Stereotactic ablative body radiation for prostate cancer
SABR


Beacon Hospital, Dublin, Ireland
## Low-Intermediate Risk Prostate
### Comparing treatment choices

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>Surgery</th>
<th>Brachy</th>
<th>SABR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
<td>Best</td>
<td>Worst</td>
<td>Intermediate</td>
<td>?</td>
</tr>
<tr>
<td>Rectal</td>
<td>Worst</td>
<td>Best</td>
<td>Intermediate</td>
<td>?</td>
</tr>
<tr>
<td>Sexual Potency</td>
<td>Same</td>
<td>Same</td>
<td>Same Partial</td>
<td>?</td>
</tr>
<tr>
<td>Ejaculation</td>
<td>Partial</td>
<td>None</td>
<td>Partial</td>
<td>?</td>
</tr>
<tr>
<td>Cost</td>
<td>Worst</td>
<td>Worst</td>
<td>A little better</td>
<td>?</td>
</tr>
<tr>
<td>Convenience</td>
<td>Worst</td>
<td>Worst</td>
<td>Best</td>
<td>?</td>
</tr>
</tbody>
</table>
Technique of SABR for prostate cancer

- Patient preparation
- Imaging
- Fiducials
- Target volumes and OARS
- DVCs
- Fractionation
- IGRT
## Methods

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Risk Category</th>
<th>Equipment</th>
<th>Rectal preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>40</td>
<td>Low</td>
<td>Linac</td>
<td>Diet to minimize gas Daily simethicone</td>
</tr>
<tr>
<td>Fort Meyers</td>
<td>65</td>
<td>Low</td>
<td>Trilogy</td>
<td>Not stated</td>
</tr>
<tr>
<td>Stanford</td>
<td>67</td>
<td>Low</td>
<td>Cyberknife</td>
<td>Not stated</td>
</tr>
<tr>
<td>Flushing</td>
<td>304</td>
<td>Low 211 Inter 81 High 12</td>
<td>Cyberknife</td>
<td>Daily intrarectal amifostine</td>
</tr>
<tr>
<td>Naples (Fla)</td>
<td>113</td>
<td>T1c-T2c GS 6 Mean PSA 6</td>
<td>Cyberknife</td>
<td>Not stated</td>
</tr>
<tr>
<td>Series</td>
<td>Fiducials</td>
<td>Immobil</td>
<td>TDF</td>
<td>CTV to PTV margins</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>---------</td>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Seattle</td>
<td>3</td>
<td>Not stated</td>
<td>33.5/5</td>
<td>4-5mm</td>
</tr>
<tr>
<td>Fort Meyers</td>
<td>Calypso real time</td>
<td>Not stated</td>
<td>40/5 Alt days</td>
<td>2mm</td>
</tr>
<tr>
<td>Stanford</td>
<td>3</td>
<td>Alpha cradle</td>
<td>36.25/5 daily then alt days</td>
<td>5 mm post 3mm</td>
</tr>
<tr>
<td>Flushing</td>
<td>4 gold</td>
<td>Not stated</td>
<td>35/5 then 36.25/5</td>
<td>5 mm post 3mm</td>
</tr>
<tr>
<td>Naples (Fla)</td>
<td>gold</td>
<td>Not stated</td>
<td>35/5</td>
<td>5 mm post 3mm</td>
</tr>
</tbody>
</table>
Gold Fiducial Markers

• Positioned at the apex, intermediate lateral zone, and base
• Minimum distance of 2 cm between them
• Angle between the different groups of fiducials should not be <15°
SABR fractionation

- Reimbursement for “Stereo” is ≤5 fractions
- William Beaumont 2005 comparing HDR 38 Gy/4 or 42 Gy/6 versus LDR (Pd-103)
- “template” for fractionation
- 5-year event-free survival (98% vs. 85%, p=0.01)
- Acute and late toxicity, potency 84% vs. 55%
- 2009 update 5-year freedom from biochemical relapse rate of 91%

Isolated Local Recurrence 12 years after RT
Re-irradiation
Conventional Fractionation
SABR techniques
Intermediate risk
PTV 30 = P+prox SV
PTV 36.25 Prostate +0.5cm (0.3 post)
PTV 40 = Prostate only
Urethra +0.3cm 30Gy

MRI 1 week after fiducials
<table>
<thead>
<tr>
<th>RTOG Grade</th>
<th>GI</th>
<th>GU</th>
<th>p</th>
<th>GI</th>
<th>GU</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Daily 56%</td>
<td>Alt Days 95%</td>
<td>0.001</td>
<td>Daily 37%</td>
<td>Alt Days 80%</td>
<td>0.003</td>
</tr>
<tr>
<td>1-2</td>
<td>Daily 44%</td>
<td>Alt Days 5%</td>
<td>0.001</td>
<td>Daily 56%</td>
<td>Alt Days 17%</td>
<td>0.07</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
<td>6%</td>
<td>2%</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Potency Preservation

