C-11 Acetate Prostate Cancer Imaging

- High Country Meeting “Spring” 2014
- Mark Tann, Indiana University
DISCLAIMER

- Have not written any research paper on C-11 acetate imaging
- Can only relay initial experience of getting into routine clinical use of C-11 acetate, our “N” is pretty small
- More experienced Acetater couldn't make it
1 man in 6 will be diagnosed with prostate cancer during his lifetime.

238,590 new cases of prostate cancer will be diagnosed

29,720 men will die of prostate cancer

3% fatal

1 in 8 (12%) women in the US will develop invasive breast cancer during their lifetime.

232,340 new cases of invasive breast cancer will be diagnosed in women.

39,620 women will die from breast cancer

3% fatal

Prostate Cancer

Breast Cancer
Autopsy studies indicate that 50% of men older than 50 years of age have prostate cancer.\(^1\),\(^2\)

In the United States and Canada, the likelihood of being diagnosed is approximately 18%.

The estimated lifetime probability of dying as a result of prostate cancer is 2.8%.\(^3\)

The incidence-to-mortality ratio is 6.4. The most common cause of death in men diagnosed with prostate cancer is cardiovascular disease.

Men with well-differentiated tumors rarely die from their disease and that men with poorly differentiated tumors frequently die within 5 to 10 years of diagnosis, often despite aggressive interventions.

Men with moderately differentiated tumors have the greatest variation in outcomes.
Initial staging/detection- PSA/TRUS model

Controversies and “Potential” Solution

- Missed
- Over sampled
- False elevated Gleason score

- Missed
- Under sampled
- False low Gleason score

NO population benefit of PSA screening, PSA>4, TRUS and Tx, 9/10 pts with low grade disease elect for aggressive Tx = higher mortality/morbidity and cost in screened population…USpreventivetable.com….
Initial staging/detection

Controversies and “Potential” Solution

Using multi-parametric MRI to better identify, location and extent of prostate cancer, fuse MRI data with US to perform targeted TRUS more accurate bx and guide/assess potential local therapies, especially for intermediate grade where therapy “can” affect outcome.
3D MRI guided Prostate BX
Role PET/MR for initial detection?
Role PET?MR for initial detection?
PET vs MRI for Initial staging of Prostate Cancer

- All tumors greater than 0.5 cm, revealed a sensitivity and specificity of 61.6% and 80.0%, respectively, for $^{11}$C-acetate PET/CT and 82.3% and 95.1%, respectively, for MRI.

- The $^{11}$C-acetate accuracy was comparable to that of MRI when only tumors greater than 0.9 cm were considered.

- Beware BPH

- Maybe PET/ MRI ? potential

Todays Focus: Biochemical Failure

Occurs in 30-50% of pts during the first 5 years of surgery/Radx = rising PSA

Post surg -0.2 ng/mL and 0.4 ng/mL
Post Radx- 2ng/ml above nadir.

Doubling times in months as predictor of survival
<3, 3-9, 9-15, >15.

1/3 of pts with BF will develop metastatic disease within 8 years,
Fifteen-year actuarial Kaplan-Meier prostate cancer–specific and all-cause estimated risk of death among patients with a prostate-specific antigen (PSA) recurrence after radical prostatectomy. Impact of PSA doubling time

A = all

B < 3m

C > 3 < 9m

D > 9m < 14m

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D0 disease challenges: Categorize Prostate Cancer treatment failure

- Systemic disease - Systemic Therapy
- Localized disease – Localized therapy
- Diagnosis of local recurrence
- Exclusion of distant disease
- Therapy monitoring

BF =
- ~30% Locally recurrent disease only
- ~25% Metastatic disease only
- ~45% Locally and Metastatic disease
Dilemma/Controversies

- How and when to treat BF?
- When and which local salvage therapy (radx/surgery).
- When and which systemic therapy - ADT (i-ADT), peripheral androgen blockade, DNA vaccine, chemotherapy (Avastin), Acai juice
- Endpoints? PSA level vs survival or metastatic free survival.
Dilemma's

- Having a Lab test that is more sensitive than imaging study may be problematic.
- Excellent sensitivity - difficult to manage (eg, TGB).
- Desire to *aggressively* treat a lab test finding to reduce Pt (and MD) anxiety instead of *appropriately* treating Pt.
Imaging prostate cancer local recurrence

- Is imaging able to detect and localize recurrent disease at low PSA levels <2
- Is it really necessary to obtain imaging or histological proof before treatment??
- Only 10-30% of pts have “locally only” recurrent disease, EBRT best given at low PSA <1.5, treat everyone – complications?
- Sensitivity of TRUS anastomotic bx 40-70%
- MR sensitivity for local recurrence 52-82%
- C-11 acetate and Choline-11?
- Prostascint – very low - don’t bother
Imaging Tools:

