

Gallium-68 Information Session



Monday, June 13, 2016
SNMMI Annual Meeting

Progress in the past year

- Submission and approval of NDA for Ga-68 DOTATATE
- Progress towards NDA for Ga-68 DOTATOC
- Initiation of collaborative multicenter trial of Ga-68 HBED-CC PSMA

Ga-68 DOTATATE

- NDA filed in summer, 2015
- Granted priority designation in September, 2015
- NDA approval on June 1, 2016

Ga-68 DOTATOC

- IND filed by University of Iowa in 2011
- Multiple studies
 - Biodistribution and repeatability
 - Comparison with In-111 Octreotide
 - Accuracy
 - Change of Management
- Meta-analysis/literature summary almost complete
- NDA should be filed in next 4-6 months

Academic consortium with Ga68-PSMA

- Multicenter trial by academic group
 - File equivalent INDs
 - Utilize the same release criteria for the agent
 - Follow the same protocol including:
 - The same indications
 - The same inclusion and exclusion criteria
 - The same image evaluation criteria
 - The same endpoints and analysis methodology
- File an NDA

68Ga-PSMA Institutions

- Stanford
- UCSF
- UCLA
- Iowa
- Indiana
- Wisconsin
- Vanderbilt
- MSKCC
- Wash U

Others as they
become
approved

Gallium 68 Information Session

1. Advanced Accelerator Applications – *Stefano Buono*
2. Patient Advocate – *Josh Mailman*
3. Eckert & Ziegler – *Hugh Evans*
4. On behalf of NRC - *Steve Mattmuller*
5. NIH - *Corina Millo*
6. Memorial Sloan-Kettering– *Wolfgang Weber*
7. Indiana University - *James Fletcher*
8. Theragnostics – *Pat Donahue*
9. UCSF- *Tom Hope*

6 year view from the trenches -

It's Difficult to Make Predictions, Especially About the Future

Josh Mailman
President NorCal CarciNET Community
COO WARMTH



What are NET Patients Option

In 2007

Only 1 drug for NETs was approved in 1988
1 specific imaging approval

In 2016

3 drugs approved - 2 in the pipeline -
1 imaging approval



We Have Come a Long Way

2008 - No US center with Ga68 for NETs

2011 - First INDs for Ga68

2013 - Orphan drug designation for Ga68

2016 - NETSPOT approved



Ga68 Many People to Thank

AAA - First NDA approved

Ga68 Working Group

Monthly meetings since mw 2012

Bonnie Clarke for leading since annual meeting 2012

JHU and SNMMI for hosting the 3rd Theranostics World Congress in March 2015

70+ patients who attended and voiced
the need for Ga68 in US

FDA who listened



Patients are Overjoyed

Have been desperately seeking any Ga scan for the last 4 years

Post on facebook about NETSPOT generated over 100 responses

Many questions on cost and availability

Quality of scan reading

Little understanding of the complexity of delivery



Education Still Key

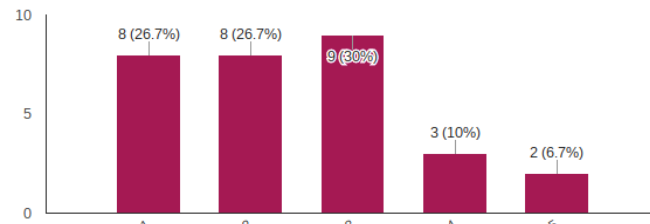
Patients are still concerned about the safety and number of scans they receive.

We have a lot going on - Gallium vs Ga68.

A little education goes along way.

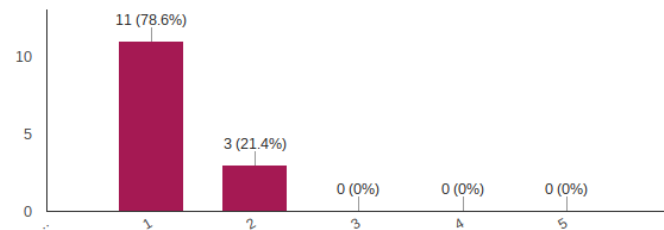
Based on what you know about nuclear scans, how safe do you think they are?

(30 responses)



Based on what you know about nuclear scans, how safe do you think they are?

(14 responses)



Thank you



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Josh@nextobject.com



GalliaPharm[®] Radionuclide Generator

NETSPOT[™] Using
GalliaPharm[®] As Source For ⁶⁸Gallium

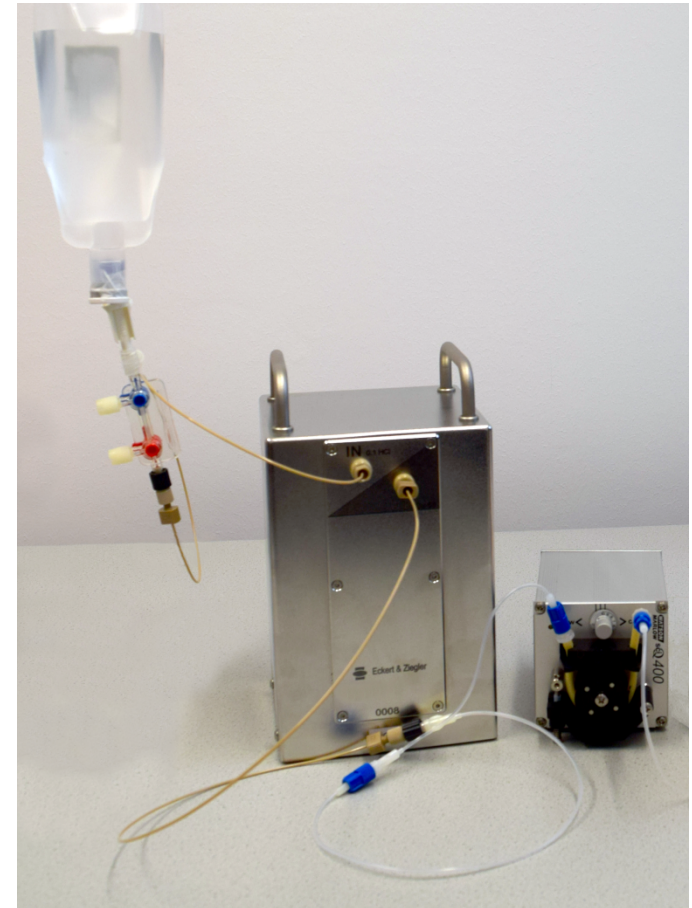
Please contact us at radiopharma@ezag.de



- Only generator registered as medicinal product in several countries of the European Union
- Only generator with a Type II DMF filed with the FDA
- Considered as a drug substance in the USA
- Eckert & Ziegler successfully passed a **FDA audit** as part of the NDA registration process
- Available activities: 20, 30 ,40 and 50 mCi
- Shelf-life: 12 months

Highest product quality and production standards

- GalliaPharm® is produced in a GMP certified facility under aseptic conditions
- Elution with Sterile, ultra pure hydrochloric acid 0.1 mol/l
- HCl is part of the registration and provided by Eckert & Ziegler
- **^{68}Ge breakthrough ≤ 0.001 %**
- Eckert & Ziegler is offering return and disposal of the GalliaPharm®



The GalliaPharm[®] eluate complies with the following specifications (excerpt):

