IMPROVING PATIENT QUALITY OF LIFE WITH MILLIMETER MARGINS

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Disclosure

The speakers have no actual or potential conflict of interest in relation to the products discussed in this presentation.
What if.......
4 Facts About Prostate Cancer
1. Prostate Size Changes With Age

**Prostate Age Cycle**

- **Age 20-25**
  - Walnut
- **Age 35-40**
  - Golf ball
- **Age 50-60**
  - Lemon
- **Age 70-80**
  - Baseball

- **AGE 20-35**
  - Most healthy males have a prostate that's the size of a walnut.

- **AGE 40-50**
  - The prostate starts to grow and swell. Minor symptoms appear, like a more frequent need to urinate and weaker erections.

- **AGE 50-70**
  - Over 50% of men over age 50 will be affected. A swollen prostate can be the size of an orange. It becomes increasingly PAINFUL, making it difficult to urinate, and sexual function is noticeably impaired.

- **AGE 70-80+**
  - Over 90% of men over 70 years of age will be affected. Prostate can swell beyond the size of a baseball. Quality of life is severely impacted.
Factors with less clear effect on prostate cancer risk

- Diet
- Smoking
- Chemical exposures
- Vasectomy
- Obesity
- Sexually transmitted infections
2. Age

- **164,690** projected new cases in 2018
- **29,430** projected deaths in 2018
3. Race

4. Family History

Family history and genes

You are two and a half times more likely to get prostate cancer if your father or brother has been diagnosed with it, compared to a man with no family history of prostate cancer.

Your risk of getting prostate cancer is higher if your mother or sister has had breast cancer.

American Cancer Society
Types of prostate cancer

-Most common is adenocarcinoma

-Other types of prostate cancer include:
  ● Sarcomas
  ● Small cell carcinomas
  ● Neuroendocrine tumors (other than small cell carcinomas)
  ● Transitional cell carcinomas
<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>Stage grouping</th>
<th>Grade</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>cT1, N0, M0</td>
<td>Grade Group 1</td>
<td>PSA less than 10</td>
</tr>
<tr>
<td>I</td>
<td>cT2a, N0, M0</td>
<td>(Gleason score 6 or less)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>pT2, N0, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>cT1, N0, M0</td>
<td>Grade Group 1</td>
<td>PSA at least 10 but less than 20</td>
</tr>
<tr>
<td>IIA</td>
<td>cT2a or pT2, N0, M0</td>
<td>(Gleason score 6 or less)</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>cT2b or cT2c, N0, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td></td>
<td>PSA less than 20</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>T1 or T2, N0, M0</td>
<td>Grade Group 2</td>
<td>PSA less than 20</td>
</tr>
<tr>
<td>IIB</td>
<td></td>
<td>(Gleason score 3+4=7)</td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>T1 or T2, N0, M0</td>
<td>Grade Group 3 or 4</td>
<td>PSA less than 20</td>
</tr>
<tr>
<td>IIC</td>
<td></td>
<td>(Gleason score 4+3=7 or 8)</td>
<td></td>
</tr>
<tr>
<td>AJCC Stage</td>
<td>Stage grouping</td>
<td>Grade</td>
<td>PSA</td>
</tr>
<tr>
<td>------------</td>
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<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1 or T2, N0, M0</td>
<td>Grade Group 1 to 4 (Gleason score 8 or less)</td>
<td>PSA at least 20</td>
</tr>
<tr>
<td>IIIIB</td>
<td>T3 or T4, N0, M0</td>
<td>Grade Group 1 to 4 (Gleason score 8 or less)</td>
<td>Any PSA</td>
</tr>
<tr>
<td>IIIIC</td>
<td>Any T, N0, M0</td>
<td>Grade Group 5 (Gleason score 9 or 10)</td>
<td>Any PSA</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T, N1, M0</td>
<td>Any Grade Group</td>
<td>Any PSA</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T, any N, M1</td>
<td>Any Grade Group</td>
<td>Any PSA</td>
</tr>
</tbody>
</table>
T1 and T2 Prostate Cancer

T1 prostate cancer
The cancer can’t be felt during a DRE or seen on scans, and can only be seen under a microscope.

