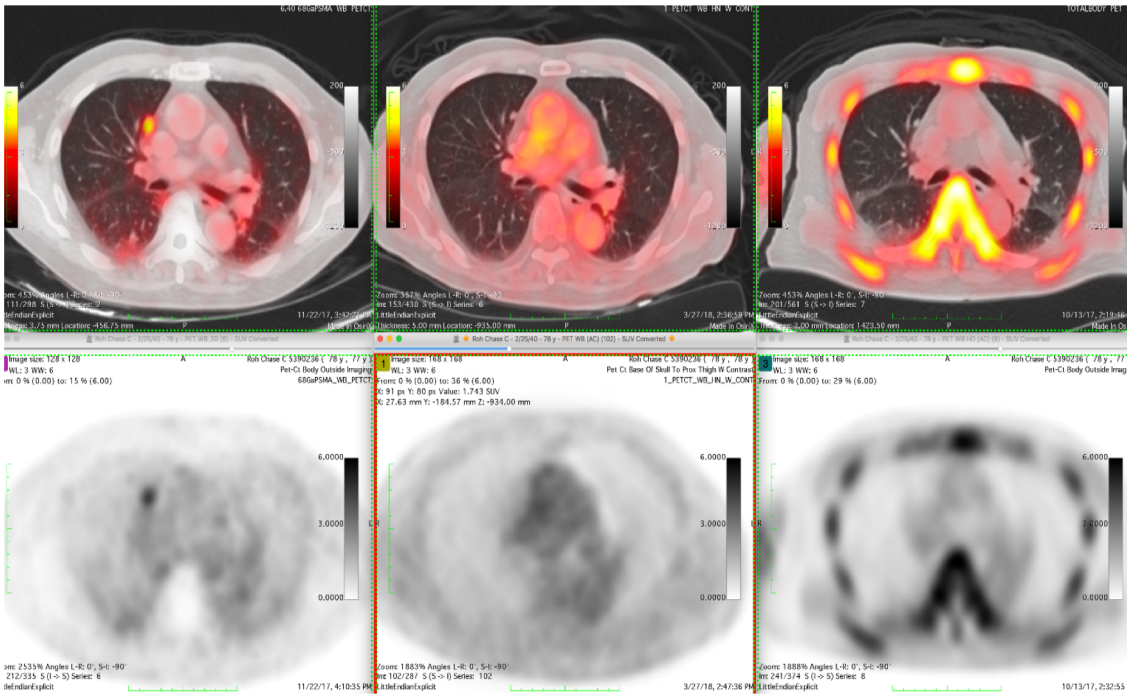
78 yo prostate cancer 2004 s/p
prostatectomy

8mm para-mediastinal nodule
suspicious for primary lung cancer

PSA 0.4

Thoracic segmental resection c/w
Adenocarcinoma of unknown origin

PSA staining confirms mucinous
adeno of prostate



PSA staining +

PSMA in High-Risk Prostate Cancer

	No LN metastases (n = 18)			LN metastases (n = 12)		
	PSMA negative (n = 18)	PSMA positive (n = 0)	p	PSMA negative (n = 8)	PSMA positive (n = 4)	p
LN removed, no. (%)	393 (64.6)	–	NA	141 (23.2)	74 (12.2)	0.833
LNMs removed, no. (%)	0 (0)	–	NA	19 (35.8)	34 (64.2)	0.808
Intranodal LNM size, mm [*] , mean, median (range)	–	–	NA	4.5, 4.3 (1.0–10.8)	12.8, 13.6 (4.0–20.0)	0.048
Overall LNM size, mm [*] , mean, median (range)	–	–	NA	19.4, 20.5 (4.0–40.0)	31.8, 25.5 (12.0–64.0)	0.368

LN = lymph node; LNM = lymph node metastasis; NA = not applicable; PSMA = prostate-specific membrane antigen.
^{*} Largest/index lymph node per patient is presented.

	No LN metastases (n = 18)	LN metastases (n = 12)	
PSMA positive (n = 4), n (%)	0 (0)	4 (33.3)	PPV 100%
PSMA negative (n = 26), n (%)	18 (100)	8 (66.7)	NPV 69.2%
	Specificity 100%	Sensitivity 33.3%	Accuracy 73.3%

LN = lymph node; NPV = negative predictive value; PPV = positive predictive value; PSMA = prostate-specific membrane antigen.

8/26 (30%)
with
negative
PSMA
had positive
nodes

PSMA in High and Intermediate Risk Disease (UCLA)

- 152 patients imaged (112 high risk, 40 intermediate risk)
 - 80 UCLA patients
 - **26/80 (32.5%) with positive PSMA/PET**
 - 8 M1
 - 18 N1
 - 19/80 elected radiation
 - 7/80 on neoadjuvant protocol prior to surgery
- 26 patient with high (21) or intermediate (5) risk prostate cancer
 - NEGATIVE PSMA PET/CT
 - Surgery at UCLA
 - Median PSA 18.5 (4.5-75.4 ng/ml)
- **8/26 (31%) had histologically confirmed lymph node metastases**
 - NPV = 65%

Does or will PSMA imaging IMPROVE outcomes?