- Bone disease = Bone scan Tc-MDP, Na/F-PET/CT scan, CT scan, MR,
- Adenopathy = CT, MRI, (MRI with Combidex), C11/F18 – Choline, C11/F18 Acetate PET/CT, (SPECT Prostascint)
- C11 choline used in Mayo clinic, FDA Approval (*Proprietary Mayo Synthesis)
- C11 Acetate comparable accuracy as C11 Choline, less bladder uptake, easier to synthesize here. (So why not?)
Mayo PET C-11 Choline prostate imaging, Tips and pearls –Rad Onc

- It is vital to know what is being treated - aim before shooting
- Hormone and/or chemo-refractory (recurrent) prostate cancer is not synonymous with “systemic” prostate cancer, sometimes relapsing prostate cancer is “focal”
Why Acetate at IU?

Dr. Mark Green, Chemist/"Alchemist"

“NO other FDA approved better agent, Already have equipment and experience in making acetate Making Choline $250,000 and more paperwork..”

Why now??

1. RadOnc and Urologists need our help to stop guessing
   Significant unmet clinical need =
2. Opportunity to increase referrals
Both 11C-acetate and 11C-choline appear to be somewhat equally useful in imaging prostate cancer in individual patients, although more comparative data are needed. Disadvantages common to both choline and acetate derivatives are their intestinal uptake [6] and potential nonspecific accumulation in lymph nodes [13].
Potential advantage of Acetate vs Choline with Androgen Deprivation

- $^{11}$C acetate uptake occurs independently of androgens and thus may be more favourable for detecting tumour viability during or following AD.
Problems

- No FDA/CMS approval. IND ?
- Who will pay ?
- Are we allowed to do this ?

Partial/Temporary Solutions

- Practice Of Medicine, USP approved pharmaceutical
- Private Pay Initially, then discuss with Insurers, Subsidized by IUH Health $2,000.
Clinical C11-Acetate in USA

- Clinical Trial in Arizona, N= 120 so far
- U of Kansas

Due to the fact that coverage for this procedure will most likely be denied The University of Kansas Hospital has allowed a significant discount for our patients who must pay out of pocket for this procedure.


Hospital Fee: $3680.00 Professional Fee: $382.00 PET Radiopharmaceutical: $841.00 PET Image Fusion: .00 Total: $4903.00

The University of Kansas Hospital Discounted Rate will be $3000.00 if services are paid in full on the day of the test.
$^{11}\text{C}$ Acetate

- $^{11}\text{C}$ decays by positron emission
- Half life is 20 min
- Has been investigated as a tumor imaging agent
- The “New” Prostascint ??
Acetate

Monocarboxylate transporter

extracellular

intracellular

Acetate

ATP

Acetyl-CoA-Synthase

AMP+PPi

Acetyl-CoA carboxylase (ACC)

Malonyl-CoA

TCA-cycle

Fatty Acid Synthase (FAS)

Fatty Acids

CO₂

Cell Membrane Phospholipids
\(^{11}\)C acetate mechanism of uptake

- Most commonly accepted explanation for increased uptake in tumor cells is increased fatty acid synthesis.
- FAS is over-expressed in many human cancers, particularly prostate cancer.
- Blocking FAS decreases \(^{11}\)C acetate uptake in prostate cancer cell lines.
Investigated uses of $^{11}$C Acetate

- **Cardiac**
  - Measuring myocardial oxygen consumption
  - Evaluating myocardial blood flow

- **Oncologic**
  - Prostate
  - HCC
  - RCC
  - Bladder
  - Brain (predicting grade of glioma)
  - Lung (adenocarcinomas and BAC)
$^{11}$C Acetate and prostate cancer

- Previously investigated in:
  - Detecting primary tumor
  - Staging/Restaging
  - Evaluating lymph node metastases
Role of Acetate in BF

- Fatty acid synthetase expression - phosphatidylcholine, MTC-1 and SMTC-1 transporter
- Very little urinary excretion
- PSA >3ng/mL = 59% true positive
- Better than FDG – 30% vs 9%
- Problem with specificity of Lymph nodes
IU experience - C11 acetate Distribution
S recc in prostate bed and rt groin

Is the disease localized or systemic?

Can it be addressed with local techniques?

PSA 5 pre surg and 0.3 post surg.
Success?
local recurrence, trus neg bx, post salvage prostatectomy nl psa
Rising PSA
Local or systemic ?, local txp ?

