HITRI plus
Heavy Ion Therapy Research Integration

Why Jump aboard "SHIPP"

(Stereotactic Heavy Ion vs Protons vs Photons)?

Mack Roach III, MD
Professor Radiation Oncology
& Urology, *UCSF*

Specialised Course on Heavy Ion Therapy Research with a Focus on Clinical Aspects
Date: 3rd to 7th July 2023
Venue: Online via Zoom (Times indicated are CEST i.e., UTC+2)
2:00 pm - 2:40 PST 6:00 AM- 7:30 AM; July 7th, 2023

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

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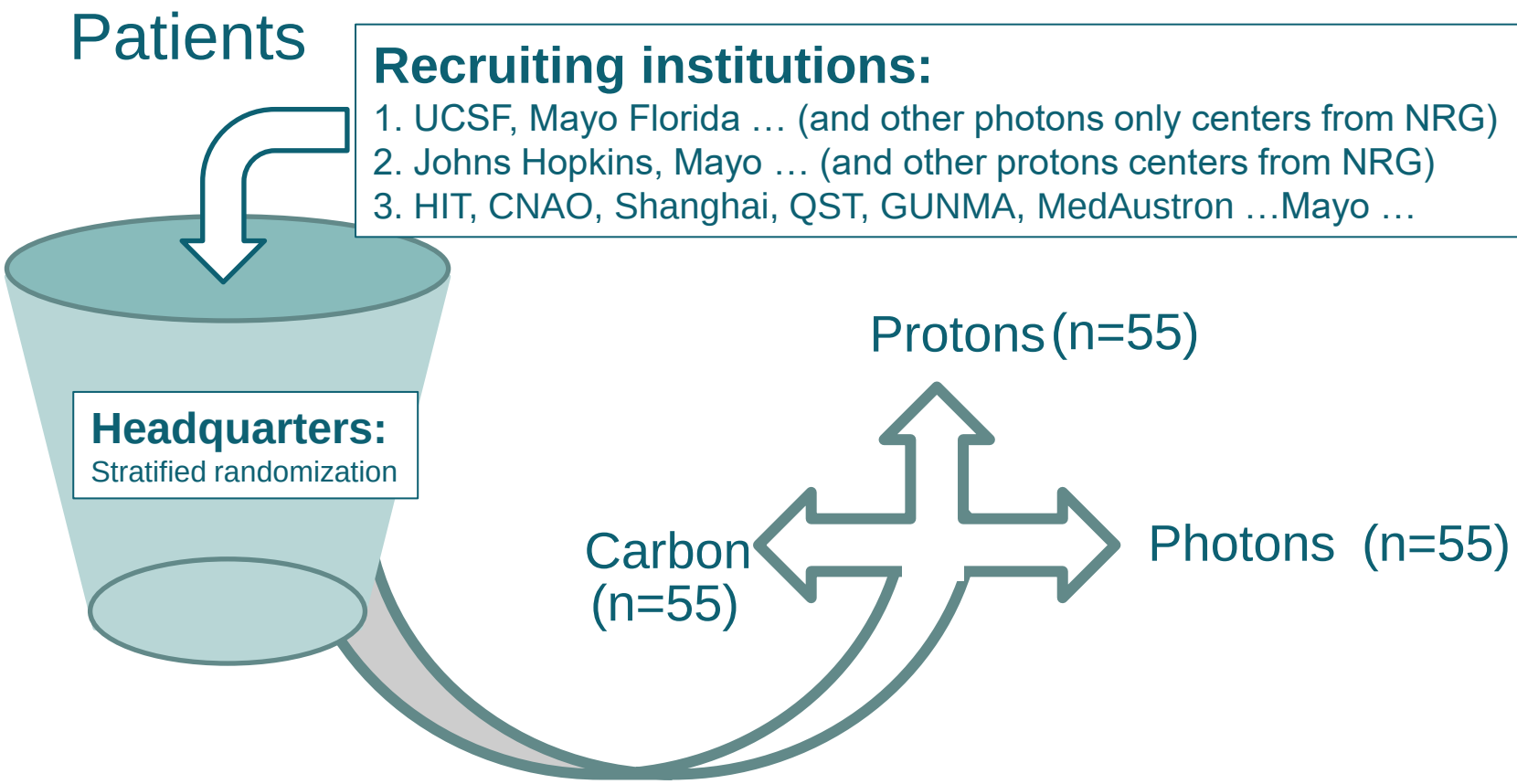
Goals of this Presentation:
Discuss the "SHIPP" Trial

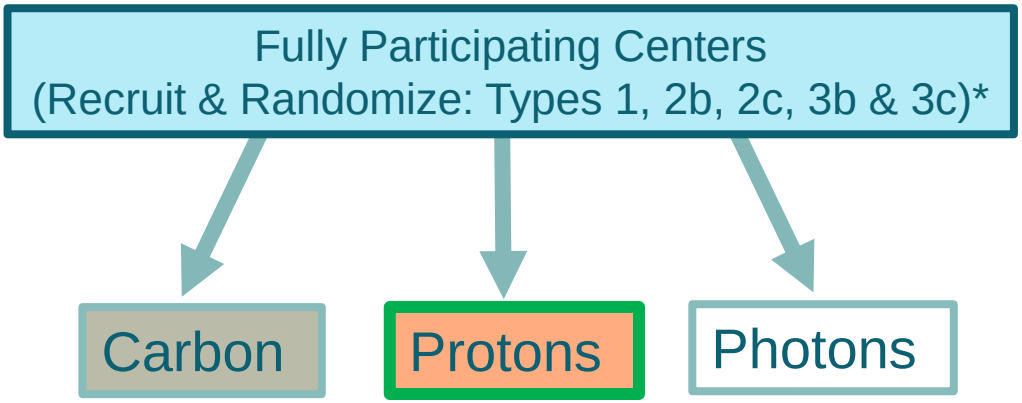
1. Schema of study
2. Primary end points and secondary/exploratory endpoints,
3. Collaborators
4. Radiobiologic model used
5. Challenges and solutions

Enrollment Scheme:



Types of Institutions Participating:

a Phase II Randomized Trial



Type 1: (Photons n=20)

10:1 (Photons vs Carbon or Protons (1:1)

Type 2: Protons (n=20)

2a Protons (R)*

2b (R) (Protons (10:1) vs [(Photons + Carbon) 10:1]**

2c [(Protons + Photons (10:1)] vs Carbon**

Type 3: (Carbon n=4)

3a Carbon (R)*

3b Carbon (10:1)

3c (Carbon vs Proton (5:1)] vs Photons (10:1)

3d (Carbon vs Proton vs Photons (10:5:1)

***R= Receive patients only**

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SHIPP Specific Aims:

Aim 1: QA

1. **Minimize uncertainties across photon, proton, and carbon delivery modalities for stereotactic prostate RT.**

