SABR (SBRT) for Prostate Cancer

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Structure

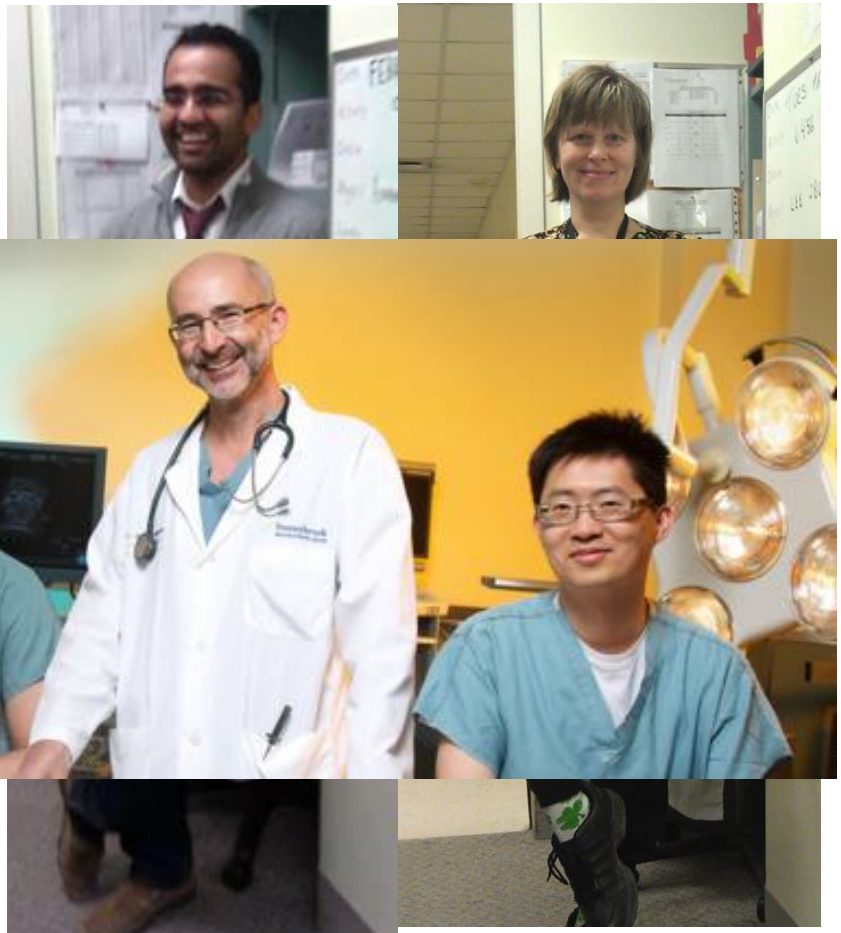
- Introduction: Prostate brachytherapy in N. Ireland

- 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



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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

Belfast Health and Social Care Trust

SABR (SBRT) – What is it?

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

- These terms are used interchangeably.

SABR UK Consortium

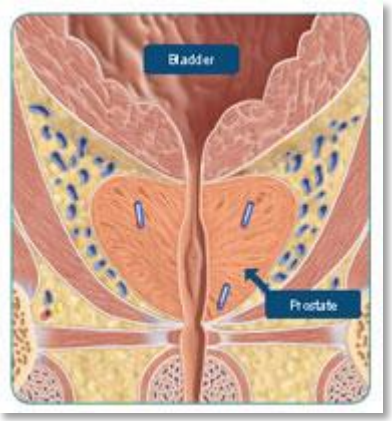
SABR – What is it?

