CyberKnife®: The Effect of Intrafraction Rotation as a Predictor of Rectal Toxicity in Prostate SBRT

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Disclosure and Disclaimer

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• An honorarium is provided by Accuray for this presentation.
Background

• Background: Prostate brachy/IGRT, Stereotactics

• March 2014:

• July 2014:

• October 2014:
Background

- October 2014:
  - New MD; RN’s; Therapists, Dosimetrists
  - One of the first patients: “Dr. Blacksburg, the fiducials don’t meet the minimum angle test. We won’t be able to adjust for rotations.”
  - “Do rotations matter? What do we lose by turning them off?”
  - “Probably not that much”
• If managing rotations don’t matter, then why is it part of the regular functionality?
• CyberKnife®’s technological appendix?
While you know Prostate size, if you turn rotations off, you don’t even know the magnitude of the rotation!

Flying “Rotating” blind

<table>
<thead>
<tr>
<th>Prostate Length (cm)</th>
<th>Maximal Deviation, in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.5 0.7 0.9 1.1 1.4 1.6 1.8</td>
</tr>
<tr>
<td>3</td>
<td>0.8 1.0 1.3 1.7 2.1 2.6 3.1</td>
</tr>
<tr>
<td>4</td>
<td>1.0 1.4 2.1 2.6 3.2 3.7 4.3</td>
</tr>
<tr>
<td>5</td>
<td>1.3 1.7 2.2 2.6 3.2 3.7 4.3</td>
</tr>
<tr>
<td>6</td>
<td>1.6 2.1 2.8 3.5 4.0 4.8 5.5</td>
</tr>
<tr>
<td>7</td>
<td>1.9 2.5 3.1 3.7 4.2 4.9 5.5</td>
</tr>
<tr>
<td>8</td>
<td>2.2 2.8 3.5 4.1 4.7 5.3 6.2</td>
</tr>
<tr>
<td>9</td>
<td>2.5 3.2 3.8 4.4 5.0 5.5 6.2</td>
</tr>
<tr>
<td>10</td>
<td>2.8 3.5 4.1 4.7 5.3 5.9 6.8</td>
</tr>
<tr>
<td>11</td>
<td>3.1 3.8 4.4 5.0 5.5 6.2 7.4</td>
</tr>
<tr>
<td>12</td>
<td>3.4 4.1 4.7 5.3 5.9 6.6 7.4</td>
</tr>
<tr>
<td>13</td>
<td>3.7 4.4 5.0 5.6 6.2 6.8 7.8</td>
</tr>
<tr>
<td>14</td>
<td>4.0 4.7 5.3 5.9 6.5 7.1 8.7</td>
</tr>
<tr>
<td>15</td>
<td>4.3 5.0 5.6 6.2 6.8 7.4 9.4</td>
</tr>
</tbody>
</table>

"I estimated the diameter of the prostate to be 6cm (on the big side) and a 5 degree rotation. For small rotations, the arc length is approximately equal to the chord, so it can be calculated both ways. Your deviation if you rotate 5 degrees about iso at the periphery of the prostate is only 2.6mm"
Building a Program of Science Around a CyberKnife Prostate SBRT Practice

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Winthrop University Hospital
New York
CyberKnife® SBRT, Current State

- CyberKnife®-based SBRT was disruptive
  - Non-coplanar and intrafraction correction
CyberKnife® Advantages

• Non-coplanar Treatment
  – Translation: should see dosimetric advantages
    • Quicker fall-off
    • Lower proxy = penile bulb dose?
    • Operator Dependent and biases difficult

Non-coplanar = Potential for Quicker fall-\text{IN} as well!

So just a few mm’s may make a big difference
CyberKnife® Advantages

- Intrafraction Motion/Rotation Adjustment
  - We know the prostate translates and rotates
  - Watching each treatment can see!

Motion Management

Continuously adapting treatment to target motion is a challenge, but the CyberKnife® System offers a expanding set of options that help track tumor types anywhere in the body — including head, prostate, lung, spine, liver, pancreas and other extracranial tumors. Our treatment delivery software provides an automatic, intuitive user interface to efficiently control all interactions between the robotic manipulator, treatment couch and imaging system. The software quickly and automatically processes live images acquired throughout treatment at user-defined intervals, calculates offsets based on Digitally Reconstructed Radiographs (DRRs) and sends offset data to the robotic manipulator for immediate and automatic motion compensation.

