Latest and Greatest in Permanent Source/Seed Implantation (PSI)

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Learning Objectives (3rd/Final Talk)

1) Understand the importance of application of multimodal imaging in PSI

2) Learn the new and advanced methodologies and technologies available for PSI
Multimodal Imaging: detection & diagnosis

- **US imaging** has been the primary modality for prostate biopsy followed by pathological findings/diagnosis
- **mpMRI (T2w, DWI, DCE, MRS)** has become more and more popular over the last decades for the diagnosis of prostate cancer due to anatomical and functional imaging ability
- **T2w MRI** is mainly used for prostate boundary detection while the diffusion-weighted imaging is the modality choice for computer-aided prostate cancer detection

**Can we avoid invasive biopsy and rely on digital biopsy?**

![Images of MRI types](T1w MRI, T2w MRI, DWI MRI, DCE MRI)

Multimodal Imaging: detection & diagnosis

**mpMRI-based radiomics and AI/ML for cancer detection**

The framework for the radiomics workflow

(a) Patient scanned with preoperative mpMRI
(b) The dominate tumor was delineated by stacking up regions of interest slice-by-slice on the ADC map and transverse T2w image on each slice. The segmented volume of interest was copied from ADC maps to DWI images
(c) High-throughput radiomics features were extracted from mpMRI
(d) Data analysis for feature selection, radiomics signature construction and testing

**Multimodal Imaging: detection & diagnosis**

**mpMRI-based radiomics for cancer detection**

- An overview of the presented framework for radiomics assisted targeted treatment radiotherapy planning (Rad-TRaP) of prostate cancer
- Rad-TRaP consists of three modules - 1) voxel-wise cancer detection on MRI based on radiomic feature analysis, 2) transference of cancer delineations to CT via deformable registration of MRI and CT, and 3) generation of targeted focal radiotherapy plans for brachytherapy and EBRT

Shiradkar, Podder et al, Radiation Oncology (2016) 11:148

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**Multimodal Imaging: detection & diagnosis**

**mpMRI-based radiomics for cancer detection**

- Quantitative results of the voxel-wise predictions using the radiomics trained machine learning classifier in terms of AUCs for individual patients
- The classifier was trained on T2w, ADC MRI sequences and T2w alone to show that misalignment between T2w and ADC MRI affects the performance of the classifier (patients 2, 5 and 6)

- Dice similarity coefficients (DSC) evaluating the co-registration of T2w MRI and CT
- The DSCs from deformable registration are typically higher than those from rigid registration

Shiradkar, Podder et al, Radiation Oncology (2016) 11:148
Deep convolutional neural networks (D-CNN) have been applied successfully for the diagnosis of cancers in general, and promising results have been achieved for prostate cancer.

Results of prostate cancer detection produced by Lemaitre et al., M1 and M2 from left to right, respectively. White contour shows the prostate boundary segmented by a radiologist, while blue contour is the ground truth of malignant lesions. Note that each row shows the same slice and each column shows the performance of the same CAD system.

The architecture of the deep convolutional encoder-decoder network and used to segment lesions in MRI. Note that the dimensions under each layer corresponds to the size of the output activations produced by same layer.

Illustration of sliding a 3D window across the input volume. Note that the label of the middle slice is considered as the label for the 3D window. In the dataset each pixel at each slice is labeled as shown in the left.


Multimodal Imaging: seed implant

DIL (mpMRI vol.) - dominant intraprostatic lesion

Aim is to cover DIL/mpMRI volume with 150% of Rx dose

- Different treatment plans for brachytherapy shown on a single slice of T2w MRI for 3 different patients in 3 rows
  - a - whole gland (WH)
  - b - ref/focal area (RF)
  - c - whole gland + focal (WF)

- Plans in WH and WF cover the entire prostate (blue contour) and have a larger dosage (maroon colored contour shows $V_{150}$)

- Number of needles (green circles) compared to RF in which only the cancerous region (bright red contour within the prostate) is covered

Shiradkar, Podder et al, Radiation Oncology (2016) 11:148
Dose painting to DIL or mpMRI Vol.