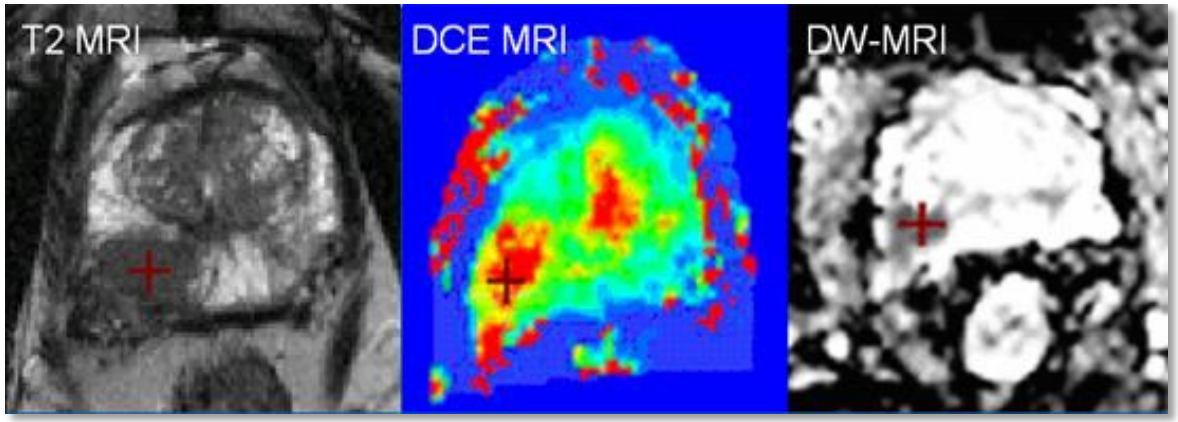
"The precise delivery of **highly conformal**, **image-guided**, **hypofractionated** (≥5 Gy/fraction) external beam radiotherapy delivered in a **single or few fraction**(s) to an extra-cranial body target, with doses at least biologically equivalent to those doses considered **radical** when given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

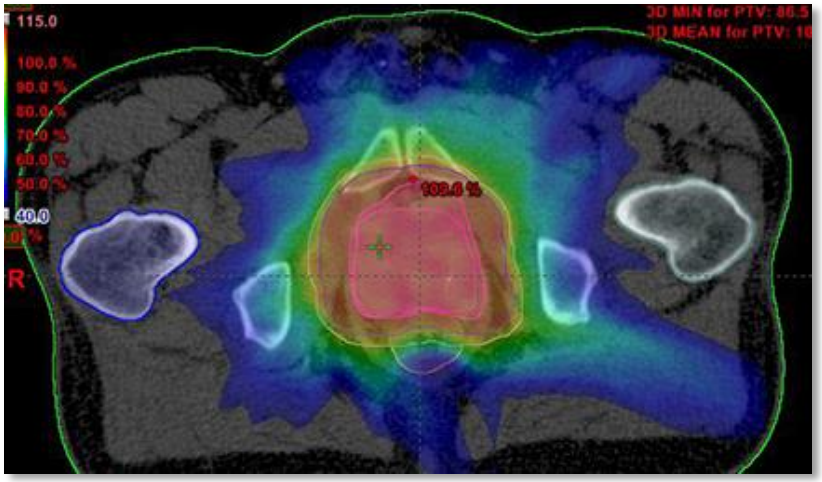
CARO (Sahgal, 2012).

- **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

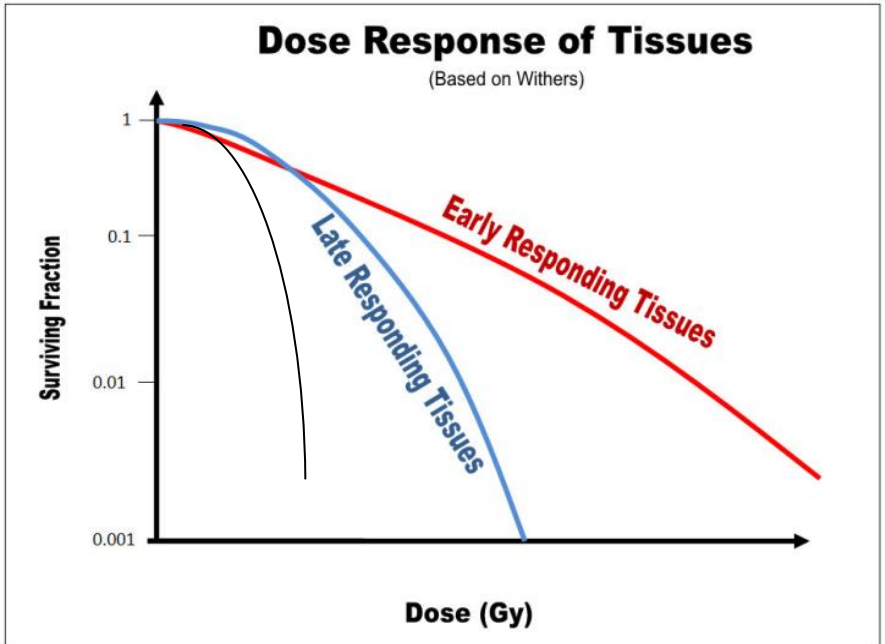
α/β ratio of prostate is low - Sensitive to fraction size

DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL INSTITUTIONAL DATASETS: α/β = 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.‖

*University Hospital, Geneva, Switzerland; †Institut Oncològic Teknon, Barcelona, Spain, ‡Health Sciences—Methodology, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, United Kingdom; §International Atomic Energy Agency, Vienna, Austria; and ‖Adlington, Macclesfield, United Kingdom

- Overall α/β 1.4 (0.9-2.2)
- CHHiP – between 1.4 and 2.4



Meta-analysis - Bentzen, Vogelius, 2012

Table 2 Equivalent doses in 2-Gy fractions (EQD_2) for a standard dose fractionation scheme and illustrative hypofractionated regimens

				$\alpha/\beta = 0.47$ Gy $\delta_{prolif} = 0$		$\alpha/\beta = 1.93$ Gy $\delta_{prolif} = 0.31$ Gy/d		$\alpha/\beta = 4.14$ Gy $\delta_{prolif} = 0.31$ Gy/d	
Dose (Gy)	Fractions	Dose/ fraction (Gy)	OT (d)	EQD_2	bNED @ 5 y (%)	EQD_2	bNED @ 5 y (%)	EQD_2	bNED @ 5 y (%)
78	39	2	53	78	70	78	70	78	70
72	30	2.4	42	84	76	83	76	80	73
57	19	3	25	80	72	80	73	75	66
60	20	3	26	84	76	84	77	78	70
58	16	3.63	26	96	85	90	83	82	75
51.6	12	4.3	19	100	88	92	85	81	74
42.7	7	6.1	15	114	94	99	89	83	76
38	5	7.6	7	124	96	106	93	87	80
40	5	8	29	137	98	108	94	87	80

Abbreviation: OT = overall treatment time.
We assumed 5-y biochemical no evidence of disease (bNED) of 70% of the current clinical standard (78 Gy/39 fractions) and used a steepness of the dose-response curve, $\gamma_{50} = 0.78$ Gy for $\delta_{prolif} = 0$ and $\gamma_{50} = 1.0$ when the synthesized time factor was taken into account ($\delta_{prolif} = 0.31$ Gy/d).

- 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

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

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

Radiotherapy and Oncology

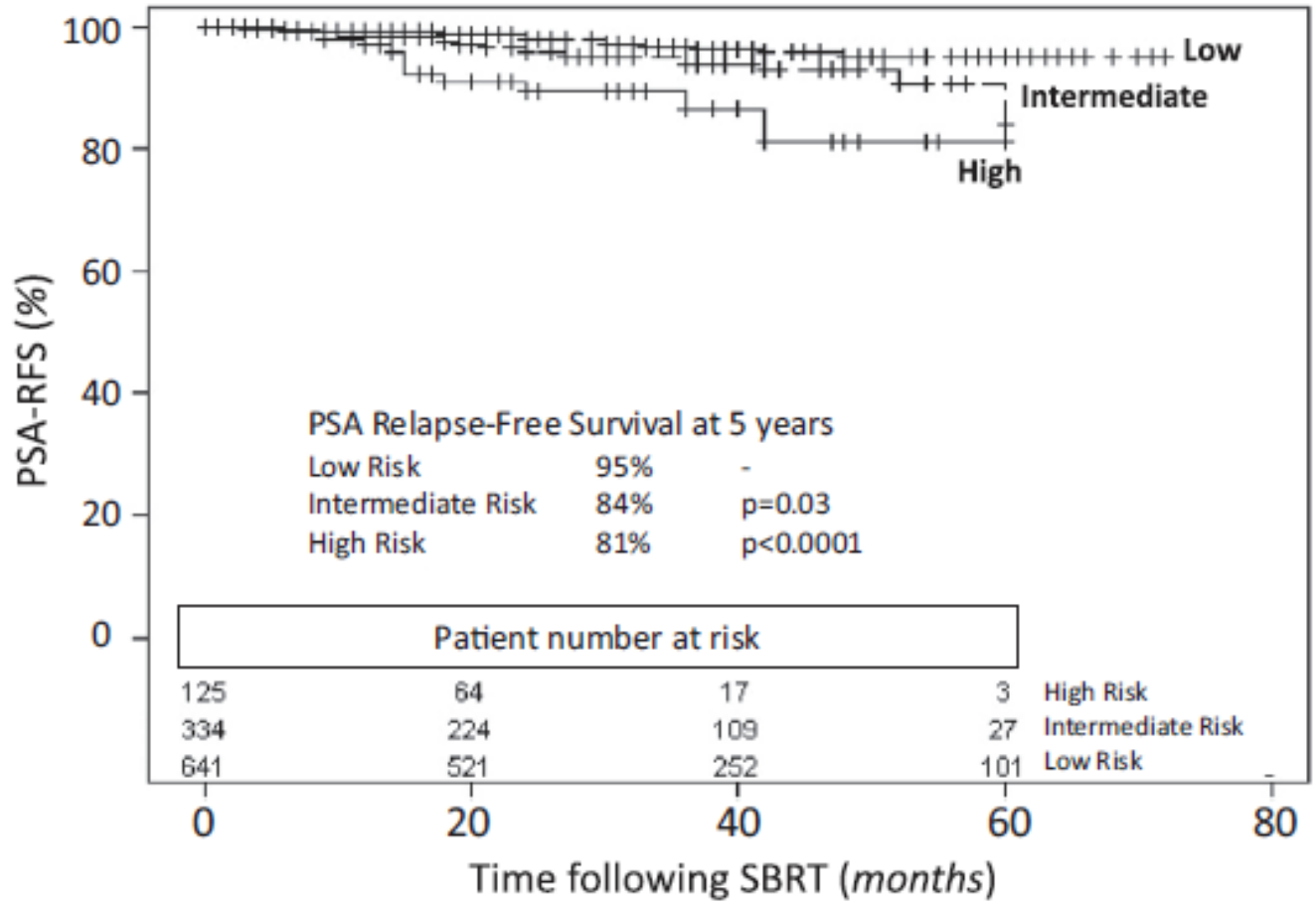
journal homepage: www.thegreenjournal.com