Xie et al, IJROBP, 2008
CyberKnife® Advantages

• Intrafraction Motion/Rotation Adjustment


• 17 pts, Calypso data overlayed on CyberKnife® plans. Rotations mattered
CyberKnife® Advantages

• Intrafraction Motion/Rotation Adjustment


• 89 pts, Calypso for non CyberKnife® tx
  – Could not assess/correct rotation
<table>
<thead>
<tr>
<th>STRATIFY</th>
<th>Treatment techniques/machine</th>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All linear accelerator based treatment (excluding Cyberknife)</td>
<td>Arm 1 36.25 Gy in 5 fractions of 7.25 Gy over two and a half weeks (in 15-17 days)*</td>
<td></td>
</tr>
<tr>
<td>2. Cyberknife</td>
<td>Arm 2 51.6 Gy in 12 daily fractions of 4.3 Gy over two and a half weeks (in 16-18 days)</td>
<td></td>
</tr>
<tr>
<td>3. Protons</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Part of Value Proposition Negated
- Where was the data proving this would result in more tx uncertainty?
Continuous Monitoring of Position Correction During Treatment: Target Coverage for Prostate Therapy

D. Michael Lovelock, PhD,* Alexander B. Gafni, MD,* Brett W. Cox, MD,* Marisa A. Kuo,* Simon J. Rabbitt, MD,* Michael J. Zelefsky, MD*  

*Memorial Sloan Kettering Cancer Center, New York, N.Y. 10065.  

Received Jun 17, 2014, and in revised form Oct 21, 2014. 

Attachments and links:
- [system of implanted electromagnetic or 3D CT systems that use x-rays will help to determine the geometry based on the treatment plan. 
- physician and attending physicist and radiation oncologist will be recorded. A rectal template will be used during the treatment to ensure that the target migrated more than 2 cm prior to radiation delivery but after the CT. 
- CT or MRI images may also be considered to make a decision. 
- coverage during treatment, periodic tracking error where tracking is utilized) from the treatment planning system. 
- percentage images or baseline data should be performed and reviewed and approved by both physician and physicist on site. 

The comparison can be done both manually and automatically. For any image-guidance method, if any deviation is larger than 2 mm, correction should be performed. 

All image-guidance data should be recorded and saved for post treatment review and analysis. In some cases, replanning (either offline or online) based on anatomy of the day may be performed. Such request will be made by the attending physician.
Pubmed Manuscripts, Prostate SBRT

Blacksburg S et al, unpublished

Comparing the two treatments, given the variability in sexual functioning with age and other medical conditions, PSA failures required further follow-up to make meaningful assessment of treatment efficacy.

In this study patients could be treated by any radiation therapy technique—CyberKnife, VMAT, IMRT, or protons—as long as the dosimetry parameters (especially normal tissue constraints) could be met. A strength of this study is the inclusion of a prospective, IRB-approved trial undertaken for quality assurance of protocol-defined dosimetry parameters. The PROs for patients treated with IMRT/VMAT technique and CyberKnife were comparable.

References
2. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of
February 2019


**Abstract**

**Objectives:** To assess long-term outcomes after stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer.

**Methods:** This cohort study analyzed individual patient data from 2,141 men treated with stereotactic body radiotherapy at 10 institutions and 29 sites. The median follow-up period was 5.2 years.

**Results:** The 5-year rates of biochemical disease-free survival were 81% for low-risk and 89% for intermediate-risk patients. The 5-year rates of distant metastases and radiation-related toxicity were 1.0% and 1.5% respectively.

**Conclusion:** Stereotactic body radiotherapy is a safe and effective treatment for low-risk and intermediate-risk prostate cancer, with excellent long-term outcomes.