- How does it or should it change how we practice?
 - Biochemical Recurrence:
 - Delay salvage radiation until site of recurrence can be located?
 - Use hormones with radiation to offset possible risk of waiting until PSA >0.2?
 - How should radiation fields be changed?
 - Salvage lymphadenectomy?
 - In whom?
 - How far do we go—retroperitoneum, peri-rectal?
 - Surgery to downstage plus radiation?

How does or should molecular imaging change how we practice?

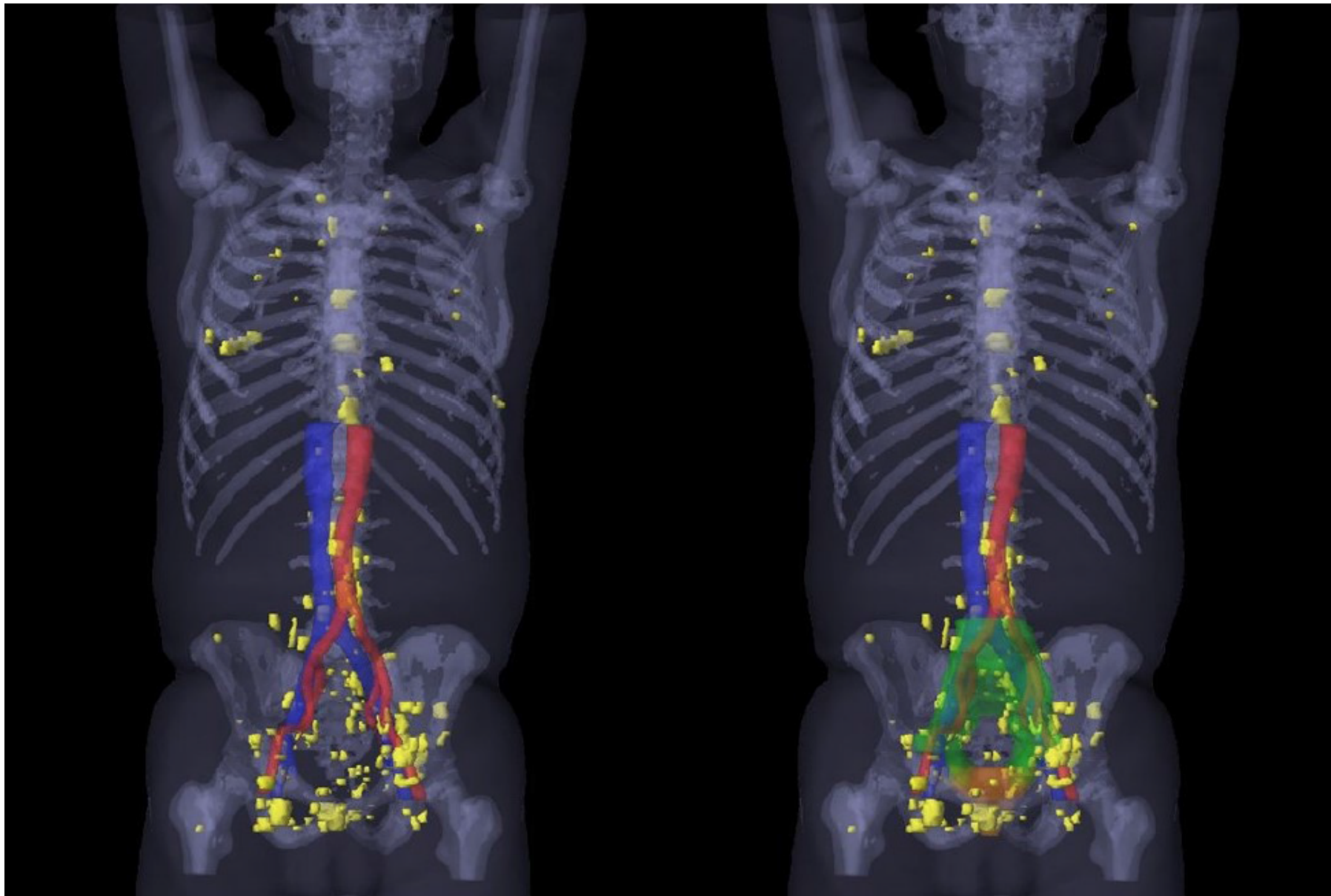
- High Risk:
 - No surgery if positive lymph nodes? Should surgery be abandoned in favor of radiation and ADT?
 - Surgical resection or SBRT to sites of PSMA positivity?
 - Earlier use of chemotherapy/enzalutamide?
 - Should we even change what we have always done without PSMA PET?
 - Was ignorance bliss?
 - How about the PSMA negative patient given significant undetection rate?