Test parameter	Specification
Appearance	Clear, colorless solution
Identity ⁶⁸ Ga	Half-life 62–74 min
Content	> 60 % of nominal activity
Chemical impurity	Fe < 10 µg / GBq Zn < 10 µg / GBq
Radionuclidic purity (γ-emitting impurities)	< 0.001 % of nominal activity
Radiochemical purity	> 95 % free ⁶⁸ Ga ³⁺
pH	0.5–2.0
Microbiological quality	Sterile
Bacterial endotoxines	< 30 EU / ml

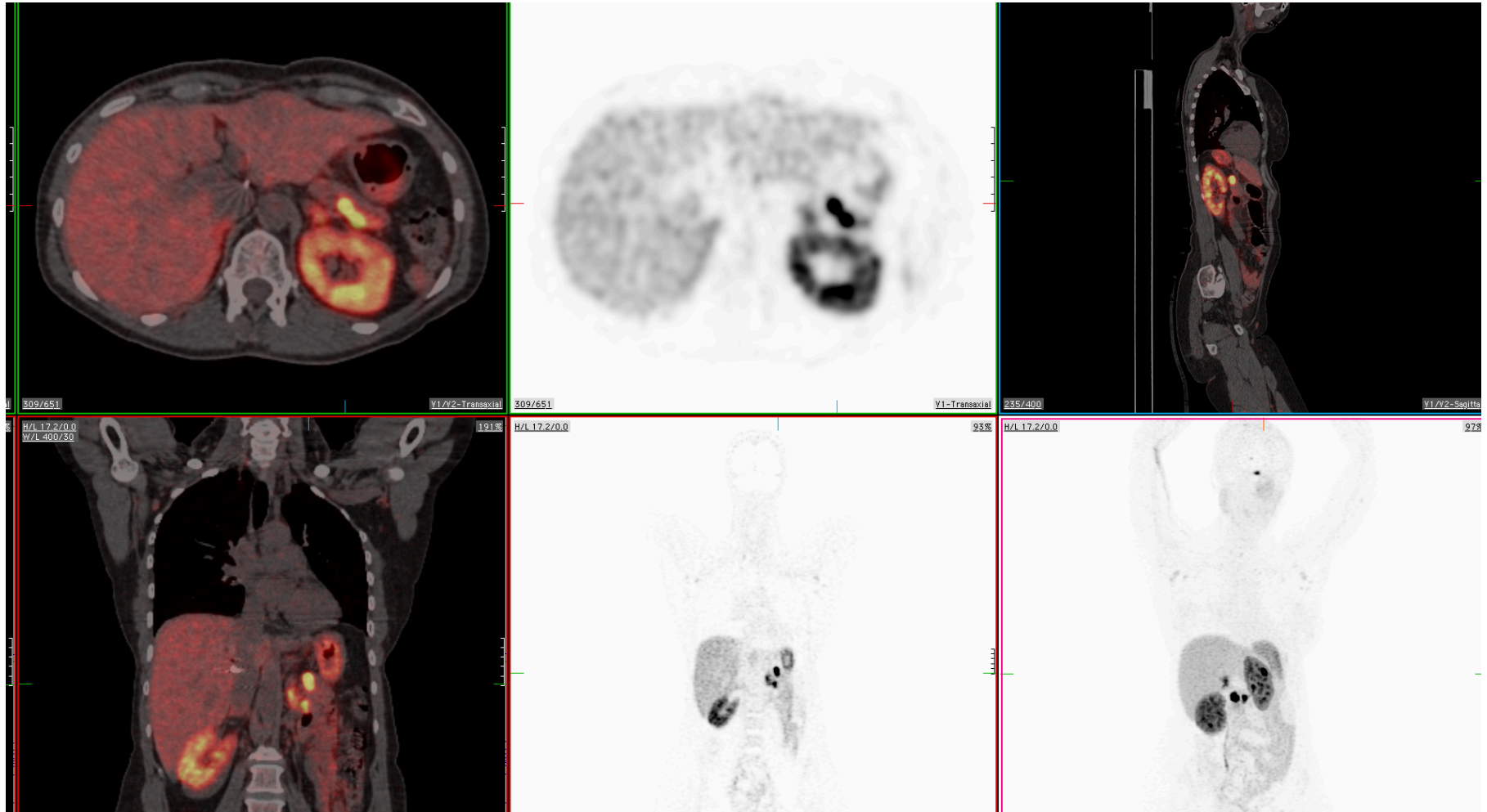
- **NETSPOT[™] is currently only approved for use with the GalliaPharm[®] ⁶⁸Ga generator**
- Other kits and ⁶⁸Ga based tracer are under development / clinical trial using GalliaPharm[®]
- Risk of kit usage: In the long run, frequent and daily manual handling of kits will lead to high hand doses

Eckert & Ziegler is working on an automated solution for kit handling, minimizing radiation exposure for users.

^{68}Ga -DOTATATE in NIH/CC

- Started in Oct. 2013
- 430 doses+297/416 scans+280/360 patients+265
- 56 FU scans+15
- 14+17 (31) doses for γ -probe guided intra-abdominal surgery
- Dose= 5 mCi; range=2.5-5.5 mCi
- Scan time= 5 min/FOV
- 4 protocols
- Estimated change in management 33%-may decline due to protocol change
- Safety is superb; one non-unanticipated adverse event
- Waiting list around 2-3 months: *abolished*

Low dose ^{68}Ga -DOTATATE PET



Protocols

- **1. Evaluation of 68Gallium- DOTATATE PET/CT for detecting primary (not metastatic) neuroendocrine tumors; includes VHL,MEN-1, no longer TIO):**
180 patients+**163**=**343** patients (12FU)
*in patients with biochemical evidence of neuroendocrine tumor:
elevated Chromogranin A, Pancreatic Polypeptide, NSE, VIP, Serotonin/5-HIAA, gastrin, SST, CC, metanephrines, calcitonin, fasting insulin, C-Peptide, glucagon
*and/or familial predisposition of NET: MEN1 and VHL, symptomatic or asymptomatic, with biochemical or anatomic evidence of disease
- **2. Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytoma and Paraganglioma:** 102 patients+**80**=**182** patients (3FU)
- **3. Evaluation of ⁶⁸Ga -DOTATATE PET/CT, ¹¹¹In-Octreotide SPECT/CT, and F-DOPA PET/CT Imaging in Patients with Ectopic Cushing Syndrome:**
16 patients+**9**=**25** patients
- **4. Natural History of Familial Midgut Carcinoid Tumor: ¹⁸F-DOPA vs. ⁶⁸Ga-DOTATATE PET/CT:** 62 patients+**13**=**75** patients

Evaluation of ^{68}Ga -DOTATATE PET/CT for detecting primary and metastatic neuroendocrine tumors

- *^{68}Ga -DOTATATE PET/CT compared to ^{111}In -pentetreotide SPECT/CT, CT/MRI and pathology*
- *180 patients with baseline scans/56 with FU scans/40 patients had surgery*
- ***Eligibility:** patients with suspicious lesions on other imaging modality*
metastatic gastrointestinal or pancreatic neuroendocrine disease
metastatic disease with unknown primary tumor
patients with biochemically active disease
- *^{68}Ga -DOTATATE PET/CT detected 95% of lesions*
- *CT/MRI detected 45.3%*
- *^{111}In -pentetreotide SPECT/CT detected 30.9%: **no longer included***
- *In 4/14 (28.6%) patients, ^{68}Ga -DOTATATE PET/CT found previously unknown primary tumor*
- *33% of patients had change in management recommendation*
- *“Awaiting results of γ probe guided surgery”: lesion-based detection rate of ^{68}Ga -DOTATATE γ -probe and CT/intraoperative visualization is 71% versus 57%.*

Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytomas and Paragangliomas

- 102 patients/360; includes children 10 yo and above
- Evaluates performance of CT/MRI, F-DOPA, F-DA, F-FDG and Ga-DOTATATE PET/CT in patients with sporadic and hereditary (mostly SDHx related) PGL and Pheochromocytomas
- In the metastatic Pheo/PGL group, both sporadic and SDHB related, and in Head and Neck PGL (mostly SDHD related), Ga-DOTATATE PET/CT was able to detect approximately 15% more lesions than (F-FDG+F-DA+F-DOPA+ anatomical imaging) combined
- Change of treatment based on additional information on Ga-DOTATATE PET/CT estimated at 20%

Feasibility of Radio-Guided Surgery with ^{68}Ga -DOTATATE in Patients with Gastro-Entero-Pancreatic Neuroendocrine Tumors

Samira M. Sadowski, MD¹, Corina Millo, MD², Vladimir Neychev, MD, PhD¹, Rachel Aufforth, MD¹, Xavier Keutgen, MD¹, Joanne Glanville, MD¹, Meghna Alimchandani, MD³, Naris Nilubol, MD, FACS¹, Peter Herscovitch, MD², Martha Quezado, MD³, and Electron Kebebew, MD, FACS¹

¹Endocrine Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; ²Positron Emission Tomography Department, Warren Grant Magnusson Clinical Center, National Institutes of Health, Bethesda, MD;

³Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD

ABSTRACT

Background. Surgery is the only definitive therapy for gastro-entero-pancreatic neuroendocrine tumors (GEPNETs), and achieving complete tumor resection is an important prognostic factor. Radiopharmaceuticals such as ^{68}Ga -DOTA peptides have been developed that offer superior accuracy for localization of GEPNETs. The study aim was to determine the feasibility of radio-guided surgery (RGS) using ^{68}Ga -DOTATATE in patients with primary and recurrent GEPNETs.

Methods. Fourteen patients with GEPNETs were enrolled onto a prospective study to determine the feasibility of RGS with ^{68}Ga -DOTATATE. Findings from preoperative imaging, intraoperative exploration, RGS, and pathology were analyzed.

Results. The median decay corrected target count rate was 172.6 (range 28.15–2341) for tumors, with a tumor-to-background ratio (TBR) of 4.46 (range 1.6–43.56). The median lesion size was 1.55 (range 0.5–15) cm. There was no significant correlation between preoperative imaging maximum standardized uptake value (SUV_{max}) of the lesions and TBR (Spearman $r = -0.01$, $p = 0.9$), TBR and tumor size (Spearman $r = 0.29$, $p = 0.14$), and SUV_{max} and tumor size (Spearman $r = 0.22$, $p = 0.28$). The probe showed correct identification for gastric and small intestine neuroendocrine tumor (NET), including

lymph node metastasis in 17 (81.0 %) of 21 cases, with a median TBR of 3.5 (1.6–40.2). For pancreatic NETs and lymph node metastasis, 16 (66.7 %) of 24 were correctly identified by RGS.

Conclusions. Our study shows that RGS with ^{68}Ga -DOTATATE is feasible and correctly confirms bowel NETs and metastatic mesenteric lymph nodes. Further studies are needed to determine the benefit of RGS with ^{68}Ga -DOTATATE.

The incidence of gastro-entero-pancreatic neuroendocrine tumors (GEPNETs) has increased to about 7.8 cases per 100,000 persons each year, and the prevalence is approximately 35 cases per 100,000 persons.^{1,2} Surgical resection is the only curative treatment option for patients with early-stage disease, and complete tumor removal is an important prognostic factor in patients with GEPNETs. A recent consensus statement emphasized that resection should be the first-line treatment option for patients with advanced GEPNETs if at least 90 % of the disease burden is resectable.³ Also, the presence of metastatic disease and tumor grade are important prognostic factors.^{4,5} Thus, an accurate assessment of the extent of disease before surgical therapy and confirming complete resection of disease is important. Further, in patients with recurrent/persistent locoregional GEPNETs, a reoperation can be challenging because of scar tissue, inflammation, altered anatomy, or low volume of disease. In some patients with functioning primary localized GEPNETs (e.g., gastrinoma, insulinoma), small primary or locoregional disease can be



Memorial Sloan Kettering
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^{68}Ga -labeled radiopharmaceuticals at MSKCC

June 13, 2016

Wolfgang Weber, Serge Lyaschenko



MSKCC INDs for Gallium pharmaceuticals

Open protocols

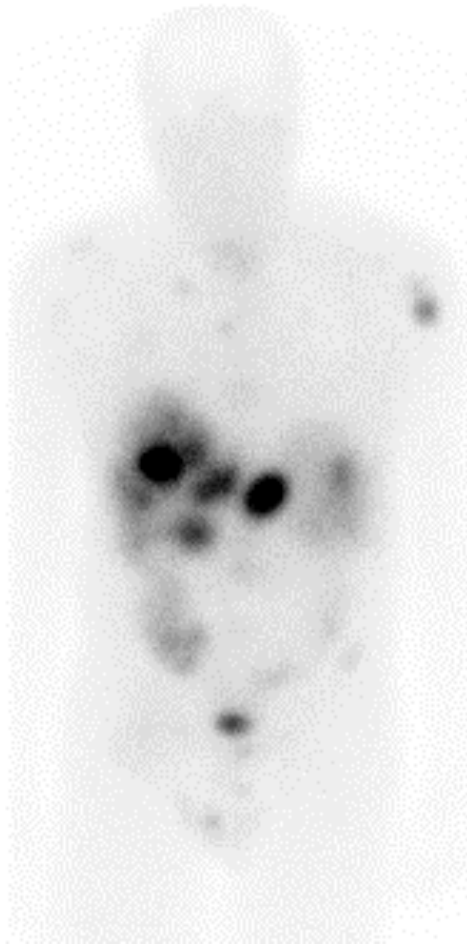
- ^{68}Ga -DOTA-TOC – NETs (cost recovery, 12 months to open)
- ^{68}Ga -PSMA – recurrent prostate cancer
(^{68}Ga -HBED-CC-PSMA, ^{68}Ga -PSMA-DFKZ, ^{68}Ga -PSMA-11, “Heidelberg compound”)
- ^{68}Ga -DOTA-JR11 (somatostatin antagonist) - NETs
- ^{68}Ga -DOTA-RM2 (GRPr antagonist) – primary prostate cancer