Pre-Operative and Post-operative dosimetric coverage of DIL volume with $^{125}$I and $^{103}$Pd

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Operative</th>
<th>Post-Operative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIL V100% (% vol)</td>
<td>$^{125}$I 99.8±2.9, $^{103}$Pd 99.9±0.2, 0.83</td>
<td>$^{125}$I 99.8±0.6, $^{103}$Pd 99.2±2.5, 0.89</td>
<td></td>
</tr>
<tr>
<td>DIL V150% (% vol)</td>
<td>$^{125}$I 96.0±10.6, $^{103}$Pd 97.2±4.4, 0.88</td>
<td>$^{125}$I 84.5±18.7, $^{103}$Pd 82.1±16.5, 0.82</td>
<td></td>
</tr>
<tr>
<td>DIL V200% (% vol)</td>
<td>$^{125}$I 63.8±17.3, $^{103}$Pd 72.1±13.5, 0.05</td>
<td>$^{125}$I 51.0±24.1, $^{103}$Pd 51.8±23.2, 0.13</td>
<td></td>
</tr>
</tbody>
</table>

(A) - Incidence of urinary toxicities for patients with and without DIL treated with $^{125}$I and $^{103}$Pd.

(B) - Incidence of urinary toxicities for patients with and without DIL treated with PSI as monotherapy and boost.

DIL (mpMRI vol.) - dominant intraprostatic lesion

Aim is to cover DIL/mpMRI volume with 150% of Rx dose

Dosimetric parameters by group.

Genitourinary toxicities by group according to CTCAE v.4.03.

NCCN = National Comprehensive Cancer Network, PSA = Prostate-Specific Antigen, Range = First Quartile and Third Quartile

CTCAE = Common Terminology Criteria for Adverse Events

DIL (mpMRI vol.) - dominant intraprostatic lesion; Boost - boost to DIL
Multimodal Imaging: dosimetric planning

Segmentation/ contouring – TRUS, CT, MRI

1) TRUS –
   - suitable for real-time, no radiation, inexpensive
   - low-contrast between the prostate and surrounding tissues, and the inter-exam variability of the prostate characteristics, inherent artifacts (speckle, shadowing, and attenuation)

2) CT – prostate contouring is challenging

3) MRI - good contrast compared to the TRUS and CT

Auto segmentation on MRI is based on automatically extracted features; used methods are CNN, deep learning for feature extraction.

Multimodal Imaging - promising results have been obtained by incorporating information of prostate gland shape from MRI with US or with CT.

Multimodal Imaging: dosimetric planning

1) Pre-Op planning – TRUS, CT, MRI
   - Determine seeds, order seeds, assay/verification (TRUS, CT, MRI)
   - Pre-loaded needles (TRUS)

2) Intra-Op planning – TRUS, real-time dosimetry

3) Post-Op planning – CT, MRI or a combination

US image of prostate with LDR brachytherapy template grid on it.
CT image of prostate prior to EBRT and LDR implant.
Post LDR CT image of prostate. Seeds are seen as bright white spots.

** Accurate contouring of prostate on CT is very challenging
Brachytherapy Dose Computation

1) 1D/2D geometric formulation (TG-43)
2) Model based computation (TG-186)
3) Dosimetric evaluation (TG-137)

1-D dosimetry formulation ( AAPM TG-43U1)

\[ D(r) = S_e \cdot \lambda \cdot \frac{G(r, \theta)}{G(0, \theta)} \cdot g_i(r, \phi) \]

- \( D(r) \) = dose rate to water at point \( P(r) \)
- \( S_e \) = air kerma strength
- \( \lambda \) = dose rate constant
- \( G(r, \theta) \) = geometric function (line source approximation)
- \( g_i(r) \) = radial dose function
- \( \phi \) = 1-D anisotropy function

2-D dosimetry formulation ( AAPM TG-43U1)

\[ D(r, \theta) = S_e \cdot \lambda \cdot \frac{G(r, \theta)}{G(0, \theta)} \cdot g_i(r, \phi) \cdot F(r, \theta) \]

- \( D(r, \theta) \) = dose rate to water at point \( P(r) \)
- \( S_e \) = air kerma strength
- \( \lambda \) = dose rate constant
- \( G(r, \theta) \) = geometric function (line source approximation)
- \( g_i(r) \) = radial dose function
- \( F(r, \theta) \) = 2-D anisotropy function

Factor-based vs Model-based

<table>
<thead>
<tr>
<th>INPUT</th>
<th>CALCULATION</th>
<th>OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TG43</strong></td>
<td>Source characterization</td>
<td>Superposition of data from source characterization</td>
</tr>
<tr>
<td><strong>MBDC</strong></td>
<td>Source characterization, Tissue/applicator information</td>
<td>Model-Based Dose Calculation Algorithms</td>
</tr>
</tbody>
</table>
Dose metrics evaluated with MCref/MBDC and TG43sim/TG43 for 613 patients and 3 example cases