T2 prostate cancer
The cancer can be felt during a DRE or seen on scans, but is still contained inside the prostate.

T2a  The cancer is in half of one side (lobe) of the prostate, or less.

T2b  The cancer is in more than half of one of the lobes, but not in both lobes of the prostate.

T2c  The cancer is in both lobes but is still inside the prostate.
Treatment Options

1. Watchful Waiting
2. Surgery
3. Radiation Therapy

1. Hormones
2. High Intensity Ultrasound
3. Focal Cryotherapy
# Identifying Treatment Options

<table>
<thead>
<tr>
<th>Type of Hormone Therapy</th>
<th>What It Does</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Androgens</td>
<td>Disrupts the interaction of testosterone with cancer cells</td>
<td>Flutamide, Casodex, Nilandron</td>
</tr>
<tr>
<td>Luteinizing Hormone Treatment</td>
<td>Shuts down luteinizing hormones that signal the production of testosterone</td>
<td>Lupron, Zoladex, Eligard, Firmagon</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Blocks enzymes and/or proteins from making testosterone</td>
<td>Zytiga, Xtandi and others in clinical trials (Orteronel and Custirsen)</td>
</tr>
</tbody>
</table>

The diagram illustrates the hormonal system involving the brain (Hypothalamus), pituitary gland, adrenal gland, testicles, and prostate. The hormones LH (Luteinizing Hormone) and LHRH (Luteinizing Hormone Releasing Hormone) are shown to regulate the production of testosterone and adrenal androgens.
<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less likely to have ED or urinary incontinence</td>
<td>Approved by the FDA in October 2015, lack of long term data</td>
</tr>
<tr>
<td>Procedure lasts an hour once the catheter is in place</td>
<td>Only suitable for localized cancer</td>
</tr>
</tbody>
</table>
- Used predominantly in early or focal disease
- Lack of long term data.
‘Trains’ of seeds already implanted

Prostate gland

Bladder

Urethra

Implant needle

Rectum

Endorectal ultrasound probe directing needle to correct position

Template through which implant needles are guided
Treating Prostate Cancer

Surgery?

Radiation?

Watchful Waiting?

Hormones/Chemo?
Types of Surgery

- Radical retropubic prostatectomy
- Radical perineal prostatectomy
- Laparoscopic radical prostatectomy
- Robotic-assisted laparoscopic radical prostatectomy
Laparoscopic Surgery
Radiation Therapy  External Beam
Types of Radiation Therapy

- BrachyTherapy
- External Beam Therapy (Photon)
  - 3D Conformal
  - IMRT
  - SBRT
- Protons
Treatment Planning
Planning and Delivery

RTOG 0415

Hypofractionation with IMRT/IGRT: 2.5Gy x 28

https://www.varian.com/oncology/products/treatment-delivery/clinac-ix-system
Treatment Planning

• Prostate prescribed $2.5\text{Gy} \times 28 = 70 \text{ Gy}$
  $\text{EQD}_2, \alpha/\beta=1.5 = 186.7 \text{ Gy}$
  Equivalent to $2.0\text{Gy} \times 39 = 78\text{Gy}$
IMRT vs. SBRT

● Randomized Phase III studies comparing hypofractionated IMRT 28 fractions of 2.5Gy to SBRT 5 fractions of 7.25Gy

○ To determine whether (SBRT) can be shown to be superior to (IMRT) in terms of:
  ■ Genitourinary (GU) and gastrointestinal (GI) toxicity.
  ■ Measure disease free survival within 24 months.
  ■ Post Complication Rates at 12 and 24 months: bowel, sexual, hormonal, urinary irritation/obstructive (12 months only) and in urinary incontinence.
  ■ Measure biochemical failure, overall survival, local failure, prostate cancer specific survival, and distant metastases.
Contouring