Protocol in preparation

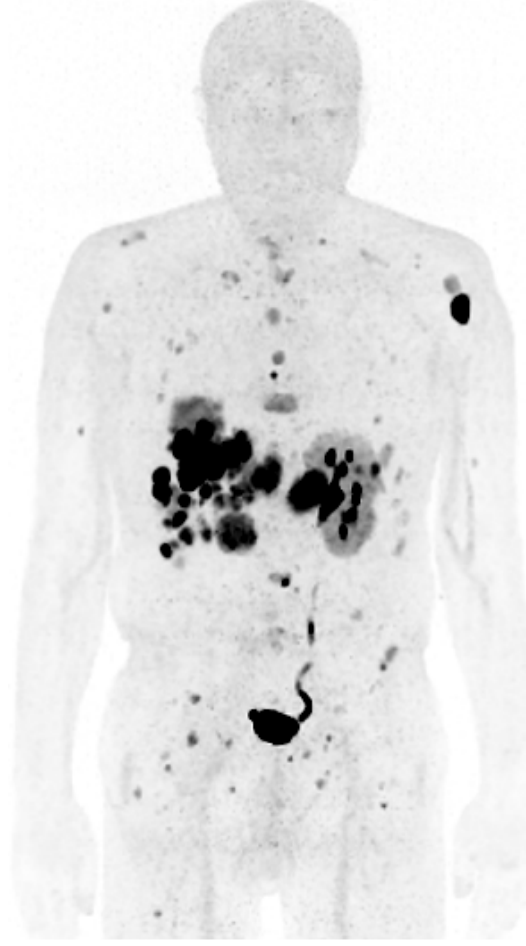
- ^{68}Ga -Pentixafor



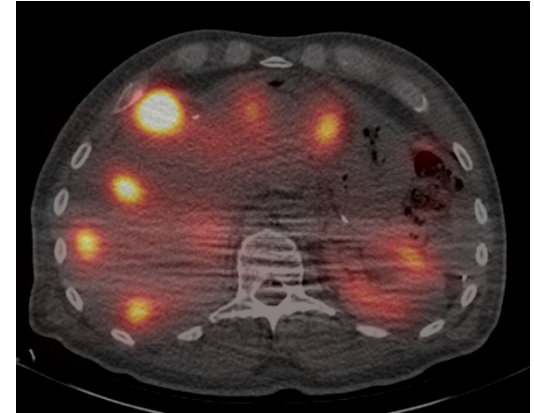
Comparison with Octreoscan Pancreatic NET



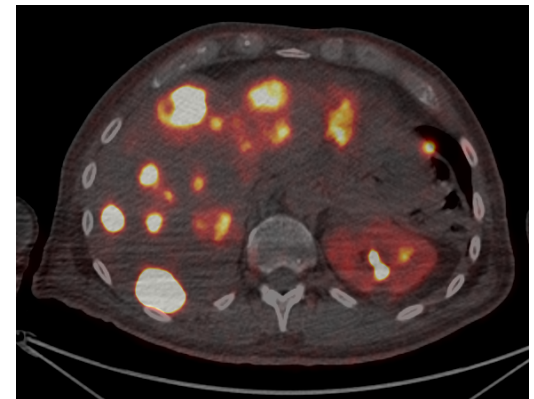
Octreoscan 24 h
(planar)



^{68}Ga DOTA-JR11 1 h
(MIP)