- 80% potency preservation rates reported by Flushing and Naples
- 40% rate reported by Stanford – impact of higher dose?
- Flushing and Naples fused MRI scans into the planning CT
- MRI scans provide more detailed views of the prostate. Smaller GTVs result in lower doses to the neurovascular bundles
Proximal neurovascular plate (PNP), accessory neurovascular plate (ANP) and predominant neurovascular bundle (PNB).
Proximal neurovascular plate (PNP), accessory neurovascular plate (ANP) and predominant neurovascular bundle (PNB).

Treat the tumour
Not the room
Health-Related Quality of Life After SABR: Consortium of Prospective Trials

- 4 trials: UCLA, San Diego, Flushing, Dumbowski all cyberknife
- Patient self-reported QOL 864 patients from phase 2 clinical trials
- Expanded Prostate Cancer Index Composite (EPIC) instrument
- Median dose of 36.25 Gy in 4 or 5 fractions.
- Short course hormones 14% of patients.
- Median follow-up was 3 years and 194 evaluable at 5 years.

King et al. IJROBP 87:939–945, 2013
Unadjusted changes vs. baseline mean scores stratified into 4 quartiles according to degree of initial decline in QOL score within the first 3 months after SABR.

A transient decline in the urinary and bowel domains was observed within the first 3 months after SBRT which returned to baseline status or better within 6 months and remained so beyond 5 years.

Sexual decline predominantly over first 9 months.

King et al. IJROBP 87:939–945, 2013
DVCs for 36.25/5 to PTV

- Prostate itself 40Gy/5
- Rectum – Solid organ: V36Gy < 1cc
- Bladder – Empty solid structure: V37Gy < 10cc
- Sigmoid / Bowel: V30Gy<1cc
- Prostatic urethra: MRI delineation: V47Gy < 20%. HDR series, Cyberknife issue, Trilogy max doses lower.
- Membranous urethra: D50 < 37 Gy
- Neurovascular bundles: If identified V38Gy<50%.
- Penile Bulb: V29.5Gy < 50%
- Testes: delineate and minimise. Non coplanar beams
Dosimetric and Patient Correlates of Quality of Life After Prostate Stereotactic Ablative Radiation Therapy

• Phase II trial  low risk SABR 35 Gy in 5 fractions, once weekly.
• N=84
• MRI, Machine and tracking not stated
• EPIC at baseline and q6 month up to 5 years.
• Eighty-four patients median follow-up was 50.8 months
• Among patients with “no problem” in the sexual domain at baseline, 63.0% averaged a “moderate problem” during follow-up, and 11.1% averaged a “big problem” over the 6-60 month follow-up.
• On univariate analysis Rectal V31.8 > 10%, D1cc > 35Gy were associated with bowel MCIC,
• Penile bulb V35>4%, V20>40% with sexual MCIC.
• On multivariate analysis rectal D1cc and Penile bulb V35 were predictors of worse QOL
• Urinary toxicity?

Helou et al ASTRO 2014 #2513 Sunny Brook
Penile bulb: V29.5 <50%

Neurovasc. bundle: V38 <50%

Rectum: V36 <1cc

Bladder: V37 < 10cc

Urethra: ?rules – ALARA avoid hot spots

* Cyberknife only
SABR for cT1c - cT3a prostate cancer with a low risk of nodal metastases (≤ 20%, Roach index): a Novalis Circle Phase II prospective randomized Trial

- **Trial structure** Random 36.25 Gy (5 x 7.25 Gy) in 9 vs. 28 days
- **Endpoints;** Response, QOL (urinary, rectal, sexual).
- **Technique:** Full bladder, daily rectal prep, endorectal balloon, tracking not mandatory