Prostate: Whole gland

- MRI fusion to assist target definition

Seminal vesicles:
- Low risk: No SV coverage necessary
- Intermediate/High risk: Unclear

Options:
- Cover to full dose the proximal 2 cm (provided OAR dose limits are respected)
- Cover to proximal SVs to lower dose level
- If SVs are grossly abnormal: Cover to full dose
# OAR Dose Constraints

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>V50 &lt; 50%</td>
</tr>
<tr>
<td></td>
<td>V60 &lt; 35%</td>
</tr>
<tr>
<td></td>
<td>V65 &lt; 25%</td>
</tr>
<tr>
<td></td>
<td>V70 &lt; 20%</td>
</tr>
<tr>
<td></td>
<td>V75 &lt; 15%</td>
</tr>
<tr>
<td>Bladder</td>
<td>V65 &lt; 50%</td>
</tr>
<tr>
<td></td>
<td>V70 &lt; 35%</td>
</tr>
<tr>
<td></td>
<td>V75 &lt; 25%</td>
</tr>
<tr>
<td>Femurs</td>
<td>V30 &lt; 15%</td>
</tr>
<tr>
<td></td>
<td>V40 &lt; 35%</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>V45 &lt; 195cc</td>
</tr>
</tbody>
</table>

Small Bowel (peritoneal cavity)
The Importance
Organ at Risk

- Rectum dose limiting factor
- Rectal Complications
- Rectal Toxicities
<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>
| 1     | Mild diarrhea  
Mild cramping  
Bowel movement  
5 times daily   
Slight rectal discharge or bleeding |
| 2     | Moderate diarrhea and colic  
Bowel movement  
>5 times daily   
Excessive rectal mucus or intermittent bleeding |
| 3     | Obstruction or bleeding requiring surgery |
| 4     | Necrosis/Perforation Fistula |
| 5     | Death Directly Related to Radiation Effects |

RTOG/EORTC Late Radiation Morbidity Scoring Schema
Department of Health Common Terminology Criteria for Adverse Events

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal fistula</td>
<td>Asymptomatic</td>
<td>Symptomatic, invasive intervention not indicated</td>
<td>Invasive intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Rectal hemorrhage</td>
<td>Mild symptoms; intervention not indicated</td>
<td>Moderate symptoms; intervention indicated</td>
<td>Transfusion indicated; invasive intervention indicated; hospitalization</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Rectal mucositis</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL</td>
<td>Life-threatening consequences; urgent operative intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Rectal necrosis</td>
<td>-</td>
<td>-</td>
<td>Tube feeding or TPN indicated; invasive intervention indicated</td>
<td>Life-threatening consequences; urgent operative intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Rectal obstruction</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; altered GI function; limiting instrumental ADL</td>
<td>Hospitalization indicated; invasive intervention indicated; limiting self care ADL</td>
<td>Life-threatening consequences; urgent operative intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Rectal pain</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self care ADL</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Rectal perforation</td>
<td>-</td>
<td>Invasive intervention not indicated</td>
<td>Invasive intervention indicated</td>
<td>Life-threatening consequences; urgent operative intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
Rectal Complications
Radiation Colitis
Ulceration and Telangiectasia
Prostate Motion

- **Short-term shifts**
  - Muscle contraction, within seconds, (e.g., due to gas passage, within several to tens of seconds)

- **Continuous Displacement**
  - Due to rectal/bladder filling

- **Combination**
  - The least movement occurred in the lateral direction
  - Anterior and superior shifts were often occasional or short-term due to gas passage and sometimes correlated with each other.
  - Posterior and inferior displacements generally occurred together, and were often continuous, slow movements, which were likely caused by bladder filling.
There is significant movement of the prostate gland based on daily gas in rectum.