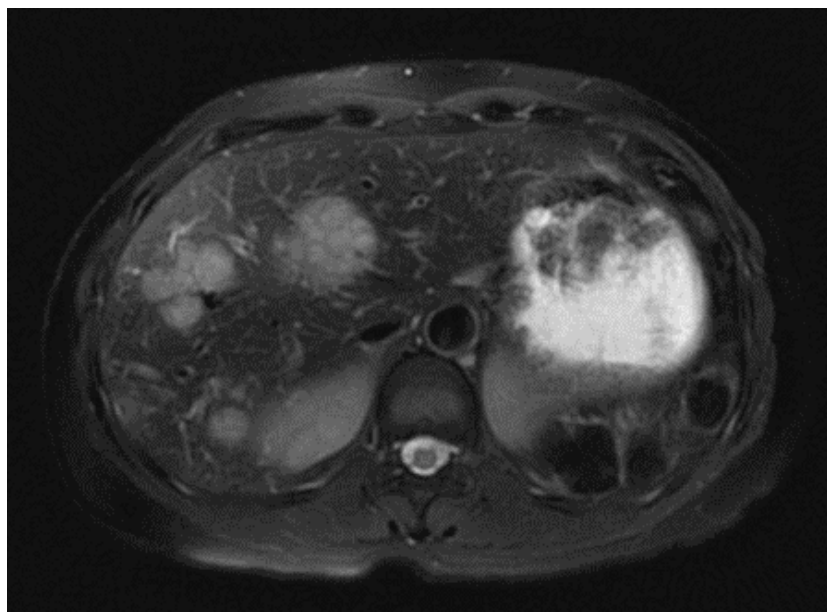
Octreoscan



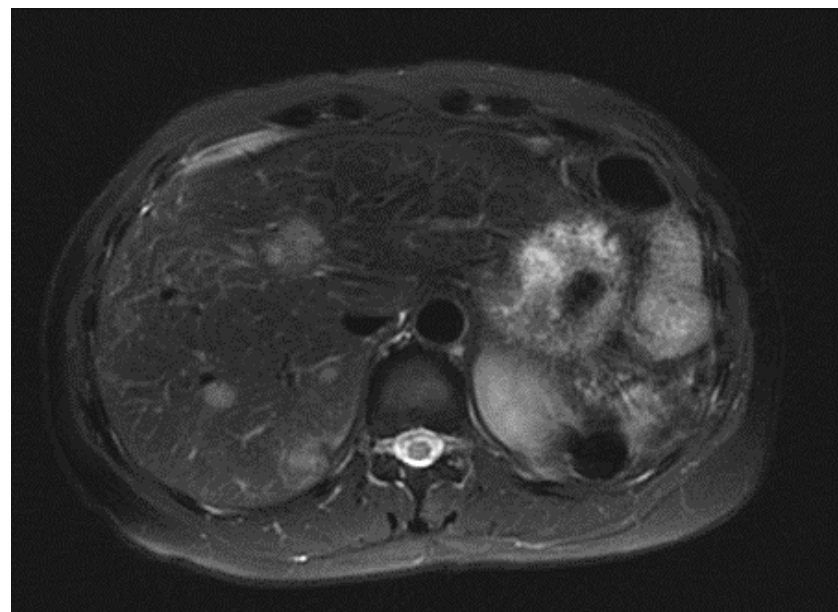
^{68}Ga DOTA-JR11 1 h



^{68}Ga -JR11/ ^{177}Lu -JR11 Theranostics



Before therapy



200 mCi ^{177}Lu JR11

120h

96h

24h

4h

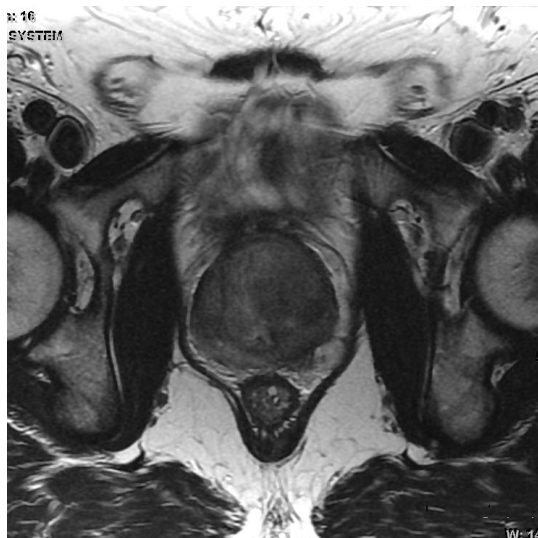
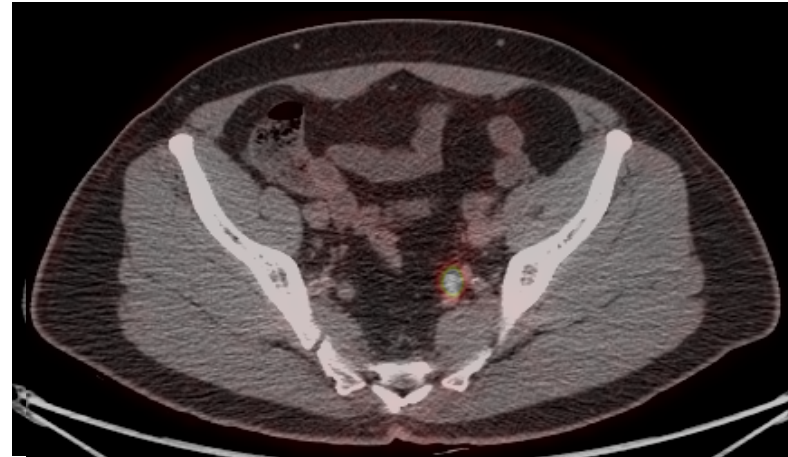
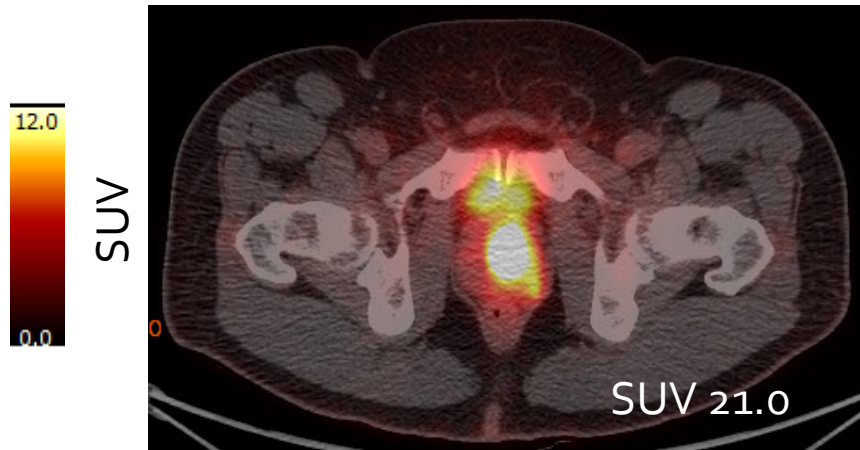
^{68}Ga DOTA-JR11 1 h
(MIP)

^{177}Lu -DOTA-JR11

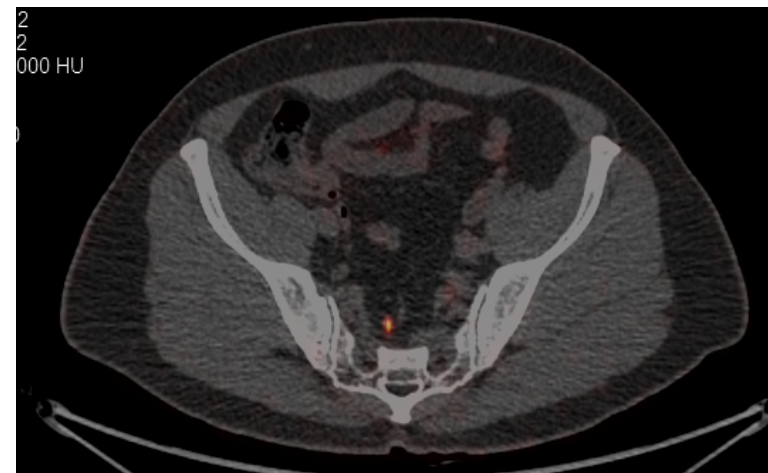


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GRPr-PET/CT and MRI in Gleason 9 prostate cancer



T2 MRI





Comparison of ^{68}Ga -PSMA and ^{11}C acetate in Recurrent Prostate Cancer: Pilot study with same day imaging

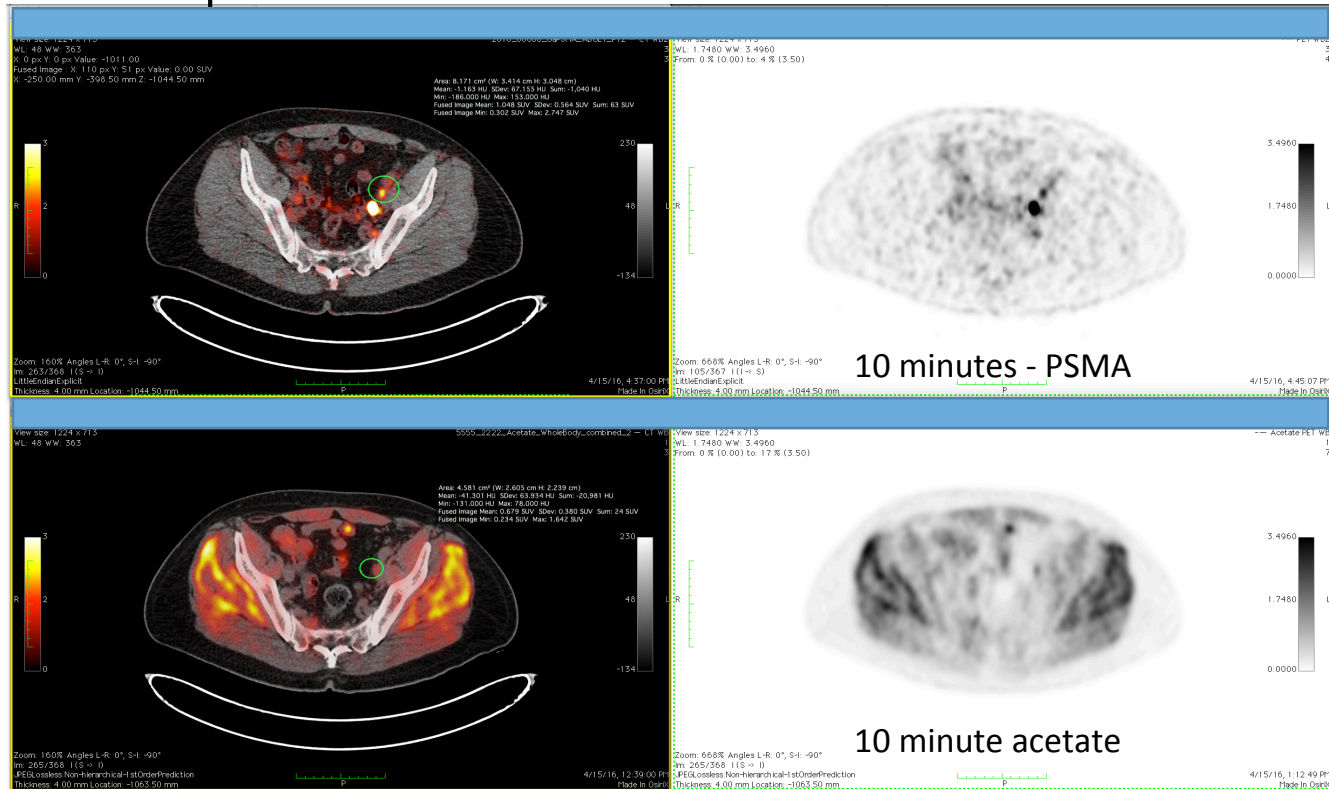
James W. Fletcher, M.D., FACR

Division of Molecular Imaging and Therapeutics, Department of Radiology
and Imaging Sciences, Indiana/Purdue University, Indianapolis, IN

