Prostate SBRT – Heterogeneous Dose Distribution: Rationale, Methods, Outcomes and Future Direction: 2017 Update

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Background Rationale:

Typical Prostate Cancer Distribution

- Early HDR Brachytherapy figure illustrating concordance of "hyperdosage" zones

Prostate SBRT – Heterogeneous Dose Distribution: Rationale, Methods, Outcomes and Future Direction: 2017 Update

Virtual HDR CyberKnife Treatment for Localized Prostatic Carcinoma: Dosimetry Comparison With HDR Brachytherapy and Preliminary Clinical Observations

Cited in Scopus: 121
Donald B. Fuller, John Naitoh, Charles Lee, Steven Hardy, Haoran Jin
International Journal of Radiation Oncology • Biology • Physics, Vol. 70, Issue 5, p1588–1597;
Published in issue: April 01, 2008
Prostate SBRT – Heterogeneous Dose Distribution: Rationale, Methods, Outcomes and Future Direction: 2017 Update

“Virtual HDR”

“Real HDR”
CyberKnife® Robotic mechanism has:

- Full rotational correction capability
- Automated feedback loop
- Sub-mm end-to-end aiming accuracy*

**Prostate SBRT – Heterogeneous Dose Distribution: Rationale, Methods, Outcomes and Future Direction: 2017 Update**

- **Summary Dosimetry Slide**
  - Extremely “HDR-Like”
  - Non-uniform margins
    - Customized to case
      - prostate + 2 mm, but . .
        - 0 mm against rectum
        - Prostate + 5 mm ~ DIL

For the treatment plans:

- **PTV:**
  - 3800 cGy/4 fx
  - nCl < 1.2
- **Urethra:**
  - 3800 cGy
- **Rectal Wall:**
  - 3800 cGy
- **Rectal Mucosa:**
  - 2850 cGy (75%)
- **Peripheral Zone:**
  - Mostly > 4750cGy (125%)
Robotic Prostate SBRT: “HDR-like” or “IMRT-like” . . . ?

• “Heterogeneous” prostate SBRT –
  – Is of HDR Brachytherapy Lineage –
  – Intended to be exactly that – “HDR brachy clone” – “Virtual HDR”
  – Smaller margins; 0 mm CTV→PTV against the rectum; 2-5 mm elsewhere
  – Much greater heterogeneity – ON PURPOSE – Escalate the PZ just like REAL HDR brachytherapy
  – 3,800cGy/4 fx; EUD =~ 4,800cGy/4 fx

• “Homogeneous” prostate SBRT
  – Is of IMRT Lineage –
  – RBE calc by Stanford team (Chris King, M.D.) – RBE equivalent to IMRT 74 Gy/37 fx assuming alpha/beta ratio 1.5
  – Slightly larger margins; 3-5 mm all around
  – Typical “IMRT-like” homogeneous dose – Only real difference is dose-fractionation
  – 3,625 cGy/5 fx; EUD = ~ 3,800 cGy/5 fx
5-year outcomes from a prospective multi-institutional trial of heterogeneous dosing stereotactic body radiotherapy (SBRT) for low- and intermediate-risk prostate cancer.

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Presented at ASCO GU Symposium, Orlando FL, 2/16/2017
5-year outcomes from a prospective multi-institutional trial of heterogeneous dosing stereotactic body radiotherapy (SBRT) for low- and intermediate-risk prostate cancer

List of participating institutions

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5-year outcomes from a prospective multi-institutional trial of heterogeneous dosing stereotactic body radiotherapy (SBRT) for low- and intermediate-risk prostate cancer.

- 269 Patients
  - Median f/u = 5 years (Maximum = 9 years)

- Age at diagnosis, years
  - 40-49 1 0%
  - 50-59 36 14%
  - 60-64 46 18%
  - 65-69 69 27%
  - 70-74 67 26%
  - 75-79 35 14%
  - 80+ 5 2%

- Risk Group
  - Low 112 43%
  - Intermediate 147 57%
  - Favorable 114 78%
  - Unfavorable 33 22%
5-year outcomes from a prospective multi-institutional trial of heterogeneous dosing stereotactic body radiotherapy (SBRT) for low- and intermediate-risk prostate cancer

ASCO GU Symposium, Orlando FL, 2/2017

SBRT PROSTATE – 3,800CGY/4 FX

Conventional” IMRT

CyberKnife SBRT

More like “Radical Prostatectomy”
Over 90% of Post-Heterogeneous SBRT PSA rises are “bounces”
  – Yet another “brachytherapy-like” trait

More likely to be a “bounce” if . .
  – Young (esp < 60)
  – Low-risk
  – Gleason 6

More likely to be “real” if . .
  – Older (esp > 70)
  – Intermediate-risk
  – Gleason 7 (esp “4+3”)

Even with “bad factors” though, >70% of all single PSA rises are still “bounces”
5-year outcomes from a prospective multi-institutional trial of heterogeneous dosing stereotactic body radiotherapy (SBRT) for low- and intermediate-risk prostate cancer

- CyberKnife SBRT Prostate – 3,800cGy/4 fx
- bRFS – Phoenix Definition (“nadir + 2”)

PRESENTED: ASCO GU Symposium, 2/2017
Prostate SBRT – Heterogeneous Dose Distribution: EPIC QOL Outcomes

Mean Urinary Score

Mean Bowel Score

Mean Sexual Score

Mean Hormonal Score

Acute decline, rapid recovery

Acute decline, rapid recovery

Acute decline, then “normal aging” pattern

Age: 70 (51-83)

Age: 76 . . .