**MCref:** CT-derived heterogeneous tissue model with interseed effects

**TG43sim**

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Photon Energy</th>
<th>Absorbed Dose</th>
<th>Attenuation</th>
<th>Shielding</th>
<th>Scattering</th>
<th>Beta/Kerma Dose</th>
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<tbody>
<tr>
<td>Prostate</td>
<td>high</td>
<td>XXX</td>
<td>XXX</td>
<td>XXX</td>
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<td></td>
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<tr>
<td></td>
<td>low</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>high</td>
<td>XXX</td>
<td></td>
<td>XXX</td>
<td></td>
<td>XXX</td>
</tr>
<tr>
<td></td>
<td>low</td>
<td>XXX</td>
<td></td>
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<td>GYN</td>
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<td></td>
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<tr>
<td></td>
<td>low</td>
<td>XXX</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin</td>
<td>high</td>
<td>XXX</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>low</td>
<td>XXX</td>
<td></td>
<td></td>
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<tr>
<td>Lung</td>
<td>high</td>
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<td></td>
<td></td>
<td></td>
<td>XXX</td>
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<tr>
<td></td>
<td>low</td>
<td>XXX</td>
<td></td>
<td></td>
<td></td>
<td>XXX</td>
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<tr>
<td>Penis</td>
<td>high</td>
<td>XXX</td>
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<td></td>
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<td>XXX</td>
</tr>
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<td></td>
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<tr>
<td></td>
<td>low</td>
<td>XXX</td>
<td></td>
<td></td>
<td></td>
<td>XXX</td>
</tr>
</tbody>
</table>

**Sensitivity of Anatomic Sites to Dosimetric Limitations of Current Planning Systems**

**Rivard, Venselaar, Beaulieu, Med Phys 36, 2138-2153 (2009)**
Multimodal Imaging: post-Op dosimetry

Imaging modality-
- CT only – commonly used
- US only – better prostate contour
- MRI only – still challenging
- CT & MRI – good, but expensive
- CT & US – take advantage from both
- US & C-arm – real time/dynamic

Post-Op plans on CT post-implantation and on US images at the start of the procedure.

<table>
<thead>
<tr>
<th>Difference</th>
<th>Mean (%)</th>
<th>σ (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9/CT-D9/US</td>
<td>6.4</td>
<td>21.6</td>
<td>0.1097</td>
</tr>
<tr>
<td>D10/CT-D10/US</td>
<td>-3.75</td>
<td>19.33</td>
<td>0.3052</td>
</tr>
<tr>
<td>V100/CT-V100/US</td>
<td>-0.17</td>
<td>9.01</td>
<td>0.9986</td>
</tr>
<tr>
<td>V150/CT-V150/US</td>
<td>7.29</td>
<td>18.03</td>
<td>0.0379</td>
</tr>
</tbody>
</table>

(a)–(c) A comparison of the visibility of implanted seeds on axial, sagittal and coronal views of a prostate implant on US images acquired using twister mode that was performed at the end of implantation procedure. (d)–(f) CT images acquired nearly 4 weeks post-implantation.


Multimodal Imaging: post-Op dosimetry

MRI only post-Op planning

The SeedNet architecture. The windows were processed with 3D CNNs. Three separate CNNs, each with the same configuration of layers, were trained to perform seed detection, classification, and localization tasks.

Data flow diagram demonstrating the integration of SeedNet into a clinical software package using DLAE.

First, each sub-window was passed to the detector to reject windows containing seeds. The seed sub-windows were then passed to a classifier to reject seed marker sub-windows that, owing to their similar shape and proximity to the seeds, were incorrectly classified as seed sub-windows. The seed sub-windows from the classifier were passed to the locator to pinpoint the precise location of the seed. Finally, the seed sub-windows were mapped back to their locations within the original image stack.

Example of SeedNet’s (left) and a CMD’s (right) seed location inferences and corresponding radiation dose distributions in MIM Software. The prostate contour was deactivated to allow for unobscured visualization of the isodose lines. The radioactive seeds are depicted as green circles.

