Why are we so interested in Prostate Cancer?

Prostate Cancer: Incidence and Mortality 2006

- Most common non-cutaneous type of cancer among American men
  - 186,320 cases in 2008

- Second leading cause of cancer death in men in U.S.
  - 234,000 projected cases
  - 27,000 projected deaths
  - Higher rates in African American men (historically, 2.4-fold higher death rate)

Background: Prostate cancer

- Myriad of treatment options and risk stratification
- High rate of recurrence in high risk groups
  - Difficulty in staging initially & with biochemical recurrence
- ProstaScint® scan FDA approved for:
  - Biopsy proven prostate cancer thought to be localized with high risk of lymph node metastases
  - Post-prostatectomy PSA relapse & negative standard metastatic work up with high risk of occult metastases
Primary Therapy Outcomes in Prostate Cancer

- Of the estimated 234,000 new cases in 2006:
  - Approximately 120,000 undergo radiation or surgery
    (10% advanced disease, about 15% cryotherapy, and 20% observation/other)

- Failure rate:
  - 20-40% of patients will recur following curative therapy (historical)
  - 12-15% currently reported by some investigators, as result of earlier intervention after earlier detection*

- Accurate staging is critical to determine appropriate patient management
Prostate Cancer Diagnosis

- Digital Rectal Exam (DRE)
- Prostate Specific Antigen (PSA)
- TRUS Biopsy
Prostate Cancer
Gleason Scoring

Gleason Sum = added sum of 1st and 2nd most prevalent histologies in a biopsy or pathology specimen
“High Risk” Factors for Lymph Node Metastases

- Gleason Sum $\geq 8$, any PSA
- Gleason Sum 7, PSA $\geq 10$ ng/ml
- Gleason Sum 6, PSA $\geq 20$ ng/ml
- Stage T3 disease (not confined to prostate)

These currently utilized “high risk” factors significantly underestimate patients at risk for metastasis.

Prostate Lymph Node Metastases

Lymph node metastasis is underestimated

- Prostate cancer is present in areas not sampled
  - 4.5% of LN in APR for colorectal CA actually prostate CA

- Extended LN dissection does not sample all areas of possible metastasis

- Even after Extended LND progression free rate is low
  - 43% 5 yr progression free rate (Allaf, J Urol 2004)
  - 39% 4 yr progression free rate (Bader, J Urol 2003)
Advances in ProstaScint Imaging

Significant improvements in imaging technology

- Image resolution
- Image processing
- Fusion of functional SPECT with anatomic MRI or CT
- Dual radioisotope fusion

• Clinical evaluation of image guided therapy
  – Brachytherapy
  – IMRT
  – Cryotherapy
Prostate Imaging and Image Fusion

1. Non nuclear imaging (anatomic)
2. Nuclear imaging (functional)
3. Physiologic-anatomic image fusion techniques

What is the status of Prostate imaging today?
Helpful Clinical Data

- Adequate patient history – When diagnosed with prostate cancer, Gleason score, prior therapy
- PSA levels – pretreatment, nadir, and present level
- Reason for doing scan – pre-surgery, post therapy looking for recurrence in pelvis, extra pelvic spread. Help tailor therapy
Restaging of patient with rising PSA

66 y/o, Increasing PSA to 11, 2 years after palladium seed implants and a nadir of 1.8. Original Gleason 7, PSA 6.7

Abdominal / pelvic CT negative. Biopsy of prostate showed recurrent / persistent adenocarcinoma, Gleason score 9.

ProstaScint showed extensive tumor adenopathy right iliac, paraaortic, mesenteric.

Management outcome as result of ProstaScint scan:

Systemic therapy
Detection of extrapelvic disease dramatically alters management

Whole body imaging excellent for extrapelvic disease

Normal distribution pattern of $^{111}$In-ProstaScint

1. Liver
   and occasionally Spleen

2. Bone marrow

3. Bowel

4. Blood pool retention

Node versus bowel?
Mild bowel uptake

Mild or moderate curvilinear or focal activity representing bowel in pelvis and abdomen is commonly seen. Bowel uptake can be confirmed by same day SPECT or additional planar imaging on subsequent days. Note difference between day 4 and day 5.
When activity is more focal and more intense differentiation between bowel and nodes is more difficult.