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 [a,*], Debra Freeman [b], Irving Kaplan [c], Donald Fuller [d], Giampaolo Bolzicco [e], Sean Collins [f],

logy, Beth Israel Deaconness, Boston, MA;
tment of Radiation Oncology,
ion Oncology, Flushing, NY, United States



- n=1100
- 2003-11
- Cyberknife
- Median 36.25/5

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2013 – SBRT Model Policy

ASTRO

TARGETING CANCER CARE

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.

NHS

National Cancer Action Team

National Radiotherapy Implementation Group Report

Stereotactic Body Radiotherapy

- 2011
- Prostate SABR recommended only within clinical trials

A cautionary tale…

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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#

Center	Dose/frac	Fraction size	EQD_2 α/β 1.4	EQD_2 α/β 3
PACE	36.25/5	6.7	92	74
Toronto	40/5	8	111	88
Texas	45/5	9	138	108
Texas	47.5/5	9.5	152	118
Texas	50/5	10	168	130

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 cm^3 ($P<.0001$), 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 ($P=.010$).

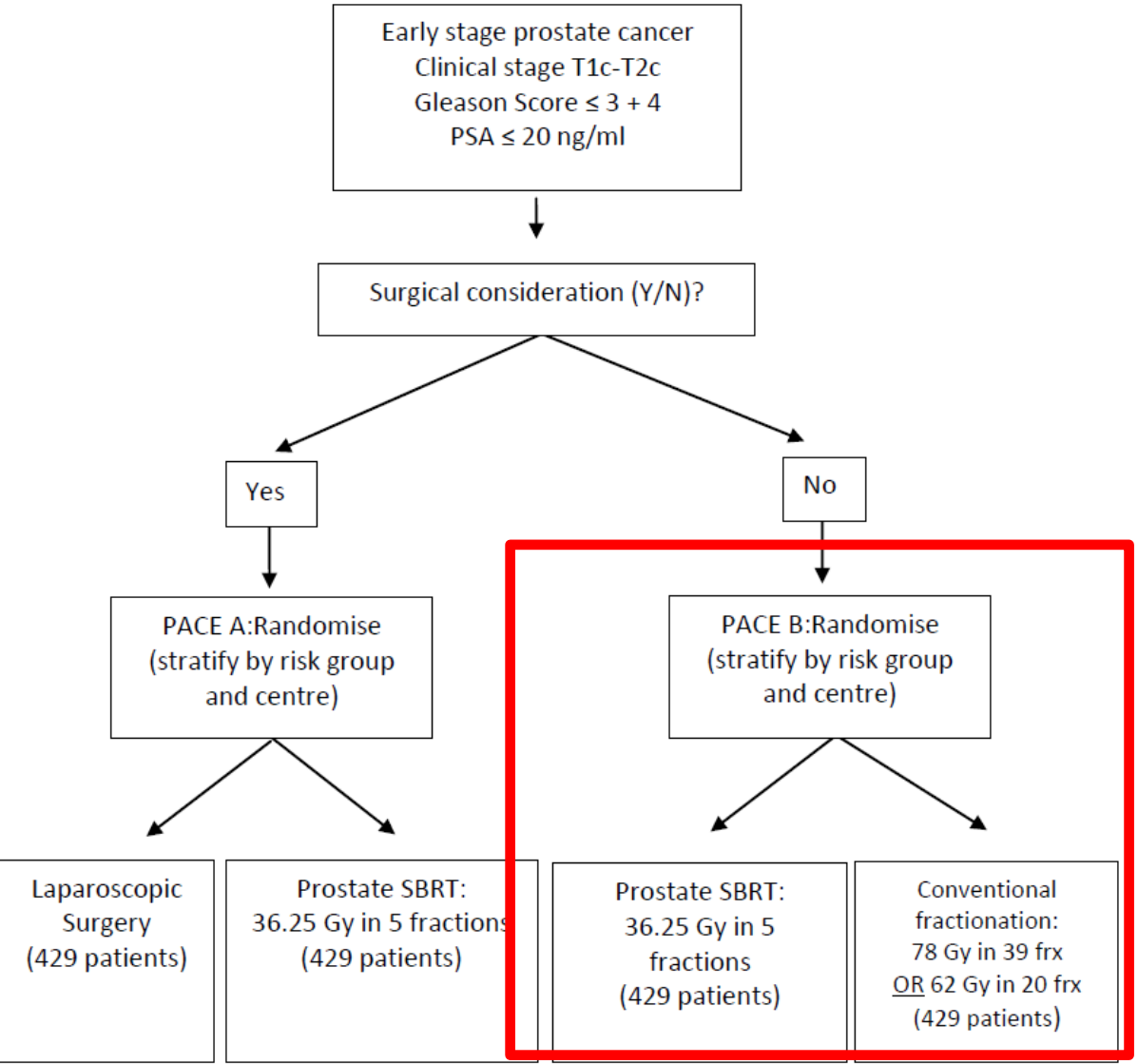
IJROBP, 2014

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

PACE (Prostate Advances in Comparative Evidence)



- 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

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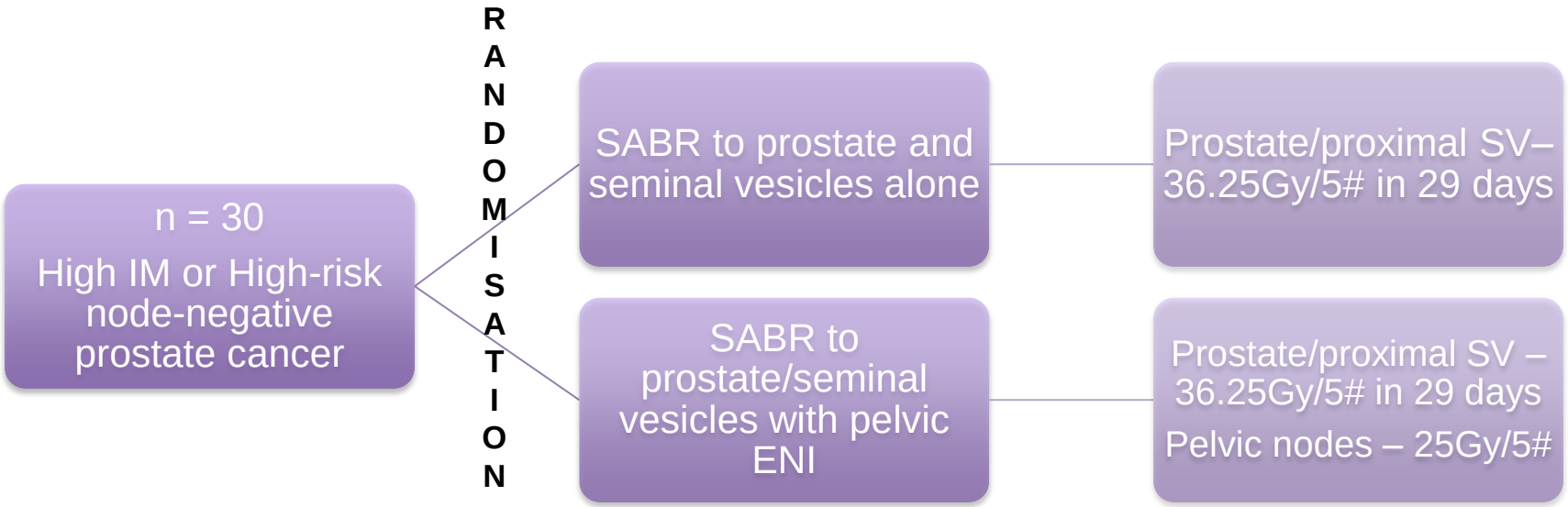
What about pelvic lymph nodes?