   ***Sub-Aim 1.1*: Establish optimal consensus planning margins to account for anatomical variations.**

   ***Sub-Aim 1.2*: Minimize uncertainties and maximize consistency by credentialing all participating institutions.**

Aim 2. Phase II Trial

***Sub-Aim 2.1*: Design, CHR approval**

***Sub-Aim 2.2*: Launch of Phase II Trial**

***Sub-Aim 2.3*: Safety and efficacy of CIRT, protons, and photons**

a) ***Safety and efficacy of CIRT, protons, and photons***

b) ***Primary Endpoints: QoL metrics including IPSS, SHIM***

c) ***Secondary endpoints: PSA endpoints (Nadir, BCF)***

Aim 3. Radiobiology

1. **Refine RBE est. and understanding for CIRT based on Aim 2.**

   ***Sub-Aim 3.1*: RBE models (LEM vs MKM vs RMF) and clinical outcomes.**

   ***Sub-Aim 3.2*: Validate, intercompare clinical RBE models.**

SHIPP

(Stereotactic Heavy Ions vs Protons vs Photons)

SBRT for Unfavorable Int. Risk* Prostate Cancer
(Carbon* vs Protons** vs Photons)

	Year 1 (2023)		Year 2 (2024)		Year 3 (2025)		Year 4 (2026)*		Year 5 (2027)**	
	1st half	2nd half	1st half	2nd half	1st half	2nd half	1st half	2nd half	1st half	2nd half
Aim 1.1 SBRT study and plan comparisons across modalities										
Aim 1.2										
Aim 1.3										
Aim 2 Clinical trial design										
Aim 2 Clinical trial CHR approval										
Aim 2 Clinical trial recruitment										
Aim 2 Clinical trial outcome analysis										
Aim 3.1 Evaluating clinical RBE models										
Aim 3.2 Cell survival RBE measurements										

*Years Mayo will launch Protons; **Years Mayo will launch Protons

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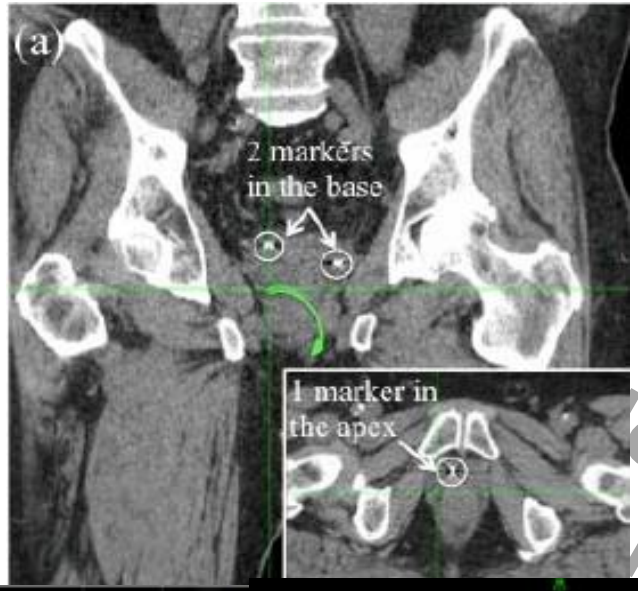
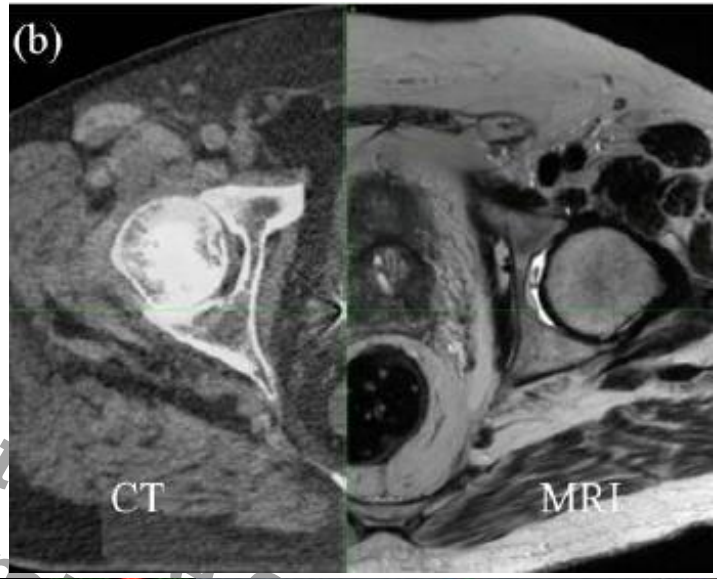
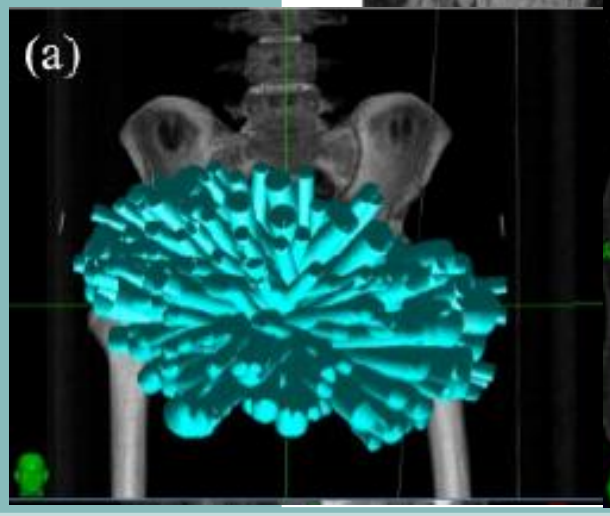
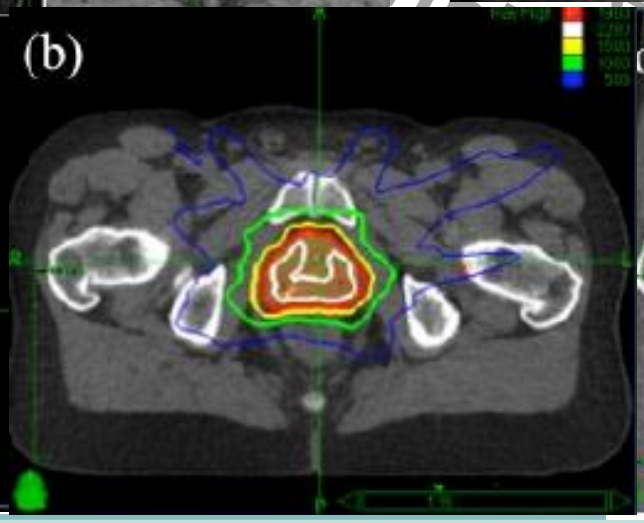
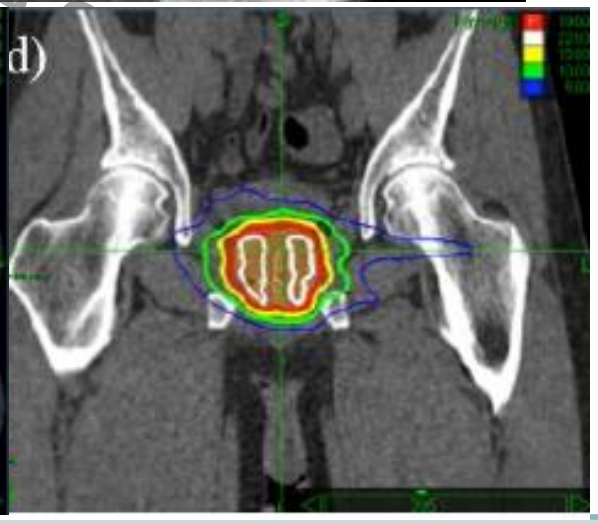
Stereotactic Body Radiotherapy (SBRT) in the management of Clinically Localized Prostate Cancer: Where are we now?
Roach et al. Current Cancer Therapy Reviews , 2018