- **PTV 36.25 Gy:** 98% of the volume receives at least 95% of 34.43 Gy ≤ 107% of the prescribed dose
- **Urethral PRV (3mm):** 32.5 Gy 98% of the volume receives ≥95% of the prescribed dose 30.87 Gy, 50% of the volume receives ≤ 32.5 Gy
- **Rectal wall** ≤ 5% to receive 36.25 Gy. V_{90%} < 10
- **Bladder wall** ≤ 10-15% to receive 36.25 Gy. V_{50%} < 50%
- **Penile bulb** D_{mean} to 95% ≤ 75% of the prescribed dose (i.e. 27.2 Gy)
<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Risk Category</th>
<th>Definition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>40</td>
<td>Low</td>
<td>5- year nadir + 2</td>
<td>93% Median PSA nadir 0.65</td>
</tr>
<tr>
<td>Fort Meyers</td>
<td>65</td>
<td>Low</td>
<td>Mean PSA values</td>
<td>Pre, 1,2,3 years 7,1, 0.4, 0.3</td>
</tr>
<tr>
<td>Stanford</td>
<td>67</td>
<td>Low</td>
<td>4- year nadir +2</td>
<td>94%</td>
</tr>
<tr>
<td>Flushing</td>
<td>304</td>
<td>Low 211</td>
<td>4- year nadir +2</td>
<td>Low 98.5% Inter 93% Hi 75% Median PSA 0.11 at 4 years</td>
</tr>
<tr>
<td>Naples (Fla)</td>
<td>113</td>
<td>T1c-T2c GS 6</td>
<td>2y mean psa</td>
<td>0.78 2 biopsy proof LR</td>
</tr>
</tbody>
</table>
SABR 6 year results
A Katz and J. Kang; Flushing, NY

- N=515 Cyberknife
- Low-risk 343, intermediate risk 134, high risk 38.
- Hormones in 70
- 35Gy/5 n=158,
- 36.25 Gy in remainder
- Rx 83-87%
- PTV = prostate +0.5 (0.3post)
- Vesicles included for intermediate+ high-risk patients.
- Vesicles – extent of inclusion? motion?
- Median follow-up 54 months

- Actuarial 6 year bRFSs 97.4% low, 92% inter, and 70.4% hi risk.
- No advantage for higher dose lo-inter risk
- Late RTOG toxicity Grade 2 rectal 4%, Grade 2 urinary 7.8%, and Grade 3 urinary 1.4% (all with 36.25 Gy).
- Late Grade 2 urinary toxicity for 35 Gy was 5.1% vs 9.9% for 36.25 Gy (p = .01).
- Mean EPIC urinary and bowel QOL declined at 1 month post-treatment and returned to baseline by 2 years where they remain.
- EPIC sexual QOL declined by 23% at 6-12 months where it remains.
- Potency preservation 74%
Patient self-reported QOL in 207 patients from two sequential phase 2 clinical trials:
- SABR to a total dose of 35 Gy in 5 fractions once weekly, n=84
- 15 Gy/1 HDR then EBRT 37.5 Gy /15 over 3 weeks, n=123
- Standard clinical characteristics not provided in abstract
- Median follow up of 50.8 and 61.2 months
- At 5 years biochemical free survival > 95% both trials.
- SABR patients higher overall urinary (p<0.0001) and bowel scores (p = 0.028) (i.e better QOL)
- The sexual domain score and function sub-score significantly decreased over time (p<0.0001) and patient treated with SBRT had higher scores (p<0.01).
- Among patients who didn’t have a problem with their sexual QOL at baseline (score 75-100), 11% SABR and 42% HDR averaged a “big problem” (<50) during follow-up (p = 0.0075).
Low and intermediate risk prostate cancer

- Radiation, Surgery, Brachytherapy apparently equivalent anti-cancer outcome
- Choice is difficult for patient, partner, doctor
- Focus on toxicity rather than tumour outcome
- No therapy perfect, No therapy bad
- Stereotactic ablative body radiotherapy attractive option in clinical practice
## Summary preliminary analysis

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>Surgery</th>
<th>Brachy</th>
<th>SABR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
<td>Best</td>
<td>Worst</td>
<td>Intermediate</td>
<td>Very promising</td>
</tr>
<tr>
<td>Rectal</td>
<td>Worst</td>
<td>Best</td>
<td>Intermediate</td>
<td>Possibly better than IMRT</td>
</tr>
<tr>
<td>Sexual Potency</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
<td>Very high preservation</td>
</tr>
<tr>
<td>Ejaculation</td>
<td>Partial</td>
<td>None</td>
<td>Partial</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Worst</td>
<td>Worst</td>
<td>A little better</td>
<td>Cheapest</td>
</tr>
<tr>
<td>Convenience</td>
<td>Worst</td>
<td>Worst</td>
<td>Best</td>
<td>Best</td>
</tr>
</tbody>
</table>
• END
Dosimetric Parameters Predict Quality of Life Outcomes for Patients Receiving Stereotactic Body Radiation Therapy for Prostate Cancer

86 patients 40 Gy in 5 fractions volumetric modulated arc therapy technique.

Tracking not stated

Expanded Prostate Cancer Index Composite (EPIC) questionnaire

Patients in the top 25th percentile of PTV100 volumes had the worst reduction in urinary QOL, but not in bowel QOL.

The association between PTV and urinary QOL is most likely related to the length of urethra irradiated.

Urinary QOL significantly decreased in patients with the top 25th percentile of bladder V100 volumes.