Planned target

No Rectal gas

Planned target, missed badly if rectal gas pushes the prostate forward

Rectal gas
Prostate Motion per Minute

Intrafractional motion vs. time

Tracking Time in Minutes

Proportion of Minutes %

Prostate Motion Total Tracking Time

Tong et al.: Intrafractional prostate motion during external beam radiotherapy

Advanced Patient Setup and Online Target Location Techniques

- Inter and intrafraction motion monitored by
  - ultrasound
  - infrared cameras
  - X-ray imaging
  - in-room CT
  - kilovoltage and megavoltage cone-beam CT (CBCT)
  - rectal balloon
  - magnetic resonance imaging
  - electromagnetic transponders, called Beacons (Calypso Medical Technologies, Seattle, WA)
What is Hydrogel ???
Hydrogel in Radiation Therapy
Placement Procedure
Placement between the Prostate and Rectum
Pre and Post Placement

Pre Hydrogel

Post Hydrogel

12 Months

Prostate

Rectum

Hydrogel
Our Experience
Pertinent Observations
Rectum DVH Dose

Prescription: 250 cGy x 28 fx = 7000 cGy

<table>
<thead>
<tr>
<th></th>
<th>Mean ± STDEV</th>
<th>D50 (cGy)</th>
<th>D1cc (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrogel</strong></td>
<td>2015 ± 896</td>
<td>6798 ± 542</td>
<td></td>
</tr>
<tr>
<td><strong>Non-hydrogel</strong></td>
<td>2575 ± 1429</td>
<td>7320 ± 89</td>
<td></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>NS</td>
<td>0.002 *</td>
<td></td>
</tr>
</tbody>
</table>

Dose Distribution Between Patient Groups
Q. How can we assess the conformity of a prostate treatment plan?
Q. Are we changing the dose spillage characteristics of a plan with hydrogel?

\[ P_X = \frac{\text{Volume of } X\% \text{ Iso} - \text{dose line}}{\text{Volume of } 100\% \text{ Iso} - \text{dose line}} \]

\[ P_{90} = \frac{\text{Volume of } 90\% \text{ Iso} - \text{dose line}}{\text{Volume of } 100\% \text{ Iso} - \text{dose line}} \]
Dose Spillage

Dose Spillage Evaluated Using Iso-dose lines

Ratio

Dosimetric Endpoints

Cl, P90, P80, P50

Hydrogel
Non-Hydrogel
## Dose Spillage Quantified

<table>
<thead>
<tr>
<th></th>
<th>Hydrogel</th>
<th>Non-Hydrogel</th>
<th>P-value</th>
<th>Rules of Thumb</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI/P100</td>
<td>1.02 ± 0.06</td>
<td>1.03 ± 0.06</td>
<td>NS</td>
<td>&lt; 1.10</td>
</tr>
<tr>
<td>P90</td>
<td>1.29 ± 0.04</td>
<td>1.28 ± 0.06</td>
<td>NS</td>
<td>30% Larger</td>
</tr>
<tr>
<td>P80</td>
<td>1.56 ± 0.06</td>
<td>1.56 ± 0.09</td>
<td>NS</td>
<td>60% Larger</td>
</tr>
<tr>
<td>P50</td>
<td>3.73 ± 0.27</td>
<td>3.74 ± 0.33</td>
<td>NS</td>
<td>375% Larger</td>
</tr>
</tbody>
</table>
Modulation Complexity Score (MCS)

A single metric ranging from 0 to 1 that accounts for: leaf positions, degree of irregularity in field shape, segment weight and area. Consists of two parameters:
- leaf sequence variability (LSV)
- aperture area variability (AAV)

\[
\text{pos}_{\text{max}} = \max_{n} (\text{pos}_{\text{L}n}) - \min_{n} (\text{pos}_{\text{R}n})
\]