Another ^{68}Ga - xxxx



Comparison of ^{68}Ga -PSMA vs. ^{11}C -acetate



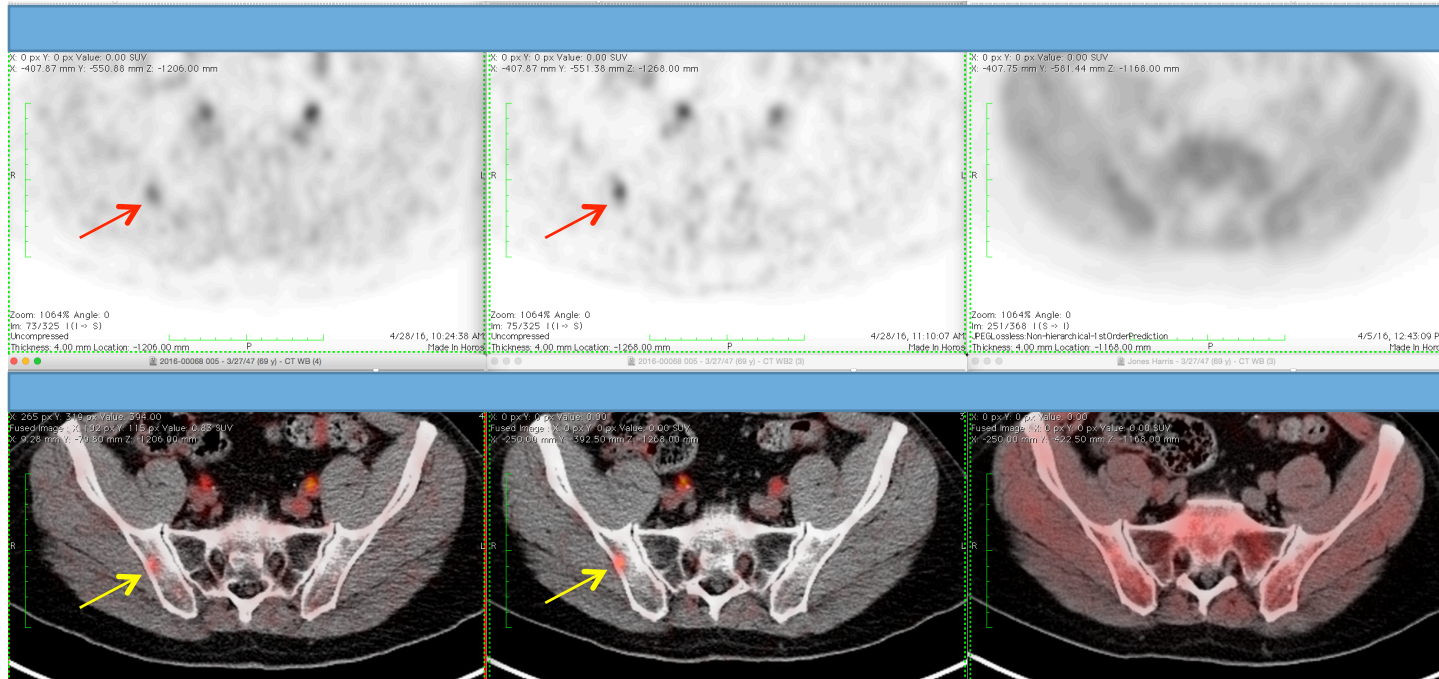
PSA = 0.3 PSMA shows “+” lymph node left pelvis - SUV = 2.7
 Acetate scan shows questionable faint uptake - SUV = 1.6

Comparison of ^{68}Ga -PSMA vs. ^{11}C -acetate

10 minutes - PSMA

40 minutes - PSMA

10 minute acetate



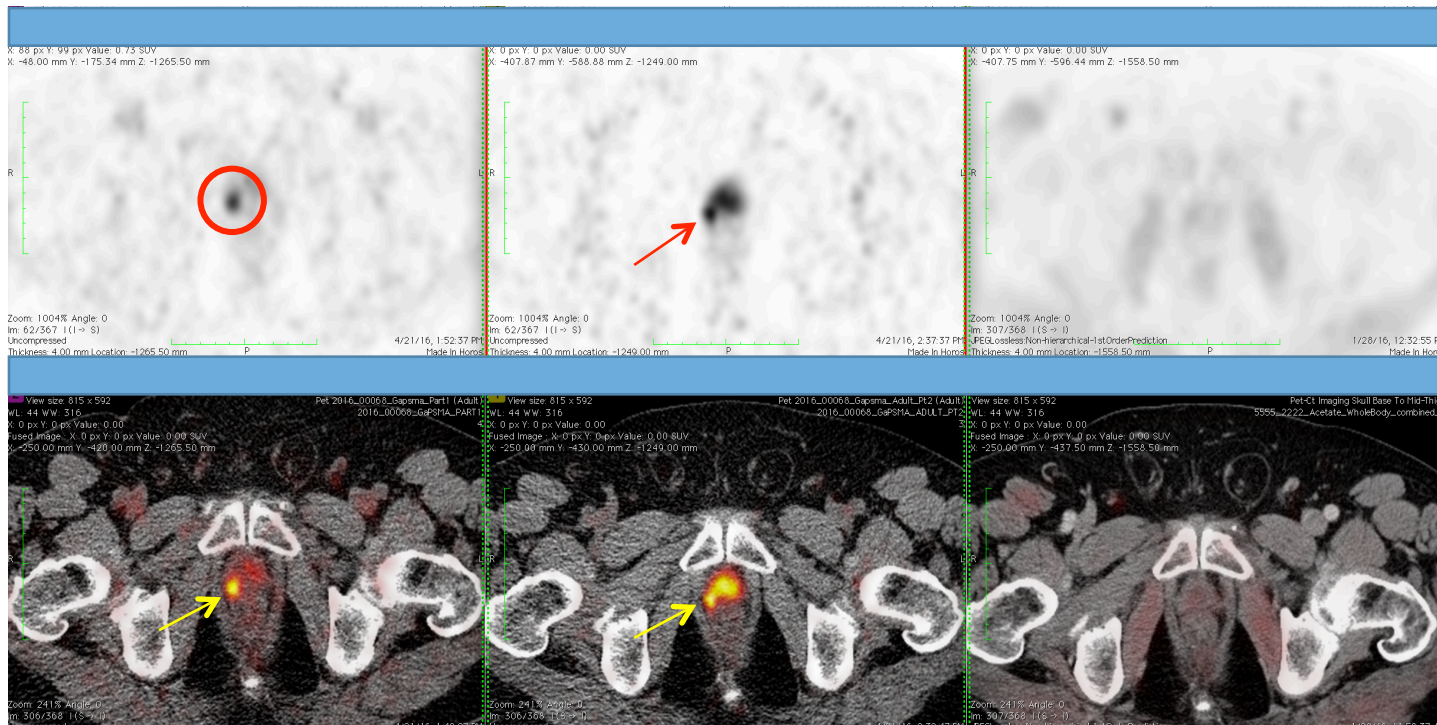
PSA = 11.3 Focus of uptake in R pelvis
Not identified on ^{11}C -acetate exam