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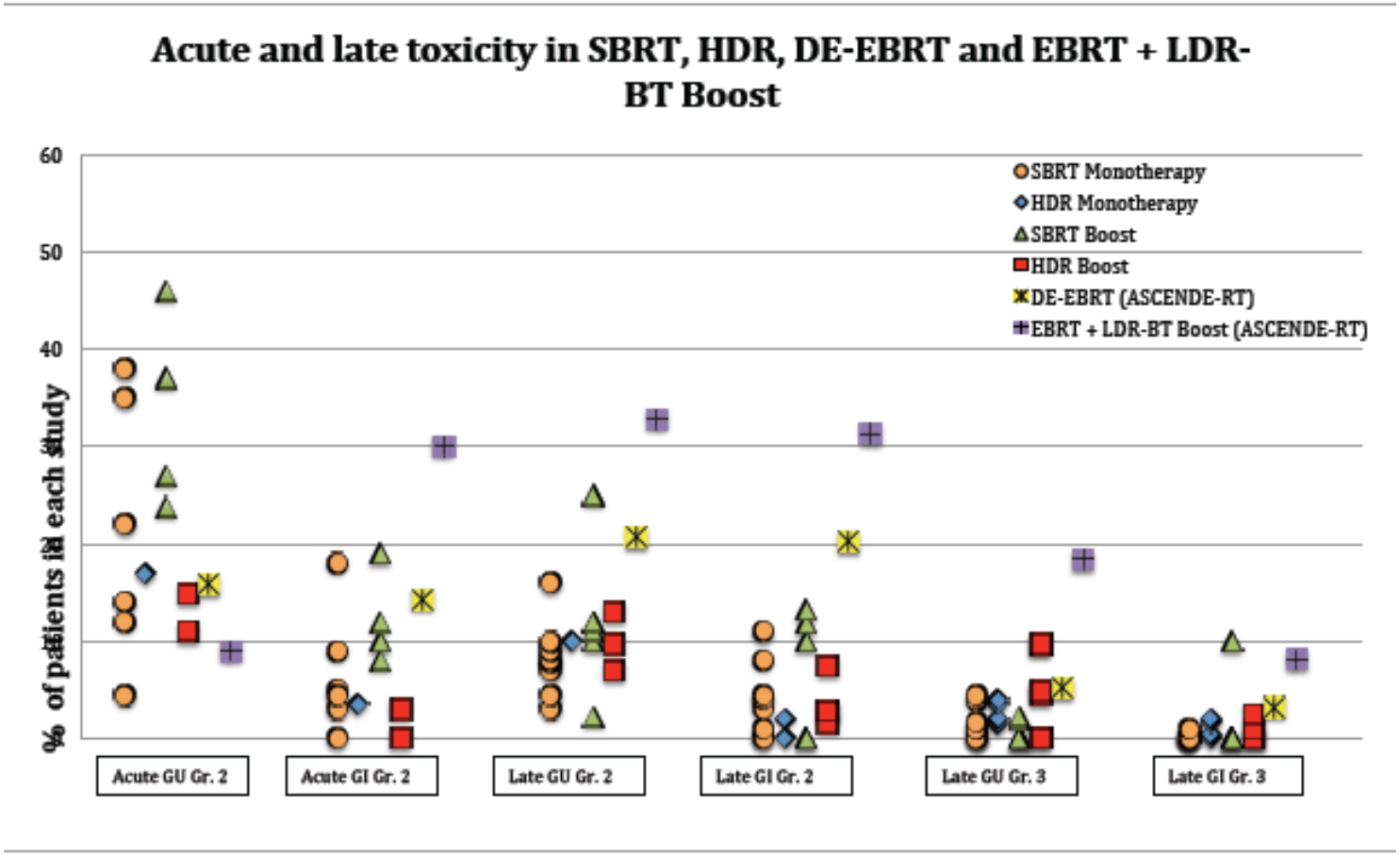
Stereotactic body radiation therapy (SBRT) for high-risk prostate cancer: Where are we now? Gonzalez-Motta & Roach, Pract Radiat Oncol. (2018)



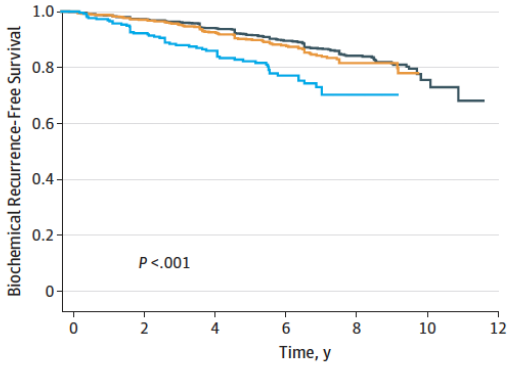
JAMA Network Open™

Original Investigation | Oncology

Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer

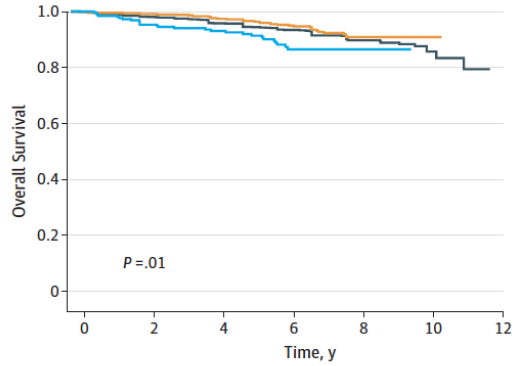
Amar U. Kishan, MD; Audrey Dang, MD; Alan J. Katz, MD, JD; Constantine A. Mantz, MD; Sean P. Collins, MD, PhD; Nima Aghdam, MD; Fang-I Chu, PhD; Irving D. Kaplan, MD; Limor Appelbaum, MD; Donald B. Fuller, MD; Robert M. Meier, MD; D. Andrew Loblaw, MD; Patrick Cheung, MD; Huong T. Pham, MD; Narek Shaverdian, MD; Naomi Jiang, MD; Ye Yuan, MD, PhD; Hilary Bagshaw, MD; Nicolas Prionas, MD, PhD; Mark K. Buyyounouski, MD, MS; Daniel E. Spratt, MD; Patrick W. Linson, MD; Robert L. Hong, MD; Nicholas G. Nickols, MD, PhD; Michael L. Steinberg, MD; Patrick A. Kupelian, MD; Christopher R. King, MD, PhD