The LSV is then calculated as follows:

\[
\text{LSV}_{\text{segment}} = \left( \frac{\Sigma_{n=1}^{N} (\text{pos}_{\text{max}} - (\text{pos}_{n} - \text{pos}_{n+1}))}{N \times \text{pos}_{\text{max}}} \right)_{\text{left bank}} \times \left( \frac{\Sigma_{n=1}^{N} (\text{pos}_{\text{max}} - (\text{pos}_{n} - \text{pos}_{n+1}))}{N \times \text{pos}_{\text{max}}} \right)_{\text{right bank}}.
\]

\[
\text{AAV}_{\text{segment}} = \frac{\Sigma_{a=1}^{A} (\text{pos}_{a})_{\text{left bank}} - (\text{pos}_{a})_{\text{right bank}}}{\Sigma_{a=1}^{A} (\max (\text{pos}_{a}))_{\text{left bank} \in \text{beam}} - (\max (\text{pos}_{a}))_{\text{right bank} \in \text{beam}}}
\]

\[
\text{MCS}_{\text{beam}} = \sum_{i=1}^{I} \text{AAV}_{\text{segment}}_{i} \times \text{LSV}_{\text{segment}}_{i} \times \frac{\text{MU}_{\text{segment}i}}{\text{MU}_{\text{beam}}}
\]

where \( I \) is the number of segments in the beam.

<table>
<thead>
<tr>
<th>Prostate with lymph nodes</th>
<th>0.1 to 0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Field</td>
<td>1.0</td>
</tr>
</tbody>
</table>
MCS Score Differences Between Patient Groups

The presence of the separation allows planners to push the VMAT complexity.

### Differences In VMAT Complexity

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>MCS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogel</td>
<td>0.286 ± 0.015</td>
</tr>
<tr>
<td>Non-hydrogel</td>
<td>0.380 ± 0.013</td>
</tr>
</tbody>
</table>

P-value: 0.0002
MCS Score Differences Between PTV Size

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>MCS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV &lt; 150 cc</td>
<td>0.353 ± 0.015</td>
</tr>
<tr>
<td>PTV &gt; 150 cc</td>
<td>0.322 ± 0.020</td>
</tr>
</tbody>
</table>

P-value: Not Significant

- Prostate with lymph nodes: 0.1 to 0.25
- Open Field: 1.0
Pneumabra Between Prostate And Rectum

Drop Off In PTV Dose

Normalized Dose (%) vs. PTV Edge Distance (cm)

- Prostate PTV < 150 cc
- Prostate PTV > 150 cc

Dose Profile Normalized to PTV Edge

PTV

RECTUM
## Dose Spillage Correlated To PTV Size

<table>
<thead>
<tr>
<th>Distance From PTV Edge (cm)</th>
<th>Normalized Dose (%) PTV &lt;150 cc</th>
<th>Normalized Dose (%) PTV &gt;150 cc</th>
<th>Rules of Thumb</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17.89 ± 4.73</td>
<td>48.57± 5.62</td>
<td>270% Larger</td>
</tr>
<tr>
<td>4</td>
<td>11.93 ± 3.70</td>
<td>33.86 ± 5.48</td>
<td>3X Larger On Average</td>
</tr>
<tr>
<td>6</td>
<td>9.91 ± 2.83</td>
<td>26.76 ± 4.40</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8.55 ± 2.56</td>
<td>22.19 ± 4.52</td>
<td></td>
</tr>
</tbody>
</table>
Future Trends
Elekta Unity – 10 systems installed – 32 systems sold

- On track for installing 1 system per month during the year
- Including 5 systems to China with revenue recognized next fiscal year
1. MRI Imaging On Treatment Machine
1. Deformable Registration
1. Auto-planning
1. Prostate SBRT
Align

Cone-beam CT
MRidian - MRI

Most accurate soft tissue alignment today

Adapt

MRidian® - On-table Adapting
FX 1 ADAPTED
FX 2 ADAPTED

Make changes to match daily soft tissue anatomy

Track

MRidian® - Direct Tracking

See what you treat as you treat

(Source: www.viewray.com)
Closing Thoughts

Hydrogel:
- Better visualized on MRI.
- Creates favorable planning anatomy.
- Has utility for improved patient quality of life
Acknowledgements

- Meri Atanas MD
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