Comparison of ^{68}Ga -PSMA vs. ^{11}C -acetate

10 minutes - PSMA

40 minutes - PSMA

10 minute acetate



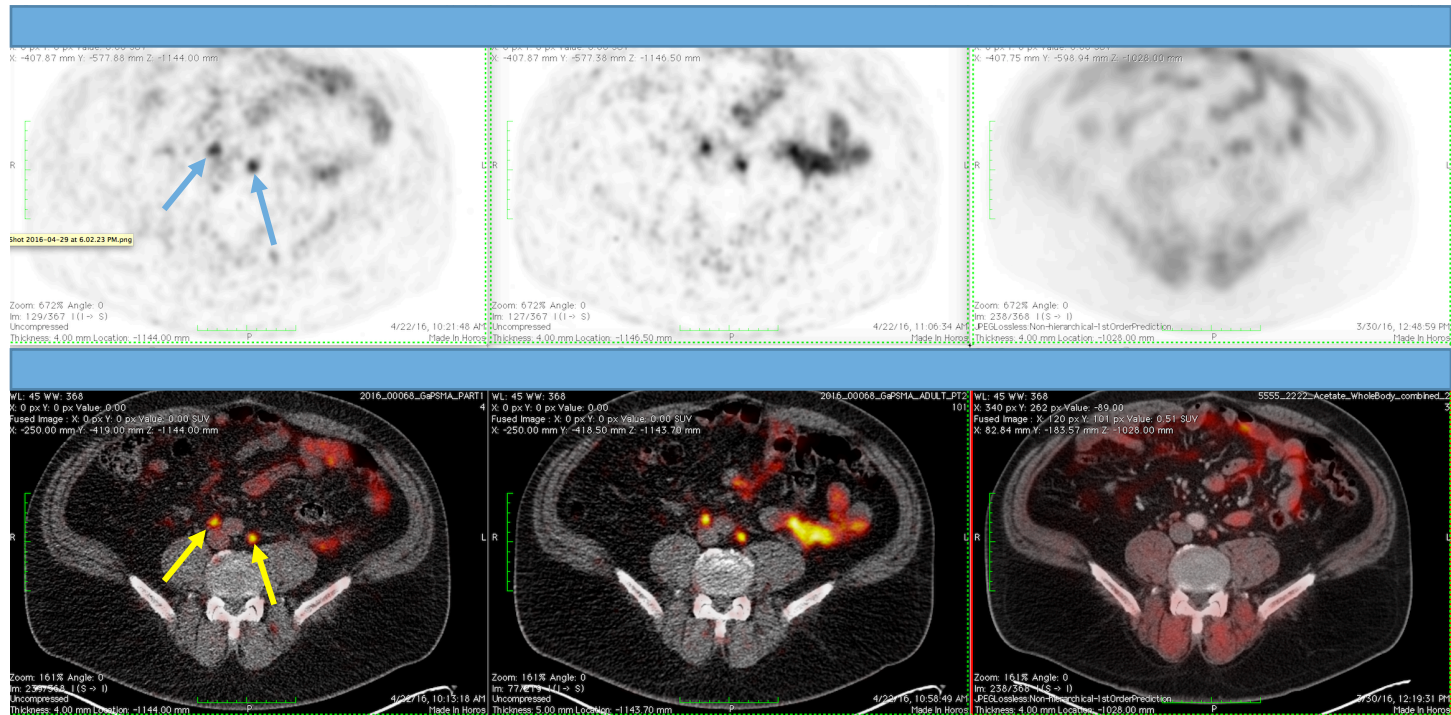
PSA 0.52 Peri-vesicular focus on PSMA – SUV 10
Not seen on ^{11}C acetate scan

Comparison of ^{68}Ga -PSMA vs. ^{11}C -acetate

10 minutes - PSMA

40 minutes - PSMA

10 minute acetate



PSA = 1.7 PSMA shows retroperitoneal lymph nodes
Acetate shows vague mild uptake



Preliminary Observations

- 10 minute PSMA images typically provide necessary information compared to delayed 40 and 90 minute images
- PSMA has lower uptake in reactive lymph nodes and soft tissues
- PSMA performs well at lower PSA and with smaller lymph nodes
 - Positive exams with PSA < 1.0 and nodes < 1 cm
- Contrast enhanced CT provides additional information in characterization of lymph nodes as benign or malignant
 - Involves comparison with prior CE CT exams and changes in size or presence or absence of enhancement



Acknowledgements



- Mark A. Green, Ph.D.
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- Wendy Territo, B.S., CNMT, ARRT
- Heather Polson, B.S., CNMT
- Mark A. Tann, M.D.

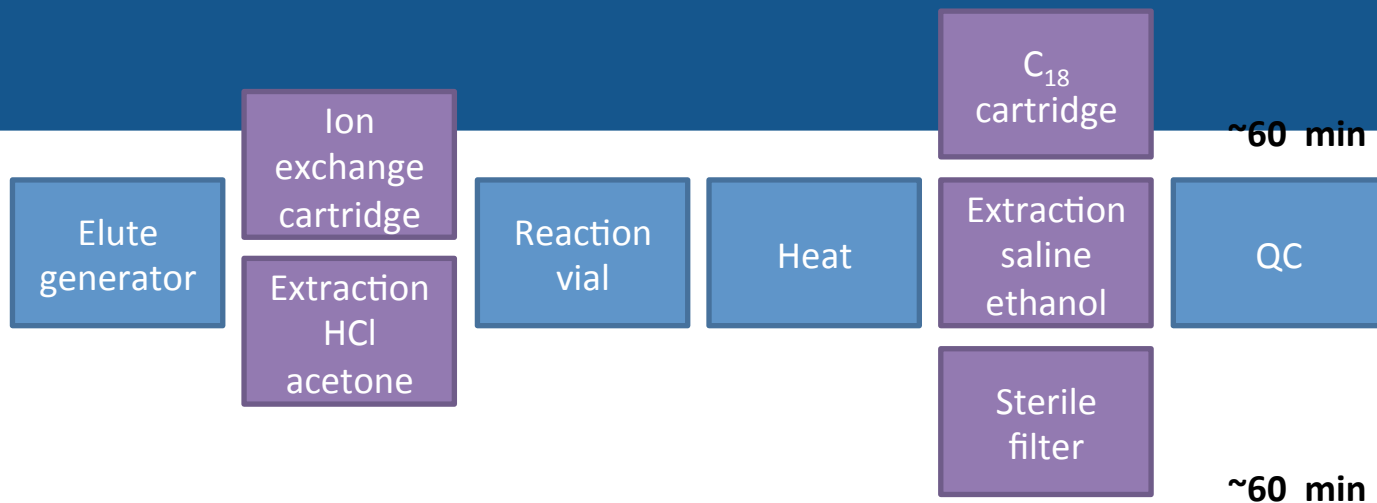


Introduction to Ga-68 specific THP Chelator and Ga-68 PSMA Kit

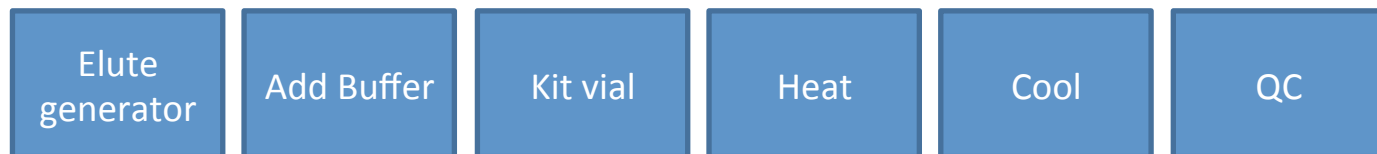
- Pat Donahue, Consultant, Blackthorn Associates
 - Greg Mullen, CTO, Theragnostics