C Biochemical recurrence-free survival



No. at risk							
Low	1185	1116	1010	811	392	44	13
Fav-Int	692	659	535	376	144	13	5
Unfav-Int	265	236	173	117	31	1	1
Cumulative No. of censoring							
Low	4	39	111	272	650	985	1013
Fav-Int	2	14	116	249	463	590	598
Unfav-Int	1	10	60	100	179	209	209

D Overall survival



No. at risk							
Low	1185	1122	1022	826	410	53	18
Fav-Int	692	671	555	390	149	15	7
Unfav-Int	265	241	182	123	33	2	1
Cumulative No. of censoring							
Low	4	42	117	292	681	1033	1067
Fav-Int	2	15	125	276	507	639	647
Unfav-Int	1	12	67	117	205	236	237

A, Cumulative incidence of biochemical recurrence ($P < .001$). B, Cumulative incidence of distant metastases ($P = .03$). C, Kaplan-Meier curve of biochemical recurrence–free survival ($P < .001$). D, Kaplan-Meier curve of overall survival ($P = .01$). Fav-Int indicates favorable intermediate-risk disease; Low, low-risk disease; and Unfav-Int, unfavorable intermediate-risk disease.

BNED after SBRT for Unfavorable Intermediate Risk (UIR) Prostate Cancer

First Author (year)	No. of pts	5-yr BNED*	Comments
Katz (2016) (1)	515	80%	9.1% UIR (n=47) authors concluded: “Patients with unfavorable intermediate-risk disease have significantly worse outcomes after SBRT, and should be considered for clinical trials ...”
Kishan (2019) (2)	2142	~80%	12.4% UIR (n=265) 7-yr cumulative incidence of late ≥ grade 3 GU toxicity ~2.4%; late ≥ grade 3 GI toxicity 0.4%.
Franzese (2020) (3)	178	75%	Authors concluded: “… Linac-based SBRT continues to be a valid option … control remains high at 5 years, albeit with some concerns regarding the optimal schedule for unfavorable intermediate-risk PC.”
Fuller (2022) (4)	259	75%	10% UIR (n=46), authors concluded: “SBRT … prescribing 38 Gy/4 fractions … provides high long-term disease control rates without ADT except … unfavorable intermediate-risk patients.”

*** BNED=Biochemical no evidence of disease (Phoenix definition); GU (genitourinary); GI (Gastrointestinal).**

1. Katz A, Formenti SC, Kang J. Predicting Biochemical Disease-Free Survival after Prostate Stereotactic Body Radiotherapy: Risk-Stratification and Patterns of Failure. Frontiers in oncology. 2016;6:168.

2. Kishan AU, Dang A, Katz AJ, Mantz CA, Collins SP, Aghdam N, et al. Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer. JAMA Netw Open. 2019;2(2):e188006.

3. Franzese C, Badalamenti M, Di Brina L, D'Agostino G, Franceschini D, Comito T, et al. Linac-based stereotactic body radiation therapy for low and intermediate-risk prostate cancer : Long-term results and factors predictive for outcome and toxicity. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2020;196(7):608-16.

4. Fuller DB, Crabtree T, Kane BL, Medbery CA, Pfeffer R, Gray JR, et al. High Dose "HDR-Like" Prostate SBRT: PSA 10-Year Results From a Mature, Multi-Institutional Clinical Trial. Frontiers in oncology. 2022;12:935310.

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Initial toxicity, quality-of-life outcomes, and dosimetric impact in randomized phase 3 trial of hypofractionated versus standard fractionated proton therapy for low-risk prostate cancer. Vargas et al. Advances in Rad Onc, 2018

Table 1 Cumulative grade 2 adverse events

Adverse event	Cumulative events		*P*-value
	44 fraction (arm 1), no. (n = 29)	5 fraction (arm 2), no. (n = 46)	
Urinary tract grade 2			
6 mo	0	9	.01
12 mo	4	11	.38
18 mo	5	12	.41
24 mo	8	13	> .99
36 mo	9	14	> .99
48 mo	10	14	.80
Overall, n (%)	10 (34.5)	14 (30.4)	.80
Bowel grade 2			
6 mo	1	5	.4
12 mo	1	6	.24
18 mo	3	7	.73
24 mo	4	9	.76
36 mo	5	9	> .99
48 mo	5	9	> .99
Overall, n (%)	5 (17.2)	9 (19.6)	> .99

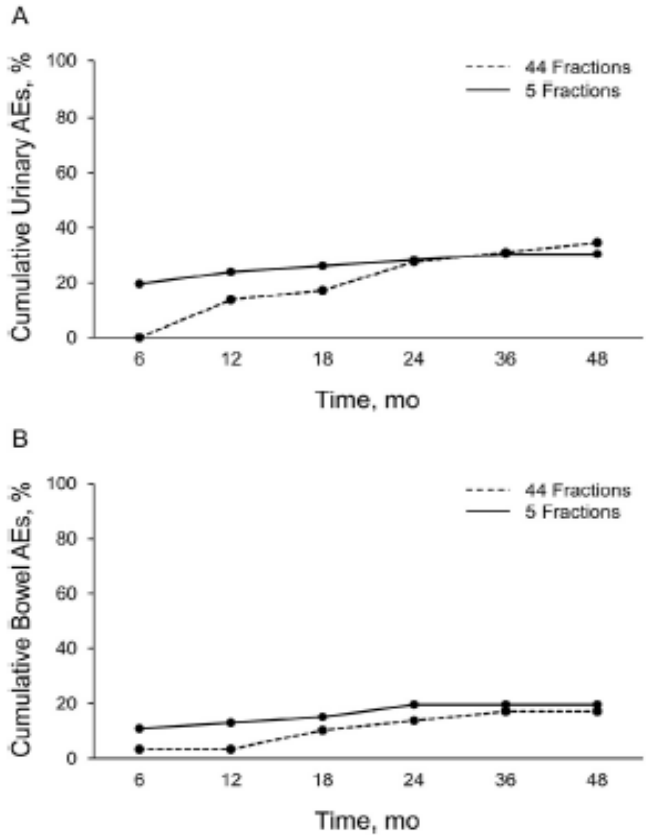
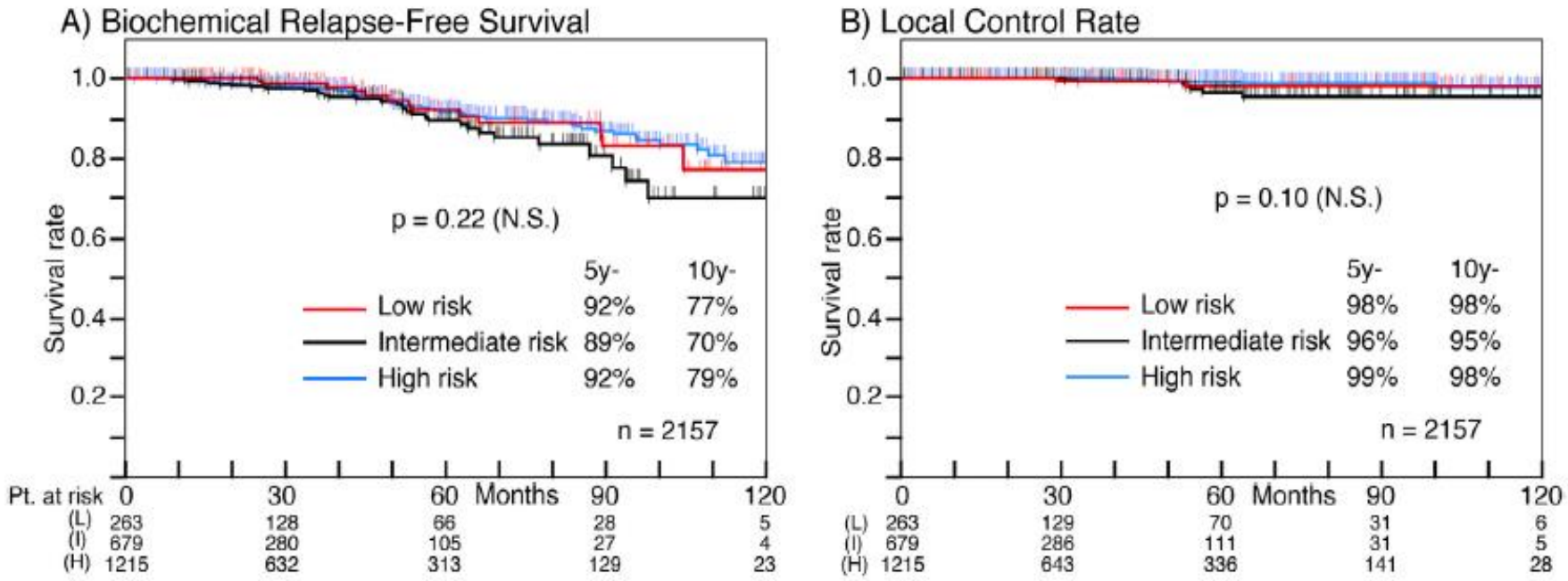