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**Table 1: Specific Planning Considerations for Individual Studies**

<table>
<thead>
<tr>
<th>Institution or Trial</th>
<th>Dose/Fraction</th>
<th>Prescription Specification</th>
<th>Margins</th>
<th>Planning Techniques</th>
<th>Image Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginia Mason</td>
<td>6-7 Gy x 5</td>
<td>90% of M to cover 100% of prostate</td>
<td>5-7 mm margin from prostate to block edge</td>
<td>Orthogonal imaging to implanted fiducial markers prior to treatment</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>Stanford</td>
<td>7-25 Gy x 5</td>
<td>100% of M to cover 100% of prostate</td>
<td>3 mm margin from prostate to 5 mm margin</td>
<td>Noncoplanar fields (360° gantry)</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>Hakin</td>
<td>6 Gy x 3 (5%)</td>
<td>100% of M to cover 100% of prostate</td>
<td>3 mm margin from prostate to 5 mm margin</td>
<td>Noncoplanar fields (360° gantry)</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>20th Century Oncology</td>
<td>8 Gy x 5</td>
<td>100% of M to cover 100% of prostate</td>
<td>5 mm margin from prostate to 5 mm margin</td>
<td>Noncoplanar fields (360° gantry)</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>NCI0043384</td>
<td>7-25 Gy x 5</td>
<td>100% of M to cover 100% of prostate</td>
<td>3 mm margin from prostate to 5 mm margin</td>
<td>Noncoplanar fields (360° gantry)</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>NCI0043384</td>
<td>7-25 Gy x 4</td>
<td>100% of M to cover 100% of prostate</td>
<td>3 mm margin from prostate to 5 mm margin</td>
<td>Noncoplanar fields (360° gantry)</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>Sunnybrook pHART 3</td>
<td>7 Gy x 3</td>
<td>90% of M to cover 90% of PTV</td>
<td>4 mm margin from prostate</td>
<td>Orthogonal imaging to implanted fiducial markers prior to treatment</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>Sunnybrook pHART 6</td>
<td>8 Gy x 5</td>
<td>90% of M to cover 90% of PTV</td>
<td>5 mm margin from prostate</td>
<td>Orthogonal imaging to implanted fiducial markers prior to treatment</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>Beth Israel Deaconess Medical Center</td>
<td>7-25 Gy x 5</td>
<td>100% of M to cover 100% of prostate</td>
<td>3 mm margin from prostate to 5 mm margin</td>
<td>Orthogonal imaging to implanted fiducial markers prior to treatment</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>University of California, Los Angeles</td>
<td>8 Gy x 5</td>
<td>100% of M to cover 100% of prostate</td>
<td>3 mm margin from prostate to 5 mm margin</td>
<td>Orthogonal imaging to implanted fiducial markers prior to treatment</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>Genesis Healthcare</td>
<td>9 Gy x 4</td>
<td>100% of M to cover 100% of prostate</td>
<td>3 mm margin from prostate to 5 mm margin</td>
<td>Orthogonal imaging to implanted fiducial markers prior to treatment</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
<tr>
<td>Georgetown</td>
<td>7 Gy x 3 (5%)</td>
<td>100% of M to cover 100% of prostate</td>
<td>5 mm margin from prostate to 5 mm margin</td>
<td>Noncoplanar fields (360° gantry)</td>
<td>Real-time tracking of implanted fiducial markers</td>
</tr>
</tbody>
</table>

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**Table 8: Multivariable Logistic Regression for Predictors of Late Composite RTOG-CTCAE Grade 2+ Toxicity**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQD (95 Gy vs. 91 Gy)*</td>
<td>1.03 (0.98-1.09)</td>
<td>0.16</td>
</tr>
<tr>
<td>Treatment: CyberKnife versus CyberKnife</td>
<td>2.22 (1.08-4.54)</td>
<td>0.03</td>
</tr>
<tr>
<td>Treatment: CyberKnife versus CyberKnife</td>
<td>1.30 (0.79-7.94)</td>
<td>0.21</td>
</tr>
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</table>

*EQD (Equivalent dose) vs. 91 Gy, **Weekly fractionation was not included because the data came from a single center*.

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**Table 7: Multivariable Logistic Regression for Predictors of Late Composite RTOG-CTCAE Grade 2 Toxicity**

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*EQD (Equivalent dose) vs. 91 Gy, **Weekly fractionation was not included because the data came from a single center*.

