SABR (SBRT) for Prostate Cancer

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Structure

• Introduction: Prostate brachytherapy in N. Ireland

• SABR:
  – What is it?
  – How is it delivered?
  – Results to date
  – Current trials
Introduction - Brachytherapy

- NI – LDR service - 2009
- Sunnybrook fellowship
  - LDR
  - HDR
  - SABR
    - HDR NI business case
HDR starts in Belfast – April 2016

- LDR or HDR monotherapy?
- HDR or LDR combined with EBRT?
- ADT – for whom?
- IM risk – need for better stratification
SABR (SBRT) – What is it?

• SABR – Stereotactic Ablative Radiotherapy
• SBRT – Stereotactic Body Radiotherapy.

• These terms are used interchangeably.
SABR – What is it?

“The precise delivery of highly conformal, image-guided, hypofractionated (>5 Gy/fraction) external beam radiotherapy delivered in a single or few fraction(s) to an extra-cranial body target, with doses at least biologically equivalent to those doses considered radical when given over a protracted conventionally (1.8-3.0 Gy/fraction) fractionated course.”

CARO (Sahgal, 2012).

• Brachytherapy vs EBRT – we cannot beat physics.
• Consider brachytherapy first, EBRT next.
Prostate SABR – Why now?

- Initially Cyberknife platform
- LINAC based – CBCT, VMAT, Flattening Filter Free enables
  - Decreased margins, hypofractionation, acceleration
\( \alpha/\beta \) ratio of prostate is low - Sensitive to fraction size

**DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL INSTITUTIONAL DATASETS: \( \alpha/\beta = 1.4 \) (0.9–2.2) GY**

RAYMOND MIRALBELL, M.D.,*† STEPHEN A. ROBERTS, PH.D.,‡ EDUARDO ZUBIZARRETA, M.D.,§ AND JOLYON H. HENDRY, PH.D.‖

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- Overall \( \alpha/\beta \) 1.4 (0.9-2.2)
- CHHiP – between 1.4 and 2.4
• Dose escalation improves biochemical control (Viani, 2009)
• Moderate hypofractionation – CHHiP (Dearnaley, GU ASCO 2016)
  – 60Gy in 20# vs 57Gy in 19# – HR 1.44 (95% CI 1.13 to 1.82)
  – Biochemical control at 5y 90.6% vs 85.9%
### SABR boost studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. pats.</th>
<th>Boost Dose</th>
<th>Platform</th>
<th>Risk</th>
<th>Outcome</th>
<th>Late Toxicity G≥2</th>
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<tbody>
<tr>
<td>Miralbell</td>
<td>2010</td>
<td>50</td>
<td>10-16Gy in 2#</td>
<td>LINAC</td>
<td>L/I/H</td>
<td>5y BC 98%</td>
<td>GU 12%, GI 10%</td>
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<tr>
<td>Oermann</td>
<td>2010</td>
<td>24</td>
<td>19.5 Gy in 3#</td>
<td>CK</td>
<td>I/H</td>
<td>PSA</td>
<td>GU 8%, GI 0%</td>
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<tr>
<td>Katz</td>
<td>2010</td>
<td>73</td>
<td>19-21 Gy in 3#</td>
<td>CK</td>
<td>I/H</td>
<td>3y BC 89-78%</td>
<td>GU 5%, GI 2%</td>
</tr>
<tr>
<td>Anwar</td>
<td>2016</td>
<td>48</td>
<td>19-21 Gy in 2#</td>
<td>CK</td>
<td>I/H</td>
<td>5y RFS 83%</td>
<td>GU 20%, GI 4%</td>
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</tbody>
</table>

- Many more studies of SABR alone
- Variation in:
  - number of fractions
  - total dose
  - Margins
  - Overall treatment duration
Phase II trial

Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials

Christopher R. King, Debra Freeman, Irving Kaplan, Donald Fuller, Giampaolo Bolzico, Sean Collins,

- n=1100
- 2003-11
- Cyberknife
- Median 36.25/5
While it is necessary to observe patients treated for prostate cancer for extended intervals to gauge the rate of long term (beyond 10 years) biochemical control and overall survival, the interim results reported appear at least as good as other forms of radiotherapy administered to patients with equivalent risk levels followed for the same duration post-treatment.