Fig 1 Cumulative incidence of urinary (A) and bowel (B) grade2 adverse events.

A multi-institutional analysis of prospective studies of carbon ion radiotherapy for prostate cancer: A report from the Japan Carbon ion Radiation Oncology Study Group (J-CROS)

Nomiya et al. Radiotherapy and Oncology 121 (2016) 288-293



International Journal of Radiation Oncology biology • physics

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Acute Toxicity and Quality of Life in Patients With Prostate Cancer Treated With Protons or Carbon Ions in a Prospective Randomized Phase II Study - The IPI Trial. Habl et al. IJROBP, 95: (435-443, 2016)

Conclusions: Hypofractionated … either carbon ions or protons results in comparable acute toxicities and QoL parameters.

… hypofractionated particle irradiation is feasible and may be safe. … we stopped using the insertion of spacer gel. Longer follow-up is necessary for evaluation of PFS and OS.

(Ion Prostate Irradiation (IPI); NCT01641185; ClinicalTrials.gov.)

Table 2 Incidence of acute toxicity (≤6 months) of proctitis, diarrhea and cystitis in both treatment arms (protons and carbon ions)*

Acute toxicity	All patients (n=91)	Protons (n=46)	Carbon ions (n=45)
Proctitis grade			
0	73 (80.2%)	34 (73.9%)	39 (86.7%)
1	11 (12.1%)	6 (13.0%)	5 (11.1%)
2	5 (5.5%)	4 (8.7%)	1 (2.2%)
3	2 (2.2%)	2 (4.3%)*	0 (0%)
Diarrhea grade			
0	34 (37.4%)	14 (30.4%)	20 (44.4%)
1	53 (58.2%)	28 (60.9%)	25 (55.6%)
2	4 (4.4%)	4 (8.7%)	0 (0%)
Cystitis grade			
0	44 (48.3%)	18 (39.2%)	26 (57.8%)
1	31 (34.1%)	18 (39.1%)	13 (28.9%)
2	16 (17.6%)	10 (21.7%)	6 (13.3%)

* GI toxicity: rectum fistula.

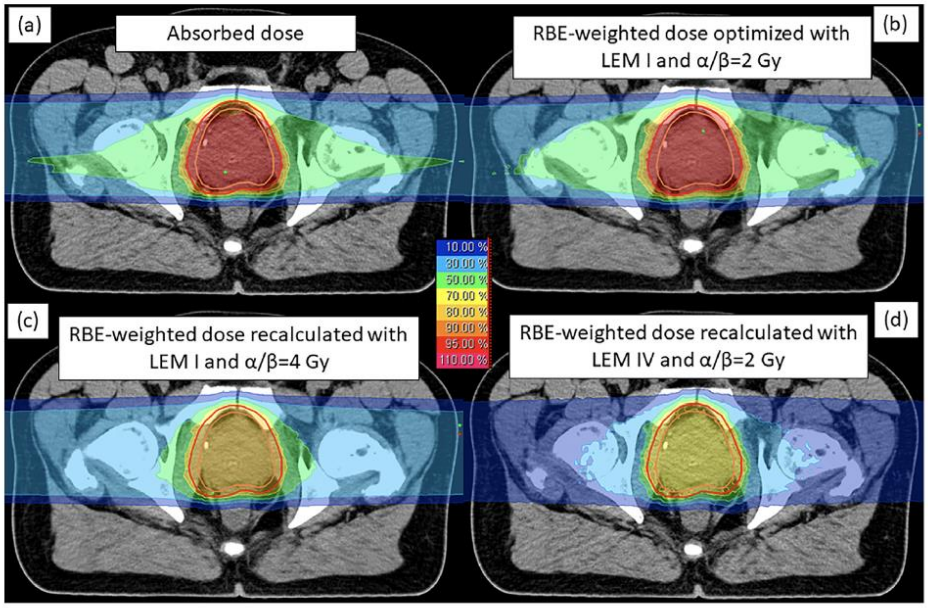


Fig. 3. Example of the delivered absorbed (a) and RBE-weighted (b) carbon ion dose distribution optimized with LEM I and *alpha/beta* = 2 Gy as well as the recalculated RBE-weighted dose distributions for LEM I with *alpha/beta* = 4 Gy (c) and LEM IV with *alpha/beta* = 4 Gy (d). CTV and PTV are represented by the orange and red contours respectively. Note: 100% dose refers to 21.97 Gy in 20 fractions for the absorbed dose (a) and to 66 Gy (RBE) in 20 fractions for the RBE-weighted dose (b-d).(Taken from Ref. #42).