Real-time Dynamic Dose Computation

- Used TRUS and C-arm fluoroscopy
- Fluoroscopy-to-TRUS registration
- Seed segmentation: 1% false negative rate and 2% false positive
- Ability to detect cold spots

Workflow of our image-guidance system for dynamic dose calculation. At least three fluoroscopic images are taken of the implanted seeds and the fiducial above the patient’s abdomen. The dark round object in the images is a Foley catheter balloon optionally filled with contrast to identify the bladder. An ultrasound volume of the seed-filled prostate is acquired. Both image sets are processed to calculate dose.

Intraoperative dosimetry result showing a cold spot. (a) TRUS image is overlaid with the prostate contour and the 100% isodose level (bright line) computed from the registered seed reconstruction (dots). (b) 3D rendering of the same prostate and 100% isodose level; cold spot is evident at the anterior base of the prostate.

• Used TRUS and C-arm fluoroscopy
• Fluoroscopy-to-TRUS registration
• Seed segmentation: 1% false negative rate and 2% false positive
• Ability to detect cold spots

Treatment Delivery

1) Loose seeds stacked in cartridge – Mick Applicator
2) Pre-loaded needles
3) Seeds in a strand – preordered/cut or make in OR
4) Mechanized device – robotic systems

Device to make strands

Seed strands: (a) seed dimension, (b) strands
**Conventional Prostate Seed Implant**

- **Fixed template** – limited maneuverability
- **PAI** (pubic arch interference) – needle angulation difficult
- **Consistency, accuracy, efficiency** – techniques & human factors
- **Clinicians’ fatigue, commitment**

**Technical Challenges in Prostate Seed Implantation**

- **Edema** – prostate volume increases, dose uncertainty, toxicities
- **Needle placement** – deflection from desired coordinates, difficulties in puncturing prostate capsule, prostate deformation deflection, i.e. challenge in immobilization
- **Seed position** – local movement, long distance migration (lungs, heart); position of delivered seeds can be significantly different from pre/intra-Op planned coordinates resulting in substantial deviation in dosimetric coverage
- **Post-Op evaluation** – challenging to delineate prostate in post-Op CT, several seeds may clamp together
Techniques for Prostate Immobilization

Methods for prostate stabilization during transperineal LDR brachytherapy

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3 Department of Radiation Oncology, University of Wisconsin, Madison, WI 53792, USA
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Online at stacks.iop.org/PMB/53/1563

Table 7. Overall prostate displacement results for all the configurations (in vitro experiment).

<table>
<thead>
<tr>
<th>Needle</th>
<th>Needle configuration</th>
<th>Resultant displacement (mm)</th>
<th>Reduction in movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stabilization</td>
<td>–</td>
<td>15.4</td>
<td>–</td>
</tr>
<tr>
<td>18G Regular</td>
<td>Parallel (0° H0° V)</td>
<td>11.5</td>
<td>25.3%</td>
</tr>
<tr>
<td>18G Regular</td>
<td>20°H 30°V</td>
<td>7.2</td>
<td>53.2%</td>
</tr>
<tr>
<td>18G Regular</td>
<td>30° H 30° V</td>
<td>6.1</td>
<td>69.4%</td>
</tr>
<tr>
<td>18G Regular</td>
<td>30° H 30° V crossed</td>
<td>5.6</td>
<td>63.6%</td>
</tr>
<tr>
<td>18G Hook</td>
<td>Parallel (0° H0° V)</td>
<td>6.5</td>
<td>57.8%</td>
</tr>
<tr>
<td>18G Hook</td>
<td>20° H 30° V</td>
<td>6.3</td>
<td>59.1%</td>
</tr>
<tr>
<td>18G Hook</td>
<td>30° H 30° V</td>
<td>5.7</td>
<td>63.9%</td>
</tr>
</tbody>
</table>


Rectilinear vs. Curvilinear Techniques for PSI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conventional rectilinear approach</th>
<th>Curvilinear conformal smart needle insertion</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (n = 20)</td>
<td>19.2 ± 5.2 (14-27)</td>
<td>15.2 ± 4.1 (10-19)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total D0 (Gy)</td>
<td>51.0 ± 0.5 (50.2-52.3)</td>
<td>50.5 ± 0.4 (50.1-52.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total activity (MBq)</td>
<td>36.5 ± 2.9 (29.4-44.3)</td>
<td>33.8 ± 2.4 (30.4-42.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prostate (average ± SD, range)</td>
<td>4.1±0.3 (3.0-5.5)</td>
<td>4.0±0.2 (3.5-5.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>D90 (Gy)</td>
<td>18.5±0.8 (17.0-20.0)</td>
<td>17.8±0.7 (16.0-20.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>D95 (Gy)</td>
<td>16.0±0.4 (15.0-17.0)</td>
<td>15.5±0.3 (14.0-16.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>V90 (cm³)</td>
<td>8.0±0.3 (7.0-9.0)</td>
<td>8.0±0.2 (7.0-9.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>V100 (cm³)</td>
<td>9.3±0.4 (8.0-10.0)</td>
<td>9.3±0.3 (8.0-10.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>V150 (cm³)</td>
<td>12.0±0.8 (10.0-14.0)</td>
<td>12.0±0.6 (10.0-14.0)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