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

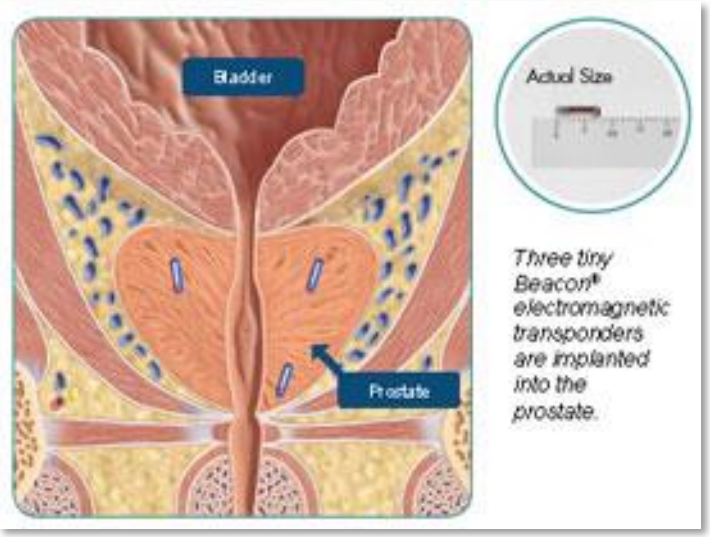
Feasibility

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

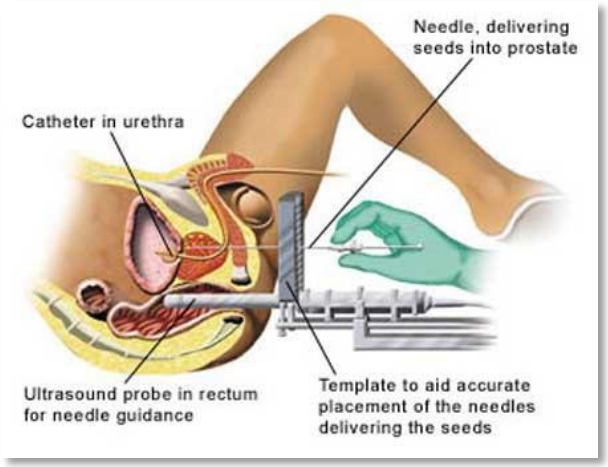
Exploratory biomarkers

- 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

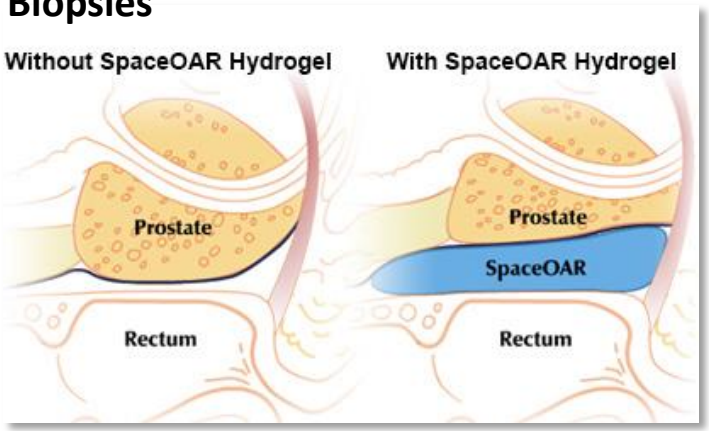
Fiducial and Biopsy Clinic



Fiducials



Biopsies



Hydrogel spacer

Friends of the cancer centre

OSL ONCOLOGY SYSTEMS LIMITED

Augmenix

When could SABR be considered?

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