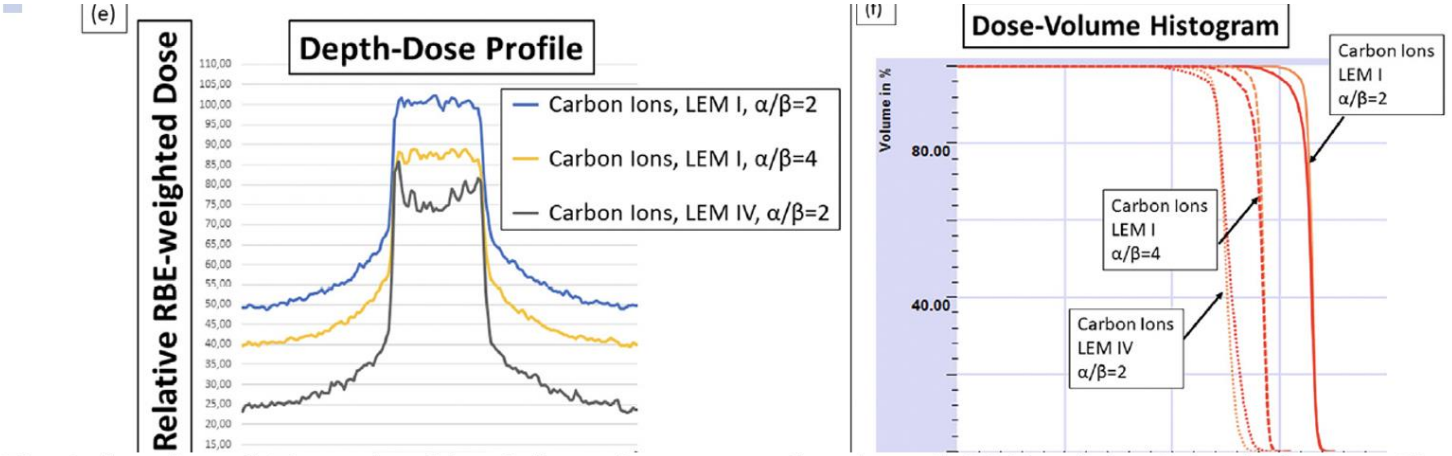


Fig. 3. (continued) Example of the delivered corresponding (to a-d) RBE-weighted depth-dose profiles starting at the right- and ending at the left femoral head (e) as well as the dose volume histograms (f) are displayed. (Taken from Ref. #42).

Results of a prospective randomized trial on long-term effectiveness of protons and carbon ions in prostate cancer: LEM I and a/b = 2 Gy overestimates the RBE. Eichkorn et al. Radiotherapy and Oncology 173 (2022) 223-230

Radiotherapy and Oncology 173 (2022) 223–230

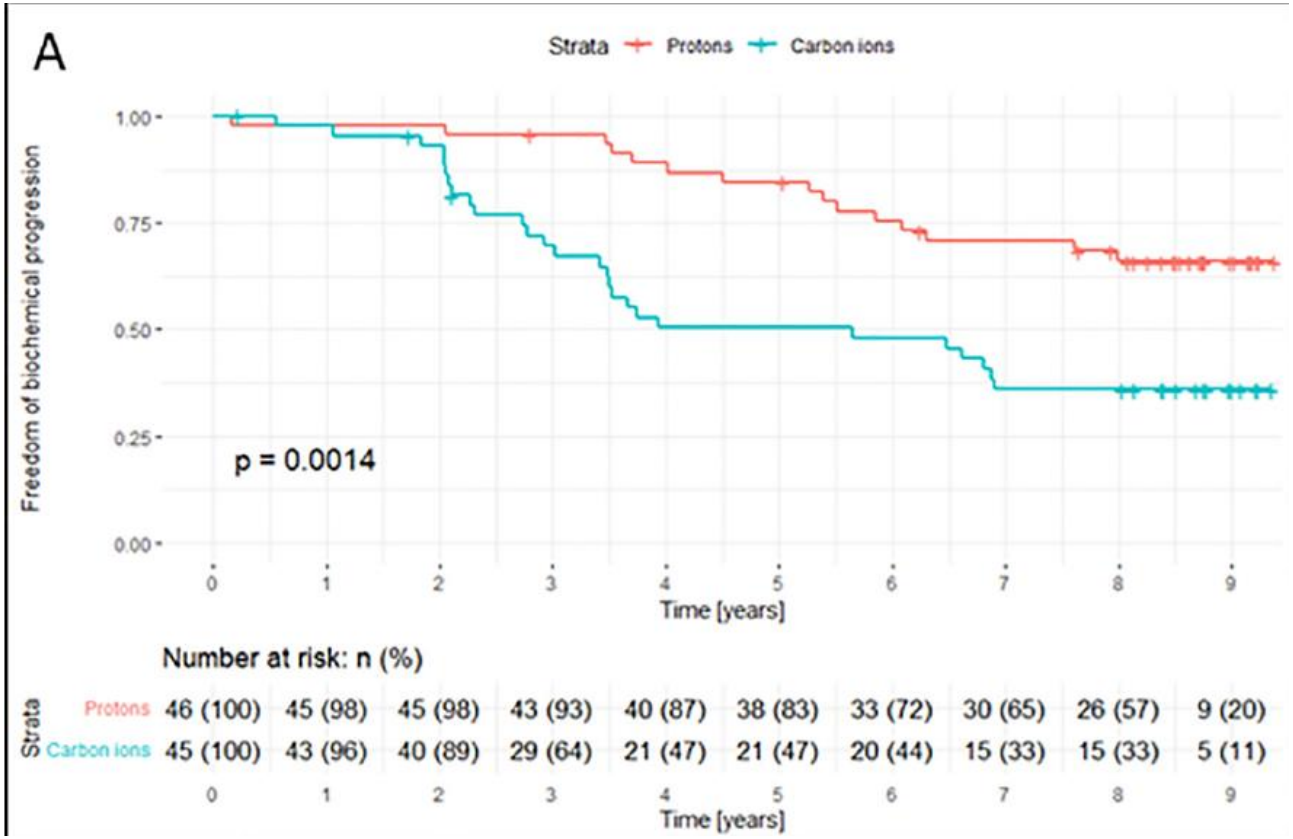
Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Results of a prospective randomized trial on long-term effectiveness of protons and carbon ions in prostate cancer: LEM I and $\alpha/\beta = 2$ Gy overestimates the RBE Eichkorn et al. Radiotherapy and Oncology 173 (2022) 223-230