No effect whatsoever . . .

Average Urinary...

Average Bowel...

Average Sexual...

Average Hormonal Score
Heterogeneous (“HDR-Like”) SBRT: Clinical Results: De Novo Patients

• Conclusions (to 5-7 years f/u):
  – Potency/Efficacy/Toxicity
    • PSA nadir <0.1 ng/mL and 5+ year median time to nadir suggests extremely high biologic potency
    • “Radical Prostatectomy by Computer”
    • First reported “surgical” PSA by an external RT source
    • Biochemical relapse is rare and limited to “int-risk” cases
    • GU/GI toxicity competitive with other RT modalities
      – Vaguely brachytherapy-like “personality, but . . .
      – Catheter-dependent obstruction rate < 0.5%
      – GI toxicity is extremely low
    • ED outcomes are competitive with other RT modalities
      – Younger guys (< 60) have a superior outcome (p<0.04)
CyberKnife® SBRT

- **CONCEPT** –
- “Radical Prostatectomy by Computer . .”
  - Tight margins
  - High Dose
  - Extreme customization
  - +/- 1 mm accuracy

But also covers **margins . . .**
So more like . .
“Radical Prostatectomy **plus** post-op RT by Computer . . .”
SBRT for Post-Radiotherapy Locally Recurrent Prostatic Carcinoma: Evaluation of Toxicity, PSA Response and Disease-free survival

- San Diego and New Jersey combined effort (Donald B. Fuller M.D. and James Wurzer, M.D., PhD)
- SBRT salvage for post-RT local recurrence –
  - Precedence Experience: HDR brachytherapy Salvage
    - UCSF, MSKCC
- **3400cGy/5 fx** – “HDR-like” –
  - Lower dose selected to decrease toxicity potential
  - 0 mm margin expansion
  - “n” =~ 50 now
SBRT for Post-Radiotherapy **Locally Recurrent** Prostatic Carcinoma: Evaluation of Toxicity, PSA Response and Disease-free survival

- 3800cGy/4 fx – De Novo
- 3400cGy/5 fx – Salvage
  - Side by Side . .

Higher Dose; Larger PTV Margin; but same exact “HDR-like” Morphology . .
SBRT for Post-Radiotherapy Locally Recurrent Prostatic Carcinoma: Evaluation of Toxicity, PSA Response and Disease-free survival

- 3400cGy/5 fx – Salvage
  - Covers > 95% of PTV
  - EUD ~ 4250-4300 cGy
    - Vs. EUD ~ 3800cGy w original Chris King 3,625 cGy/5 fx
High-dose-rate stereotactic body radiation therapy for post-radiation therapy locally recurrent prostatic carcinoma: Preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment

• PRO; 2015; 5(6); e615
High-dose-rate stereotactic body radiation therapy for post-radiation therapy locally recurrent prostatic carcinoma: Preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment

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• Preliminary Conclusions:
  – Efficacy/Observations
    • Efficacy exceeds expectation
      – Same PSA response as “de novo” SBRT cases
        » (Though UNLIKE De Novo SBRT, about 20% just keep rising)
        » Tougher group of patients, some w very aggressive disease
      – Disease remains localized longer than we think in most...
  – Toxicity
    • GU domain: 7% incidence of Grade 3+ toxicity; 18% Grade 2
    • Only slightly higher than our “de novo” SBRT cases
      – (de novo Grade 3+ and Grade 2+ GU toxicity =~3% and ~15%, respectively)
    • GI domain: To date – a complete NON-issue in this study
What have we learned since 2006???

• Heterogeneous Series - 3800cGy
  – By 5 years, median PSA reaches 0.1 ng/mL and by 7 years it reaches < 0.1 ng/mL
    • (Do we really need a “0” PSA??)
  – Question: Is “HDR-like” 3,800cGy regimen “Overkill?”
    • Answer (DF): “maybe, however, local recurrence is a 10 year endpoint and we are still not there!”
  – 3,400cGy “salvage regimen” gives an ~ identical “PSA-response” kinetic (small “n” and more ltd f/u though . .)
    • NOTE: EUD =~4300cGy; Same PZ dose escalation design
  – Based on preliminary favorable PSA response/DFS from our lower dose CyberKnife SBRT salvage regimen, as well as multiple other investigators that use lower dose regimens, we commissioned a lower dose arm in 2012 (while also maintaining the “high dose” arm)
CyberKnife® as a Noninvasive Prostate HDR Dosimetry Delivery Mechanism: Feasibility and Preliminary Clinical Results

Which treatment is “better?”