---

**Key Points**

- Stereotactic body radiotherapy is safe and effective for low-risk and intermediate-risk prostate cancer.
- The 5-year rates of biochemical disease-free survival were 81% for low-risk and 89% for intermediate-risk patients.
- The 5-year rates of distant metastases and radiation-related toxicity were 1.0% and 1.5% respectively.

---

**On multivariable logistic regression, only acute composite RTOG and CTCAE grade 3 or higher toxic events (GI or GU) were associated with late composite GI or GU RTOG and CTCAE grade 3 or higher toxic events (odds ratio, 19.42; 95% CI, 5.14-73.42; P = 0.008), while EQD3, fractionation, and treatment platform were not (eTables 7 and 8 in the Supplement).** Both fractionation and acute composite RTOG and CTCAE grade 2 or higher toxic events (GI or GU) were associated with late toxic events (odds ratio, 2.75; 95% CI, 1.47-5.16; P = 0.002).
CyberKnife® Advantages

- How a LINAC-based Believer sees it:
  - CyberKnife® corrects for the problem it causes
    - *Longer treatment*, so more motion, so CyberKnife® needs to correct for it
Rotations

• 2017-2018, SB: “You do more than correct translation/rotation; you should be the KEEPERS of this data!”

• “We will help. But we can only give you translations OR rotations, not both...”

“Nothing that we can write-up and won’t change practices/minds, but there is merit!”
Characterizing Intrafraction Target Rotation Correction for Patients Undergoing SBRT for Prostate Cancer

Seth R. Blacksburg, M.D., M.B.A., Matthew R. Witten, Ph.D., Matthew Core, B.S., Anna Theriault, B.Sc., Lauren Perry, B.S., Ren-Dih Sheu, Ph.D., Awais Mirza, RTT, Gizem Demircioglu, M.A., Todd J. Carpenter, M.D., Jason Morgenstern, M.S., and Jonathan A. Haas, M.D.

NYU Winthrop Hospital, Mineola, NY, *Accuray Incorporated, Sunnyvale, CA, ‡Icahn School of Medicine at Mount Sinai, New York

PURPOSE / OBJECTIVE(s)

• Prostate intrafraction translation is a well-described phenomenon during the course of radiotherapy.
• There is a paucity of literature which characterizes the accompanying rotation, which is often uncorrected during the course of treatment.
• Robotic-based Stereotactic Body Radiation Therapy (SBRT) has the ability to correct for intrafraction rotations and translations, with time stamps and movement recorded.
• The purpose of this investigation was to assess the magnitude of prostate intrafraction rotation, as well as to determine the predictors thereof.

RESULTS

• This study represents the largest series characterizing intrafraction prostate rotation during the course of robotic-based SBRT.
• Prostate rotation independent of translation can be significant during the course of treatment, with a high percentage of patients experiencing rotations ≥5°.
• This can occur early during the course of treatment.
• Patients aged ≥65 and those receiving ADT have the highest likelihood of significant intrafraction prostate rotation.
• Radiation facilities administering SBRT for patients with prostate cancer should remain cognizant of the likelihood and magnitude of significant intrafraction prostate rotation during treatment.

MATERIAL & METHODS

• We queried the data management system of 172 patients receiving robotic-based SBRT for localized prostate cancer.
• From September 28, 2015 to January 12, 2018, 13,368 intrafraction prostate rotation corrections occurred for this cohort.
• Patients were treated with a median dose of 3500cGy (2100-3625) over 5 (3-5) fractions.
• The mean age was 66 (41-93).
• The mean CTV, PTV, and Bladder sizes were 75cc's (17.8-215.2), 129.7cc's (34.7-320.8), and 143.9cc's (36.4-408.8), respectively.
• Based on NCCN risk categories, 16.1%, 65.7% and 18.2% had low, intermediate, and high risk disease.
• 19.8% of patients received neoadjuvant and concurrent Androgen Deprivation Therapy (ADT) during treatment.