Day 4 Whole body

Movement of tracer, lessoning of intensity, and loss of focality all favor bowel activity. More movement away from central abdomen would further increase certainty. ?Day6
Pelvic and abdominal disease

- Important to detect.
- Alters therapy
Mesenteric lymph nodes

Mesenteric lymph nodes, especially when small, are difficult to detect on CT imaging, even when bowel contrast agents are used.

A. Transaxial CT, at level of MN

B. Planar whole body

C. Coronal CT, reformatted, in plane of MN

These are images with so called “central abdominal uptake” CAU.
Outcomes Data: Central Abdominal Uptake

- 341 patients with at least two years of clinical follow-up
- 69 patients (20%) exhibited positive central abdominal uptake (CAU+)
- CAU+ patients were 2.8 times more likely to have died during the median 4-year follow-up period

Prostate cancer-specific death rates were 10 times higher in the centrally positive patients and these death rates were independent of either the use of androgen blockade or the timing of androgen blockade

Extrapelvic disease

- Often unsuspected
- May need to get additional CT
Prostascint® image analysis

Emphasizing correlative imaging with anatomic-functional image registration and fusion
The aim of image registration is to find a common coordinate system between two image sets in order to correlate a patient’s anatomical and functional information.
VASCULAR ALIGNMENT
Prior to analyzing registered or fused data set for disease

Verify that registration is accurate

Most systems allow for manual adjustment of automatically generated registered datasets.
Registration check: triangulate on right femoral artery and vein
Prostate Fossa
Pre-treatment: 68-year-old with PSA 4.0 ng/mL, Gleason 7, for staging prior to definitive therapy

Although extracapsular extension of tumor (ECP) might be suggested, most referring clinicians currently want to make that diagnosis at surgery since false positive impression might preclude salvage therapy.

Extracapsular extension is much easier to appreciate in fusion imaging. There are many choices of color scale that can be used to display tracer uptake.
Cervical lymph nodes

Cervical node chain blends into supraclavicular region. On ProstaScint scans alone, it is often difficult to be specific, especially if the neck is flexed or rotated.

Images courtesy of Lawrence E. Holder, MD, Leslie Frye, LNMT, Shands Jacksonville, Jacksonville, Florida.
Hilar lymph nodes (peribronchial, mediastinal)

Hilar node metastasis have been reported in up to 40% of patients in autopsy series, although during clinical imaging these are much less commonly seen.
Status post-radiation therapy, rising PSA


Diagnosing tumor confined to the prostate, allows consideration for cryotherapy
Rising PSA post prostatectomy

Concerning scan for metastasis to external iliac lymph node
Follow up with rising PSA

Second primary: lymphoma
Central Abdominal Uptake

Imaging artifact or para-aortic lymph node involvement?
PROCEDURE FOR UNMASKING LOCALIZATION INFORMATION FROM PROSTASCINT SCANS FOR PROSTATE RADIATION THERAPY TREATMENT PLANNING

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Purpose: To demonstrate a method to extract the meaningful biologic information from 111In-radiolabeled exogenous peptide (ProstaScint) SPECT scans for use in radiation therapy treatment planning by removing that component of the 111In SPECT images associated with normal structures.

Methods and Materials: We examined 20 of more than 80 patients who underwent simultaneous 99mTc/111In SPECT scans, which were subsequently registered to the corresponding CT/MRI scans. A thresholding algorithm was used to identify 99mTc uptake associated with blood vessels and CT electron density associated with bone marrow. Corresponding vessels were removed from the 111In image set.