Bowel QOL was significantly decreased in patients with the top 25th percentile of rectal V90 and V100 volumes. It was also significantly reduced in patients with rectal V50 above the median in the presence of comorbid conditions.

“The volumes of the rectum and bladder receiving >80% of the prescribed dose should be minimized in order to maximize recovery to baseline QOL after prostate SBRT.”

Common sense but doesn’t supply usable DVC data!

Gomez et al UCLA @ ASTRO 2014
SABR for cT1c - cT3a prostate cancer
with a low risk of nodal metastases (≤ 20%, Roach index):
a Novalis Circle Phase II prospective randomized Trial

- 36.25 Gy (5 x 7.25 Gy) in 9 vs. 28 days
- Endpoints; Response, Tolerance (urinary, rectal, sexual). QOL

- 32.5 Gy (6.5 Gy/fraction) to the urethral PRV
- PTV 36.25 Gy: 98% of the volume receives at least 95% of the prescribed dose 34.43 Gy
- PTV 36.25 GY: ≤ 107% of the prescribed dose (i.e., 2% of the volume receives a maximum dose equivalent to the 107% of the prescribed dose: 38.78 Gy)
  - Homogeneity index (HI): (D_{2\%} - D_{98\%}) / D_{50\%}. The ratio must be trending to “0” for the PTV.
  - Dice similarity coefficient (DSC): (TV_{98\%} \cap PTV) / (TV_{98\%} \cup PTV) (TV_{98\%} or treatment volume 98% is the volume enclosed within the 98% isodose level; “\cap” for intersection; “\cup” for union). The ratio must be as close to “1” as possible.
- Urethral PRV: 32.5 Gy
- D_{98\%} (D_{\text{near min}}) ≥ 95% of the prescribed dose (i.e., 98% of the volume receives at least 95% of the prescribed dose if achievable: 30.87 Gy)
- D_{50\%} ≤ 100% of the prescribed dose (i.e., 50% of the volume receives at most 100% of the prescribed dose if achievable: 32.5 Gy)
- D_{5\%} ≤ 107% of the prescribed dose (i.e., 5% of the volume receives a maximum dose equivalent to the 107% of the prescribed dose: 34.77 Gy)
- D_{2\%} (D_{\text{near max}}) ≤ 110% of the prescribed dose (i.e., 2% of the volume receives a maximum dose equivalent to the 110% of the prescribed dose: 35.75 Gy)
- 5.2. Rectal wall
- V_{100\%} < 5% (i.e., no more than 5% of the rectal wall to receive 100% of the prescribed dose: 36.25 Gy).
- V_{90\%} < 10% (i.e., no more than 10% of the rectal wall to receive 90% of the prescribed dose: 32.62 Gy). An acceptable deviation for VMAT: V_{90\%} < 15% (i.e., no more than 15% of the rectal wall to receive 90% of the
• 40 low risk
• Linac 6 non-coplanar
• diet to minimize gas and took daily simethicone
• Daily localization with 3 fiducials
• 33.5 Gy in 5, margins 4-5mm
• Late GI:30% (22.5% grade 1 and 7.5% grade 2).
• Late GU:37.5% (22.5% grade 1, 12.5% grade 2, and 2.5% grade 3).
• 5- year (nadir + 2) BRFS= 93%.Median PSA nadir 0.65
Comparison of Active Surveillance, Low-Dose-Rate Brachytherapy, Stereotactic Ablative Body Radiation Therapy, and Standard External Beam in Low-Risk Prostate Cancer
Musunuru et al Sunny Brook Toronto ASTRO 2014

178 had AS, 76 had 76 Gy/38 fractions, 83 had SABR (35 Gy/5 fractions), 185 had LDR

Median follow up was 51 months

In the AS cohort, 38 pts (21.3%) underwent active treatment.

6 year bDFS were 97%, 93%, 97%, and 96 % for the AS, LDR, SABR, and EBRT groups (p = 0.28).

Rectal bleeding: AS 2.24%, LDR 3.13%, SABR 7.14%, and EBRT 9.88%.

Higher incidence of haematuria in the LDR cohort (11.98%), compared to other groups.
• N= 269 35-36.25 Gy in 5 fractions delivered with the CyberKnife
• Bowel domain of the Expanded Prostate Index Composite (EPIC)-26
• Median follow-up 3.9 years minimum 2 years.
• Late rectal bleeding ≥ Grade 2 actuarial risk at 2 years was 1.5%.
• At 1 month post-SBRT, 11.2% and 8.5% of patients reported a moderate-big problem with urgency and frequency, respectively.
• The EPIC bowel summary scores declined transiently at 1 month and then experienced a second, more protracted decline between 6 months and 18 months before returning to near-baseline at 2 years post-SBRT