Zelefsky, et al. Urology (77); 986-993; 2011

**Figure 1.** PSA relapse-free survival for favorable risk patients. PSA relapse-free survival rate for brachytherapy versus IMRT at 7 years was 95% and 89%, respectively ($P = .004$).
Which treatment is “better?”

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**Figure 1.** PSA relapse-free survival for favorable risk patients. PSA relapse-free survival rate for brachytherapy versus IMRT at 7 years was 95% and 89%, respectively ($P = .004$).
What about the few patients that do relapse?? (And this question applies to all local treatments, not just CyberKnife®. Happens after IMRT, proton, Radical Prostatectomy, etc.)

- **Traditional Pathways**
  - Primary local treatment
    - If relapse
  - Secondary local treatment if feasible
    - If relapse again
  - Androgen Deprivation Therapy (ADT)
    - AKA – “Hormone treatment”
What about the few patients that do relapse?? (And this question applies to all local treatments, not just CyberKnife®. Happens after IMRT, proton, Radical Prostatectomy)

• **Traditional Pathways . .**
  – Primary local treatment
    • If relapse . .
  – Secondary local treatment if feasible
    • If relapse again . .
  – Androgen Deprivation Therapy (ADT)
  – There is another emerging pathway!
  – Image-guided “Hunt and Destroy” . .
Case Example

- Stage T2b, Gleason 4+3, PSA 6.7ng/mL
- 1 year later . . PSA 24 ng/mL
- Biochemical Relapse – “Phoenix definition (‘Nadir + 2’)”
  - (In his case . . “more like ‘nadir + 20 . .’”)
- Radiology w/u (CT abd/pel; bone scan) – Solitary large focus L pelvic LN
PB

- L pelvic LN – 4000cGy/5 fx
  - 3/26/2014 – Pre-CK salvage PSA 24.1 ng/mL
  - 4/26/2014 - Salvage CK # 2 . . . L pelvic LN
  - 6/2/2014 – PSA 5.9 ng/mL . . and still dropping
  - 5/5/2015 – PSA 0.4 ng/mL . . and still dropping
  - 5/4/2016 – PSA 0.1 ng/mL . . and still dropping
  - 5/30/2017 – PSA 0.079 ng/mL!

- He now has a slightly lower PSA than our primary cured population (their median PSA at this 4 years is 0.1 ng/mL)

- . . . and still has his testosterone!
Newer Imaging

- $^{18}$F Fluciclovine PET/CT
  - “Axumin”
- $^{11}$C Acetate PET/CT
- $^{68}$Ga PET/CT

- ALL of these have about 10 times greater sensitivity to prostate cancer versus prior FDG PET/CT

- New phenomenon
18^F Fluciclovine PET/CT
Solitary hypermetabolic focus R external iliac LN
CyberKnife® . . Round two . . .
5-year outcomes from a prospective multi-institutional trial of heterogeneous dosing stereotactic body radiotherapy (SBRT) for low- and intermediate-risk prostate cancer

- PRESENTED: ASCO GU Symposium, 2/2017

• SBRT Prostate – 3,800cGy/4 fx
Conclusions

• For those few who DO relapse post-SBRT
  – (intermediate-risk only thus far)

• They are **not** failing in the prostate
  – (At least not if SBRT methodology is “High Dose HDR-like”)

• Next generation imaging sometimes finds a solitary focus

• Sometimes we see a relapse in a ?sentinel LN?
  – Response rate of that one in particular is extremely high
    • Well worth looking for before we unleash Lupron on them . . .

• Also high response if relapse in a solitary bone

• If it doesn’t work, we STILL have Lupron, etc . .
Conclusions

• Is Robotic “HDR-like” SBRT “better” than uniform-dosed SBRT?
  – Beauty is in the eye of the beholder!

• For “HDR-like” . . .
  – The most customized match of highest dose to greatest cancer cell burden
  – Allows for extreme dose escalation . . “safe and effective”
  – More “Surgical” precision and margins . . More “prostatectomy-like”
  – Produces a surgical PSA nadir (<0.1 ng/mL) after 7 years
  – Appears precise enough to use as a salvage against local failure of prior RT – Just like “real” HDR brachytherapy . . .
Conclusions

• “SBRT doesn’t have to be better than conventional fractionation, it just has to be not worse!”

• It still wins!
  – Cost . .
  – Convenience to the patient . .

• And . . PSA nadir data suggest . . It just might be better than “conventional fractionation”
Conclusions

• "They are who we thought they were!"...

2007 – 8 patients...

2017 – 8 years!...

![Graph showing PSA levels over time](image-url)
Thank You . . .
Thank You . . .