Results: No single threshold value was found to be associated with the 99mTc uptake that corresponded to the blood vessels. Intensity values were normalized to a global maximum and, as such, were dependent upon the quantity of 99mTc pooled in the bladder. The reduced ProstaScint volume sets were segmented by use of a thresholding feature of the planning system and superimposed on the CT/MRI scans.

Conclusions: ProstaScint images are now closer to becoming a biologically and therapeutically useful and accurate image set. After known sources of normal intensity are stripped away, the remaining areas that demonstrate uptake may be segmented and superimposed on the treatment-planning CT/MRI volume.

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ProstaScint® Guides
Brachytherapy Planning

Non-synchronous CT scan and ProstaScint® with antibody concentration in the right mid-gland peripherally


Ultrasound scan of the prostate

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Co registration or fusion can increase certainty of disease – making unclear medicine, clear medicine.
Safety

- Well tolerated
- 4% incidence of adverse reactions
- No serious adverse reactions reported
Repeat Administration

- 74 repeat infusions in 61 patients
- No increased incidence of adverse reactions compared with single infusion
- Frequency of HAMA (human antimouse antibody) 8% after single infusion
- Frequency of HAMA 19% following repeat infusions
- Biodistribution unaltered in 93% (65/70) repeat scans
Pitfalls and Pearls

- Learning curve
- Not all things are as simple as you think
Cost analysis
Study Design

- Reviewed the last 150 ProstaScint® scans at MUSC
- Areas of radiotracer uptake outside the prostate/prostate fossa & seminal vesicles
- Classified areas of activity as:
  - Normal: <2x background muscle
  - Equivocal: 2-3x background muscle
  - Concerning: >3x background muscle
- Reviewed studies with managing clinicians to determine the study results impact on patient management
Results

n = 150

Pre-treatment
40 pts

EPA Concerning
1 pt

Systemic therapy initiated

EPA Equivocal
1 pt

Local therapy initiated

Post-treatment
110 pts

EPA Concerning
11 pts

Local salvage therapy withheld
10 pts

EPA Equivocal
7 pts

Local salvage therapy withheld
3 pts
Post-treatment Scans

- 11 Scans were concerning for recurrent disease

- Changes in management:
  - 7 Withheld local salvage therapy and initiated systemic therapy
  - 1 Initiated cytotoxic chemotherapy
  - 2 Diagnosed with second malignancy
    - Hodgkin’s lymphoma
    - Schwannoma
Utility Considerations

- Cost of ProstaScint® & high resolution CT for fusion: $9,500
- Cost of salvage radiation therapy (IMRT): $110,000
  - Professional: $85,000
  - Technical: $25,000
- Other variables unaccounted for:
  - Costs to workup abnormal findings on ProstaScint®
  - Costs & morbidity associated with acute and long-term salvage radiation toxicity to the pelvis
  - Costs of potential delay in initiating systemic therapy in those with metastatic disease
Cursory Cost Benefit Analysis

- **Pre-treatment:**
  - 40 pretreatment ProstaScint® scans with 1 change in treatment: $40 ÷ 1 = 40$ scans for one change in treatment
  - ProstaScint® expense: $9,500 \times 40$ pts = $380,000

- **Post-treatment:**
  - 110 ProstaScint® scans with 13 changes in treatment: $110 ÷ 13 = 8.5$ scans for one change in treatment
  - $9,500 \times 8.5$ ProstaScint® scans = $80,750
  - vs.
  - One course of IMRT for salvage = $110,000
Conclusions

- Considering the cost & morbidity associated with local therapy, systemic staging of patients with recurrent prostate cancer by ProstaScint® results in meaningful changes in management in select patients.

- Niché for ProstaScint® seems to lie in assessing biochemical failure.

- The utility of ProstaScint® for staging before initial curative therapy is less clear.
ProstaScint: Summary

- Detects occult metastases in high risk patients with presumed localized disease
- Superior to CT and MRI in evaluating prostate cancer metastases
- Complimentary to Gleason, PSA, and Clinical Staging
- May influence the choice of appropriate therapy
- Safe and repeatable