Response after PET-guided therapy

- 23 patients received salvage surgery or radiotherapy targeting PET-positive lesions

Outcome	n	%
PSA undetectable	7	30
PSA decrease >50%	11	48
PSA increase/decrease <50%	5	22

Why do patients fail? Underdetection of metastases despite PSMA? (yes) Wrong template for radiation or surgery? Inherent resistance to radiation or insufficient dose?



52/270 (19%) patients with recurrence outside the standard salvage radiation template (Green is pelvic template and orange is prostate bed template)

Phase III randomized trial of ⁶⁸Ga-PSMA-11 PET/CT molecular imaging for prostate cancer salvage radiotherapy planning

<p>Primary Endpoint</p>	<p>Success rate of SRT measured as biochemical progression-free survival after initiation of SRT (Time Frame: from date of initiation of SRT to first occurrence of progression). Biochemical progression is defined by PSA \geq 0.2 ng/mL and rising after completion of SRT (second confirmatory value must be rising and separated by \geq one month).</p>
<p>Secondary Endpoints</p>	<ol style="list-style-type: none"> 1) 5-year progression-free survival rate (from date of initiation of SRT) 2) Metastasis free-survival 3) Initiation of additional salvage therapy after completion of SRT 4) Change in initial treatment intent
<p>Inclusion Criteria</p>	<ol style="list-style-type: none"> 1) Histopathology proven prostate cancer 2) Planned SRT for recurrence after primary prostatectomy 3) PSA \geq 0.1ng/ml at time of enrollment 4) Willingness to undergo radiotherapy. <p>1) Treating radiation oncologist intends to incorporate ⁶⁸Ga-PSMA-11 PET/CT findings into the radiotherapy plan if patient undergoes ⁶⁸Ga-PSMA-11 PET/CT</p>

Phase III randomized trial of ⁶⁸Ga-PSMA PET/CT for prostate cancer salvage radiotherapy planning

Inclusion criteria:

1. Histopathology proven prostate cancer
2. Planned salvage RT for biochemical recurrence after primary prostatectomy
3. PSA > 0.1 ng/ml
4. Willingness to undergo radiotherapy.
5. Treating radiation oncologist intends to incorporate ⁶⁸Ga-PSMA-11 PET/CT findings into the radiotherapy plan (if patient undergoes ⁶⁸Ga-PSMA-11 PET/CT)

Exclusion criteria:

1. Extra-pelvic metastasis on any imaging or biopsy
2. Prior PSMA PET/CT
3. Prior pelvic RT
4. Androgen deprivation therapy (ADT) within 3 months before ⁶⁸Ga-PSMA-11 PET/CT
5. Contraindications to radiotherapy (including active inflammatory bowel disease)
6. Concurrent systemic therapy for prostate cancer with investigational agents.

n = 193

RANDOMIZATION 1:1.13

n = 90

n = 103

Arm 1:

Patient does not undergo ⁶⁸Ga-PSMA PET/CT for SRT planning. Salvage RT will be performed as routinely planned per discretion of the referring radiation oncologist (i.e. +/- prostate bed RT +/- pelvic RT +/- 6 months of ADT). Other imaging is allowed if done per routine care.

n = 90

Arm 2:

Intervention:

Whole body ⁶⁸Ga-PSMA PET/CT

Free for patients. Sponsored by the UCLA nuclear medicine department.

Salvage RT will be performed incorporating the ⁶⁸Ga-PSMA PET/CT information as per discretion of the referring radiation oncologist (i.e. +/- prostate bed RT +/- pelvic RT +/- 6 months of ADT).

50% 'like conventional'

30% pelvic covered

7% pelvic not covered

13% extra-pelvic

Pelvic SRT

PSMA guided Pelvic SRT +/- boost

+/- PSMA guided SBRT +/- ADT +/- chemo

n = 90

n = 13

SRT success rate at 5 years

~ 40% SRT failure

~ 60% SRT success

vs.

~ 20% SRT failure

~ 80% SRT success

Excluded for further analysis

Failure = PSA ≥ 0.2 ng/ml and rising [Time Frame: from date of initiation of SRT to first occurrence of progression]

Other Areas

- PSMA or other PET agent for primary disease detection
 - Is it better than MRI?
 - Does it complement MRI?
 - Can it display tumor volume better?
 - Can it be used to assess response and recurrence after focal therapy?
- PSMA as a theranostic
 - PSMA-lutetium
 - PSMA-actinium
 - Are there better agents? Antibody or antibody fragments?
 - Lots of excitement? Valid? Toxicity? Phase 3 of PSMA-lutetium initiated.