THP Technology – a “Game Changer” for Ga-68

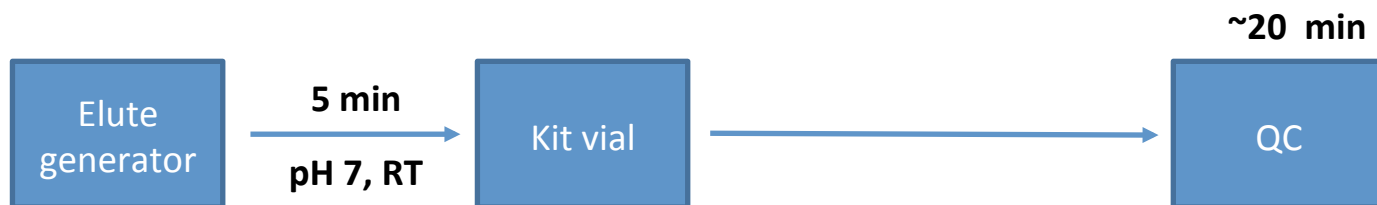
Semi-Automated Synthesis (e.g. DOTA, HBED)



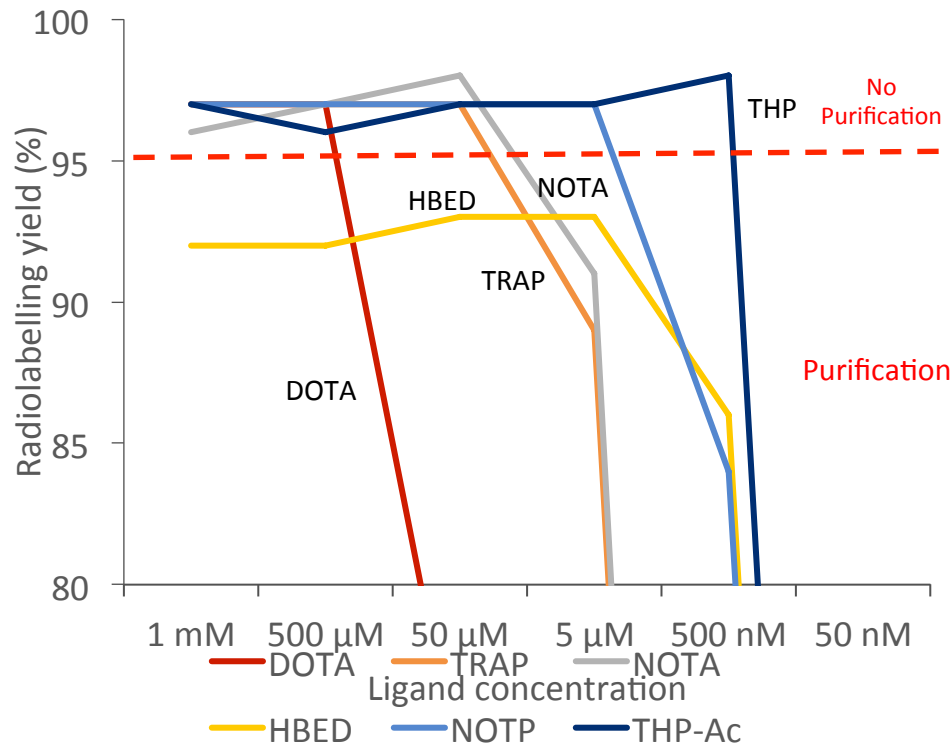
Two Step Kit (e.g. DOTA, HBED)



THP One Step Kit

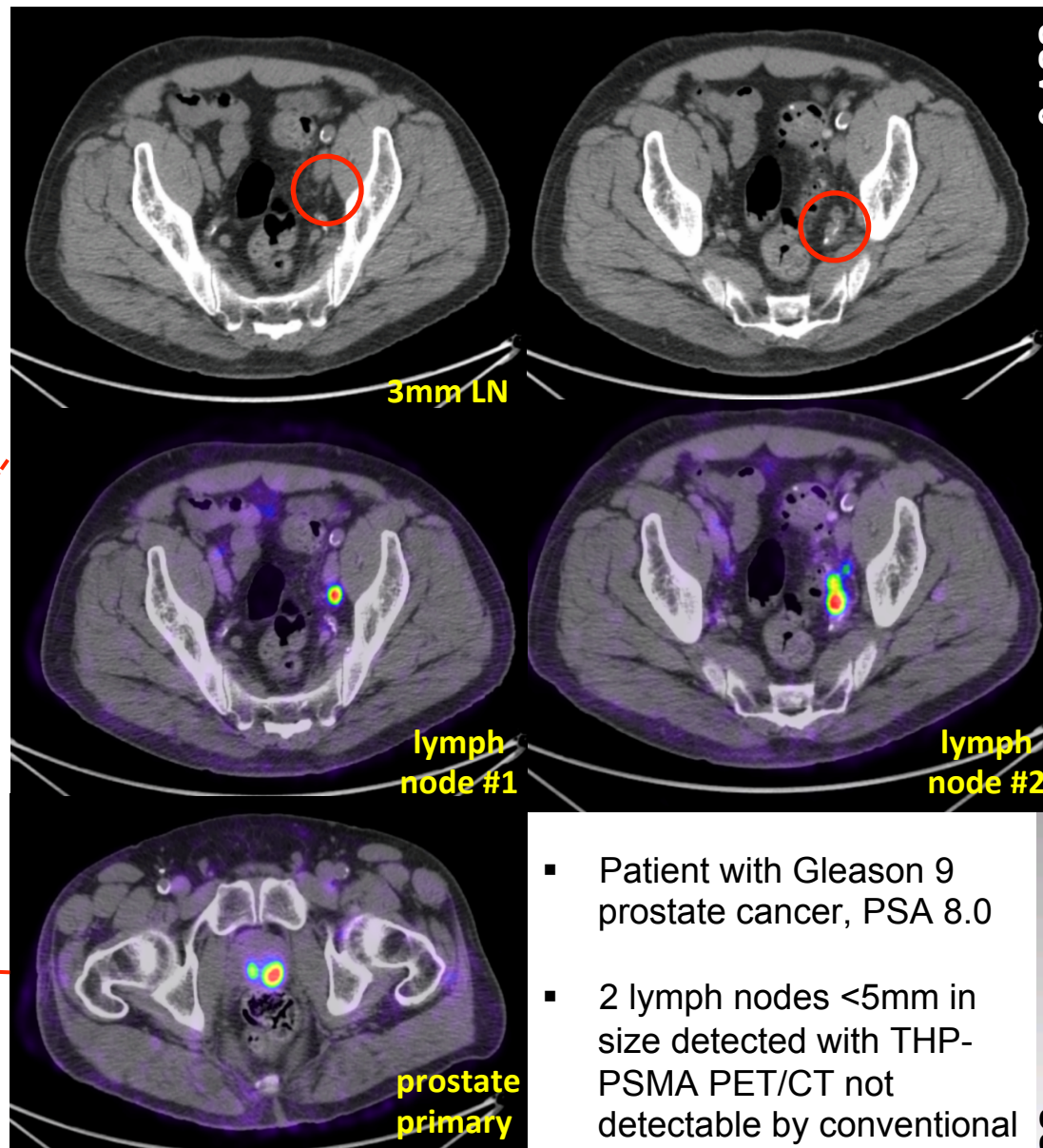


THP Technology – a “Game Changer” for Ga-68



Standardized radiolabelling conditions:

- Room temp
- pH 7
- 10 min incubation time
- ITLC and HPLC analysis
- Same generator eluate sample
- THP still best at pH 4.0
- THP still best with 90°C heating



3mm LN

lymph
node #1lymph
node #2prostate
primary

- Patient with Gleason 9 prostate cancer, PSA 8.0
- 2 lymph nodes <5mm in size detected with THP-PSMA PET/CT not detectable by conventional imaging

^{68}Ga -THP-PSMA PET