- Pos rt pelvic node only 20 nodes bil sampled at surg.
Problems and limitations of acetate in BF- Psa level, spec of nodes.

What are all these nodes, not just ext iliac and groin ?
Problems and limitations of acetate in BF- Psa level, spec of nodes.

- False pos nodes low Psa 2 yrs Psa from 0.07 to 0.57. Small cold groin nodes, prior from 2011 showing stability.
- Ignore ext Iliac nodes and groin?
Problems and limitations of acetate in BF- Psa level,

- False positive nodes low PSA 2 yrs PSA from 0.07 to 0.57 small cold groin nodes, prior from 2011 showing stability
Hx of radx – rising psa - Recurrence in prostate ?

There is focal recurrence in the Prostate ?
There is not focal recurrence in the Prostate ?
There may or may not be recurrence in the Prostate !?
Hx of radx – rising psa - Recurrence in prostate ?

Prostate BX pos ......
Adding insult to injury – all negative nodes, but stable = Prior CT comparison more useful than Acetate PET !!
1-$^{11}\text{C}$-Acetate Kinetics of Prostate Cancer

- Time–activity-curves from iliac arteries (squares, solid line), metabolite-corrected input function (open squares, dashed line), and prostate tumor (triangles, dotted line). Uptake is expressed in SUV (standardized uptake value).

- (A) A 65-y-old man with primary prostate cancer (patient in Fig. 2).
- (B) A 57-y-old man with recurrent cancer; note lower SUV of tumor.
- (C) A 49-y-old volunteer with BPH.

C-11 acetate pharmacokinetics
Average values of kinetic parameters for 3 subgroups: primary and recurrent cancer as well as BPH. Error bar denotes 1 SD. Primary and recurrent prostate cancer show significant differences (*\(P < 0.01\)) for k1 and K.

- Time–activity-curve representing mean of all patients, using iliac artery (purple), prostate tumor (blue), BPH foci (green), and normal prostate (red). Uptake is expressed in SUV. Tumor and BPH foci showed rapid uptake of $^{11}$C-acetate in prostate, peaking at approximately 3–5 min, followed by relative plateau after 10 min.
Rising PSA: Local or systemic? Local txp?
Rising PSA: Local or systemic? Local txp?
Bladder activity, stable groin node
Rising PSA: Local or systemic?
Local txp?

30 nodes submitted, all negative by final path. PSA continues to rise post OP...
Cant always trust path

- Data from Haseebuddin et al, 2013, even if path neg worse outcome for pts inadequte surg resection, no of path slices.
How others have diagnosed prostate cancer on acetate

- **Initial detection** – Oyama et al, n=22 2002, 20 min suv >3.2, good sensitivity-specificity ??

- **Recurrent** disease, Oyama 2003, n=46, dynamic 0-15, static 20 min, criteria ? Dynamic ? Specificity ?

- **Recurrent** 2006, Vees et al, n=11, consensus > background ? sens 66 % spec ?

- **Initial** – mena 2012, n=39, dynamic 6 min then statics every 5 min-25 min, consensus > bg, logan and patlak, mr> pet when lesions, 0.5 cm, sens 89%, spec 90% > .9 cm, bph=ca
How others have diagnosed prostate cancer on acetate

- Initial staging for nodes, Haseebuddin et al, 2013, n=107, static PET 15 min, consensus reading, likert scale, sens – 68%, spec – 78%, PPV – 49%*, NPV 89%

- Recurrence, Bucheger et al, (c11 vs FCH) 2014, n=23, 5, 22, 45 min static scans, pos if hot at 5 and 23 min scan, suv node 4.8 +/- 2.7, 100% spec?

- Initial and recurrence, LN, Hellstrom et al, 2013, n=19, 10 bf, 9 initial, 484 LN’s, sen 90%, spec 67%

Criteria ??

Initial staging for LN’s, Schumacher et al, 2009, n=30, 33%FP, 47%TN, criteria ? Technique ?
Problems so far:

- Can not detect in Post Radx setting recurrent cancer in prostate
- Comparing size of LN’s on serial CT scans is more accurate than C-11 acetate, size=activity
- Bone fractures are also “hot”
Solutions

- Different agents? Choline, PSMA?
- Dynamic scanning? Patlak analysis?
- Use CT or MR characteristics, shape, growth, enhancement, density, signal/proton density/diffusion??
- Meanwhile need prior ct scan to look for interval growth.
Still better than Prostascint

- Rectum vs prostate Bed? NI bone marrow vs Mets,