20 patient PSI cases


Cumulative DVH

Conventional rectilinear implantation (dotted lines) Proposed curvilinear implantation (solid lines)
Other Challenges

- Brachytherapy is underrated/underappreciated
- Shadowed by proton therapy and IMRT
- Decreasing expertise
- Increasing lack of BT training; needs to shorten and make it popular

Robotic BT devices can mitigate some of the above issues

Robot-assisted Brachytherapy

Main Objectives are to -
1) Improve accuracy of needle/catheter placement
2) Improve consistency of source placement/delivery
3) Improve avoidance of OARs
4) Improve dose optimization
5) Reduce the clinician’s learning curve
6) Reduce clinician’s fatigue
7) Reduce radiation exposure to clinical staff
8) Streamline the brachytherapy procedure

AAPM TG-192, MedPhys (2014) 41(10)
Available/developed Robotic Systems for Brachytherapy

1) Thomas Jefferson University, USA (2) – Podder, Yu
2) Johns Hopkins University, USA (4) – Fichtinger, Stoianovici, Song
3) University of Wisconsin, USA (1) – Thomadsen, et al.
4) University of British Columbia, Canada (1) – Salcudean, Spadinger
5) Robarts Research Institute, Canada (1) – Fenster, et al.
6) University of Western Ontario, Canada (1) – Patel, et al.
7) Elekta/Nucletron - SeedSelectron/FIRST, Netherlands (discontinued) – Elekta
8) Univ. Medical Center Utrecht, Netherlands (1) – Moerland, Lagerburg
9) Grenoble University Hospital, France (1) – Troccaz, Hungr
10) Univ. of California at San Diego/ Univ. of Iowa (1) – Watkins, Song
11) Univ. of Cluj-Napoca, Romania (1) – Galdău, Pișlă
12) Tianjin Univ, China (1) – Dou, Yang, et al.
13) CoBra (MRI guided) - European project

Total = 17 robotic systems
Summary of Brachy Robots

Some of the Brachy Robots

|----------------|------------------|-----------------------------|-----------------------------|

[Table 1: Summary of the currently available robotic brachytherapy systems.
Total = 17 (2 are not listed here, shown later)]
CT-guided Robotic System for Lung Brachy

Robot-assisted seed implantation for lung cancer.
Used this system for treating over 34 NSCLC patients since 2015.

coBra robotic system (MRI-guided)

- Multiple sensors (force/torque, optical range, radiation) — improve safety and reliability
- Automatic seed deposition — less burden for clinicians
- Needle rotation — reduces insertion force, improves targeting
- Needle angulation — a few puncture at the perineum, avoidance of PAI
- Cartridge with 100 seeds — less radiation exposure, saves time

https://youtu.be/3f41dV8EIT4
https://cobra-2seas.eu/
## Future Directions

1) Use of multimodal imaging and mpMRI for cancer detection and diagnosis – radiomics, AI/ML, ANN/CNN etc.

2) Consider focal therapy – reduce toxicity, improve quality of life

3) Improve dosimetric computation – MC, MBDC, etc.

4) Improve delivery of Tx – target stabilization, accurate needle placement and seed deposition, real-time dynamic dose verification and adaptation

5) Training of new generation – physicians & physicists

6) Use mechanized/robotic systems – reduce clinician’s burden, improve Tx consistency

7) Respect and follow the science

## Summary

- Multimodal imaging is critical for PSI
- Radiomics, AI/ML may play important role
- Dose paining to DIL/mpMRI can reduce toxicity and may improve clinical outcome
- Mechanized/robot-assisted Tx delivery can improve consistency & quality of implant and may reduce some burdens of the clinicians
Thank You!
Stay Safe!!

Any Question?