SUMMARY / CONCLUSION

• The mean intrafraction rotation corrections in the Yaw, Pitch, and Roll planes were 0.6° (0-5.2), 1.3° (0-14.1), and 0.9° (0-8.9), Table 1.
• The mean treatment time per fraction was 19.3 minutes (9-59).
• 60.5%, 37.2%, and 21.5% of patients experienced prostate rotation ≥4°, 5°, or 6° during the course of treatment.
• The mean time to rotation ≥5° was 16 minutes (1-57).
• Patients aged ≥65 were more likely to experience prostate rotation ≥5° during treatment (44.4% vs. 26.4%, p=.016).
• This also occurred for men receiving ADT (58.8% vs. 27.8%, p=.001) and for those with CTV sizes <35cc's (85.7% vs. 32.6%, p=.004), Table 2.
• On multivariate analysis, age ≥65 (OR 2.314, CI 1.073-4.990, p=.032) and the use of ADT (OR 3.611, CI 1.590 -8.200 p=.002) predicted for prostatic rotation ≥5° during treatment (Table 3).

TABLE
Rotations

Not to be a pig, but....
SBRT for prostate cancer is well tolerated with a low actuarial risk of grade 2+ proctitis.

Prostate rotation independent of translation has the potential to modestly affect rectal toxicity.

In patients treated on robotic platforms with pre-treatment administration of amifostine, intrafraction translation and rotation correction minimizes long-term rates of rectal bleeding.

**PURPOSE / OBJECTIVE(s)**

- Stereotactic Body Radiation Therapy (SBRT) is an emerging treatment option for men with localized prostate cancer.

- While the extent of prostate intrafraction translation and rotation has been previously investigated, the clinical impact of rotation independent of translation has not.

- Several series have characterized low rates of rectal toxicity when SBRT is used with different dose regimens.

- This study attempts to quantify the impact of intrafraction rotation on grade 2+ rectal toxicity for men diagnosed with prostate cancer treated with SBRT.

**RESULTS**

- 13 patients developed grade 2 proctitis while 7 developed the grade 3 endpoint.

- 0.41% of all patients required hyperbaric oxygen or procedural intervention to manage toxicity.

- With a mean follow-up of 29 months (6-148), the 5-year freedom from grade 2+ proctitis was 97.8%.

- Rectal bleeding was more likely for patients older than age 75 (7.4% vs. 2.0%, p=.003).

- In rare cases where intrafraction rotation was not corrected, a higher rate of patients experienced rectal bleeding (10.5% vs. 2.9%, p=.03).

- Dosimetrically, a rectal V3600cGy <3cc predicted for decreased risk of bleeding (2.6% vs. 7.8%, p=.006), as did Rectal V3400cGy <6cc’s (1.9% vs. 4.3%, p=.021).

- NCCN risk grouping, ADT, Race, and prescription dose (3500cGy vs. 3625cGy) were not significant.

- On multivariate analysis, the lone predictor of grade 2+ proctitis was intrafraction rotation non-correction (OR 4.033, CI 1.042-15.610, p=.043).

**SUMMARY / CONCLUSION**

- SBRT for prostate cancer is well tolerated with a low actuarial risk of grade 2+ proctitis.

- Prostate rotation independent of translation has the potential to modestly affect rectal toxicity.

- In patients treated on robotic platforms with pre-treatment administration of amifostine, intrafraction translation and rotation correction minimizes long-term rates of rectal bleeding.
ASTRO 2019 Rotations

In general (and of course), rotations matter!
But, a word of caution...

• 2019: Peter Stafford, Grant Weldon, Awais Mirza
  Part II: Attempting to pull Translations AND Rotations...
Thank you!

Acknowledgements

- Jonathan Haas, M.D.
- Matthew Witten, Ph.D.
- Aaron Svoboda, M.A.
- Awais Mirza, RTT
- Todd Carpenter, M.D.
- Gizem Demircioğlu, M.A.
- Ren-Dih Sheu, Ph.D.
- Matthew Core, B.S.
- Anna Theriault, B.Sc.
- Peter Stafford, B.B.A., M.B.A.
- Grant Weldon, M.S.
- Lauren Perry, B.S.
- Mary Coakley, RTT
- Mariann Mieles, RTT
- Andwele O. Murray, RTT
- Christopher Mendez, B.A.
- Jason Morgenstern, M.S.
- (and so many more)