It is ASTRO’s opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease.
National Radiotherapy Implementation Group Report

Stereotactic Body Radiotherapy

- 2011
- Prostate SABR recommended only within clinical trials
A cautionary tale...
Phase I Dose-Escalation Study of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer

Thomas P. Boike, Yair Lotan, L. Chinsoo Cho, Jeffrey Brindle, Paul DeRose, Xian-Jin Xie, Jingsheng Yan, Ryan Foster, David Pistenmaa, Alida Perkins, Susan Cooley, and Robert Timmerman

See accompanying editorial on page 1940

- Phase I dose escalation study
- 15 patients per cohort
- 36h between fractions
- HDR dose/fractions +
- Escalation allowed if 4 or less of 15 patients experienced DLTs (G3-5)
- Phase II at 50Gy in 5#

<table>
<thead>
<tr>
<th>Center</th>
<th>Dose/frac</th>
<th>Fraction size</th>
<th>$\alpha/\beta$ 1.4</th>
<th>$\alpha/\beta$ 3</th>
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<tbody>
<tr>
<td>PACE</td>
<td>36.25/5</td>
<td>6.7</td>
<td>92</td>
<td>74</td>
</tr>
<tr>
<td>Toronto</td>
<td>40/5</td>
<td>8</td>
<td>111</td>
<td>88</td>
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<tr>
<td>Texas</td>
<td>45/5</td>
<td>9</td>
<td>138</td>
<td>108</td>
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<tr>
<td>Texas</td>
<td>47.5/5</td>
<td>9.5</td>
<td>152</td>
<td>118</td>
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<tr>
<td>Texas</td>
<td>50/5</td>
<td>10</td>
<td>168</td>
<td>130</td>
</tr>
</tbody>
</table>
Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD, † Christopher Straka, BS,* Alana Christie, MS, ‡ Yair Lotan, MD, § David Pistenmaa, MD,* Brian D. Kavanagh, MD, ¶ Akash Nanda, MD, PhD, ¶¶ Patrick Kueplian, MD, # Jeffrey Brindle, MD, ** Susan Cooley, RN,* Alida Perkins, ANP,* David Raben, MD, ‖ Xian-Jin Xie, PhD, ‡ and Robert D. Timmerman, MD*

**Results:** At the highest dose level, 6.6% of patients treated (6 of 91) developed high-grade rectal toxicity, 5 of whom required colostomy. Grade 3+ delayed rectal toxicity was strongly correlated with volume of rectal wall receiving 50 Gy >3 cm³ (P<.0001), and treatment of >35% circumference of rectal wall to 39 Gy (P = .003). Grade 2+ acute rectal toxicity was significantly correlated with treatment of >50% circumference of rectal wall to 24 Gy (P = .010).
There is a need for prospective randomised controlled trials
HYPO RT – Widmark et al.

- n= 592
- 42.7 Gy in 7 fractions in 15-19 days
- Vs 78Gy in 39 fractions
- Superiority trial (improve bFFS by 10% at 5y)
- In follow-up

Intermediate Risk Patients

\[
\begin{align*}
\text{Conv:} & \quad 2 \text{ Gy} \times 39 \quad = 78 \text{ Gy} \\
\text{HYPO:} & \quad 6.1 \text{ Gy} \times 7 \quad = 42.7 \text{ Gy}
\end{align*}
\]
PACE (Prostate Advances in Comparative Evidence)

- Early stage prostate cancer
  - Clinical stage T1c-T2c
  - Gleason Score ≤ 3 + 4
  - PSA ≤ 20 ng/ml

- Surgical consideration (Y/N)?
  - Yes
    - PACE A: Randomise (stratify by risk group and centre)
    - Laparoscopic Surgery (429 patients)
    - Prostate SBRT: 36.25 Gy in 5 fractions (429 patients)
  - No
    - PACE B: Randomise (stratify by risk group and centre)
    - Conventional fractionation: 78 Gy in 39 frx OR 62 Gy in 20 frx (429 patients)
    - Prostate SBRT: 36.25 Gy in 5 fractions (429 patients)

- PACE C – in planning
- High-tier IM or high risk
- 36.25 Gy in 5# vs 62 Gy in 20#
- 6-12 months ADT
- N=858
What about pelvic lymph nodes?
SPORT High-Risk – A Randomised Feasibility Study Evaluating Stereotactic PrOstate RadioTherapy in High-Risk Localised Prostate Cancer with or without Elective Nodal Irradiation

**Primary End-pt**

**Feasibility**

- Technical feasibility
- Adequate recruitment rate
- Acute toxicity
- Calculation of the sample size for the Phase II

**Exploratory biomarkers**

- Tissue – DDRD, PTEN, Tumour initiating cells
- Blood - γ-H2AX, 53BP1, citrulline (small bowel), ceramide, cytokines (CXCL1, CXCL6, CXCL8, CXCL10, TNF-α), HMGB1, Raman spectroscopy (DIT)
- Urine - ATP and urinary neurotrophins
Fiducial and Biopsy Clinic

Fiducials

Biopsies

Without SpaceOAR Hydrogel

With SpaceOAR Hydrogel

Hydrogel spacer

Friends of the cancer centre

Oncology Systems Limited

Augmenix
When could SABR be considered?

- Patient preference
- Unfit for GA
- LUTS?
- Prostate size?
- Lack of access/capacity