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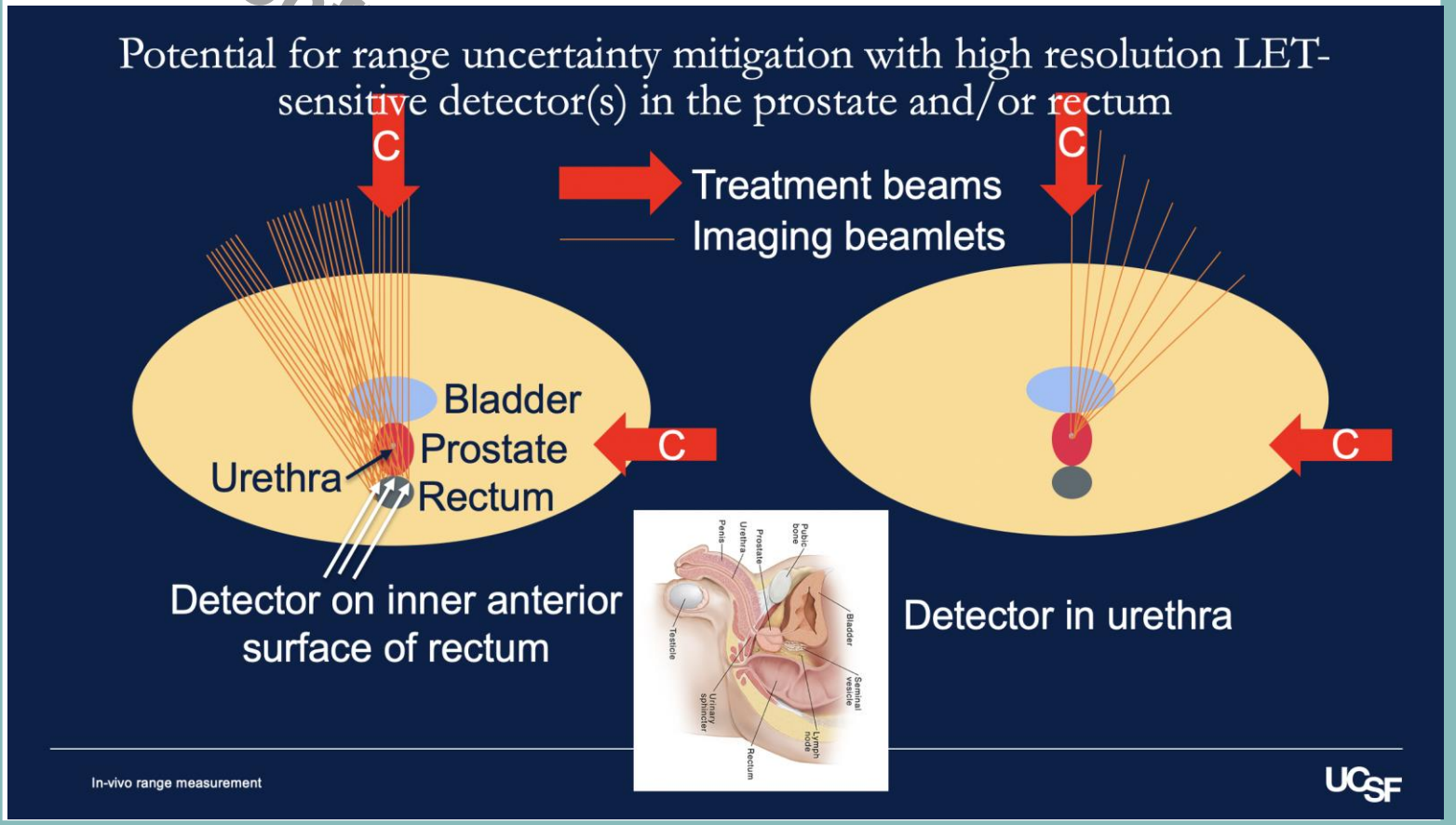
SBRT Photons vs Protons vs Carbon a perfect "proof of principle": Rationale for Study

a) Dose distribution advantages "important"?

b) RBE really "important"?

c) "devil is in the details" more important?



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Objectives: The "feasibility" (*primary endpoint*)

1. ***"Feasibility"***:

   a. Design the study and launch trial for Localized Prostate Cancer (why this site?)

   b. IGRT QA for delivery of protons or carbon ions across international sites ~ photons.

   c. Model funding travel & cost of RT abroad

PER CASE REIMBURSEMENT (PCR) MODEL (LAZAR & ROACH)

Estimated Lazar & Roach PCR using the formula:

PCR Equation = $\frac{\left(\sum_{i=1}^{n} T_i + L_i - R_i\right)}{n}$

- T = Cost of Treatment (all patients),
- L= Cost of Logistics (e.g., flight, hotel)
- R = Revenue/Funding
  - for $i = 1 \ldots n$;
  - n = 225 subjects vs 155
    - >25 randomized to carbon vs 55
    - >50 randomized to protons vs 55
    - >150 randomized to photons vs 55

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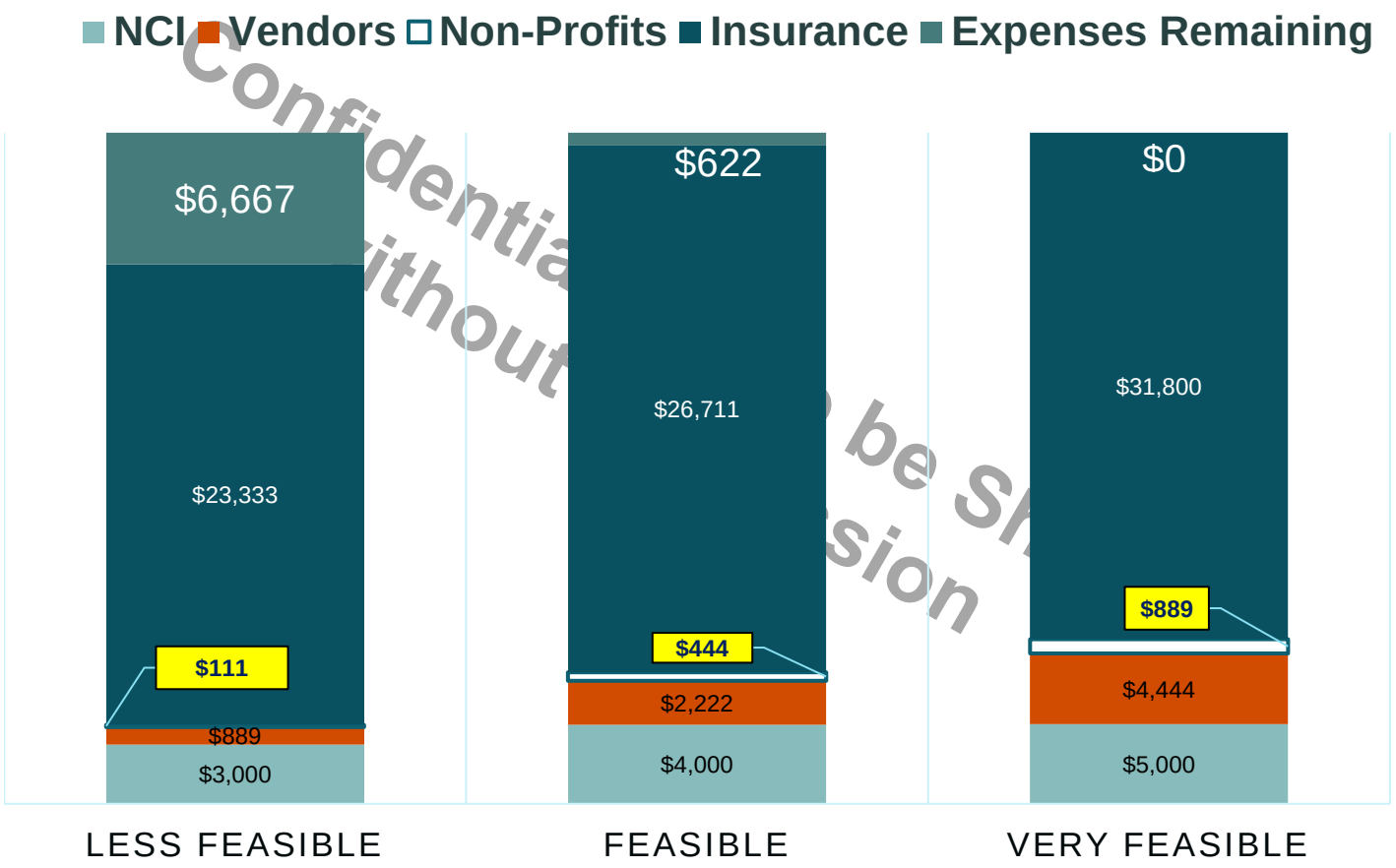
Estimated cost per case (CPC) Funding Feasibility Model*:

(potential funding sources ~ assuming avg. CPC $34k)



*Lazar & Roach

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Objectives (contd.): Assess the … "tolerability and potential clinical utility", "PSA control" and QoL endpoints and (*secondary of proof of principle*) …

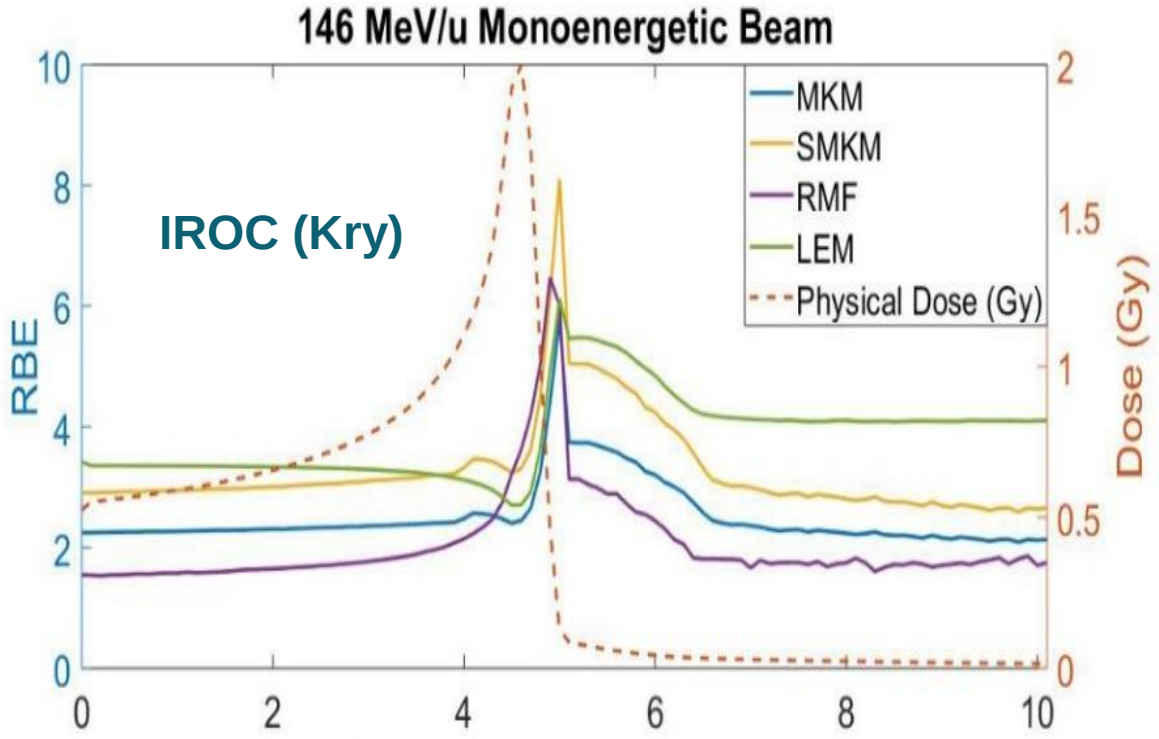
2. Phase II Trial with *QOL endpoints*
   1. Health-related QoL (bowel, urinary domains)
   2. Changes in sexual function.
3. *Proof of principle* "surrogate" endpoints:
   a. PSA failure, PSA Nadir
4. Radiobiology modeling and validation

If successful, expand to Phase III to assess clinically relevant endpoints:

1. *RBE*: photons vs protons vs carbon
2. *Improved dose distribution:* photons vs particles

Key Investigators and Collaborators

- **NAPTA@: Blakely, *Faddegon, Lazar, Mao, Roach, **Schulte**
- **IROC: #Kry, Taylor**
- **Carbon**
  - Heidelberg (Debus)
  - CNAO (Vischioni, Sandro)
  - Shanghai (Zhang)
  - Japan (Gunma,QST, …***)
  - Austria (Fossati, Hug)
  - Mayo (Hoppe …)
- **Protons**
  - Hoppe (pending)
  - Vargas
  - (***)
- **Photons**
  - UCSF (Roach) ***



@Funded previously by NCI for Carbon research; *Funded - TOPAZ; **Funded - Proton-CT
#Funded by the NCI past 3 yrs to build QA Program for Carbon RT, * Many options**

RTOG 0924

Report Based on Data Through: 10/31/2018

Androgen Deprivation Therapy and High Dose Radiotherapy With or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial

<table>
<tr>
<td rowspan="3">S
T
R
A
T
I
F
Y</td>
<td>Risk Group
1. GS 7-10 + T1c-T2b + PSA < 50 ng/ml
2. GS 6 + T2c-T4 or ≥ 50% biopsies + PSA < 50 ng/ml
3. GS 6 + T1c-T2b + PSA > 20 ng/ml</td>
<td rowspan="3">R
A
N
D
O
M
I
Z
E</td>
<td>Arm 1:
Neoadjuvant androgen deprivation therapy
+ prostate & seminal vesicle RT
+ boost to prostate & proximal seminal vesicles</td>
</tr>
<tr>
<td>Type of RT Boost
1. IMRT
2. Brachytherapy (LDR using PPI or HDR)</td>
<td rowspan="2">Arm 2:
Neoadjuvant Androgen Deprivation Therapy
+ whole-pelvic RT
+ boost to prostate & proximal seminal vesicles</td>
</tr>
<tr>
<td>Duration of Androgen Deprivation Therapy**
1. Short Term (6 months)
2. Long Term (32 months)*
3. Short term (4 months)

**LHRH duration is per physician discretion to be declared at registration as 4 months, 6 months or 32 months</td>
</tr>
<tr>
<td colspan="4">* 32 months chosen because RTOG 9202 used 28 months and EORTC used 36 months = average 32 months
<u>Note</u>: As this protocol allows for treatment with exclusively EBRT or EBRT + brachytherapy (at the discretion of the treating physician), this must be specified at the time of study enrollment. Should a patient who was originally intended to receive brachytherapy be found, post enrollment, to be a poor brachytherapy candidate based on transrectal ultrasound examination, he will no longer be eligible for participation in this study. Therefore, it is strongly recommended to obtain ultrasound assessment of prospective brachytherapy patients before enrollment on this study.</td>
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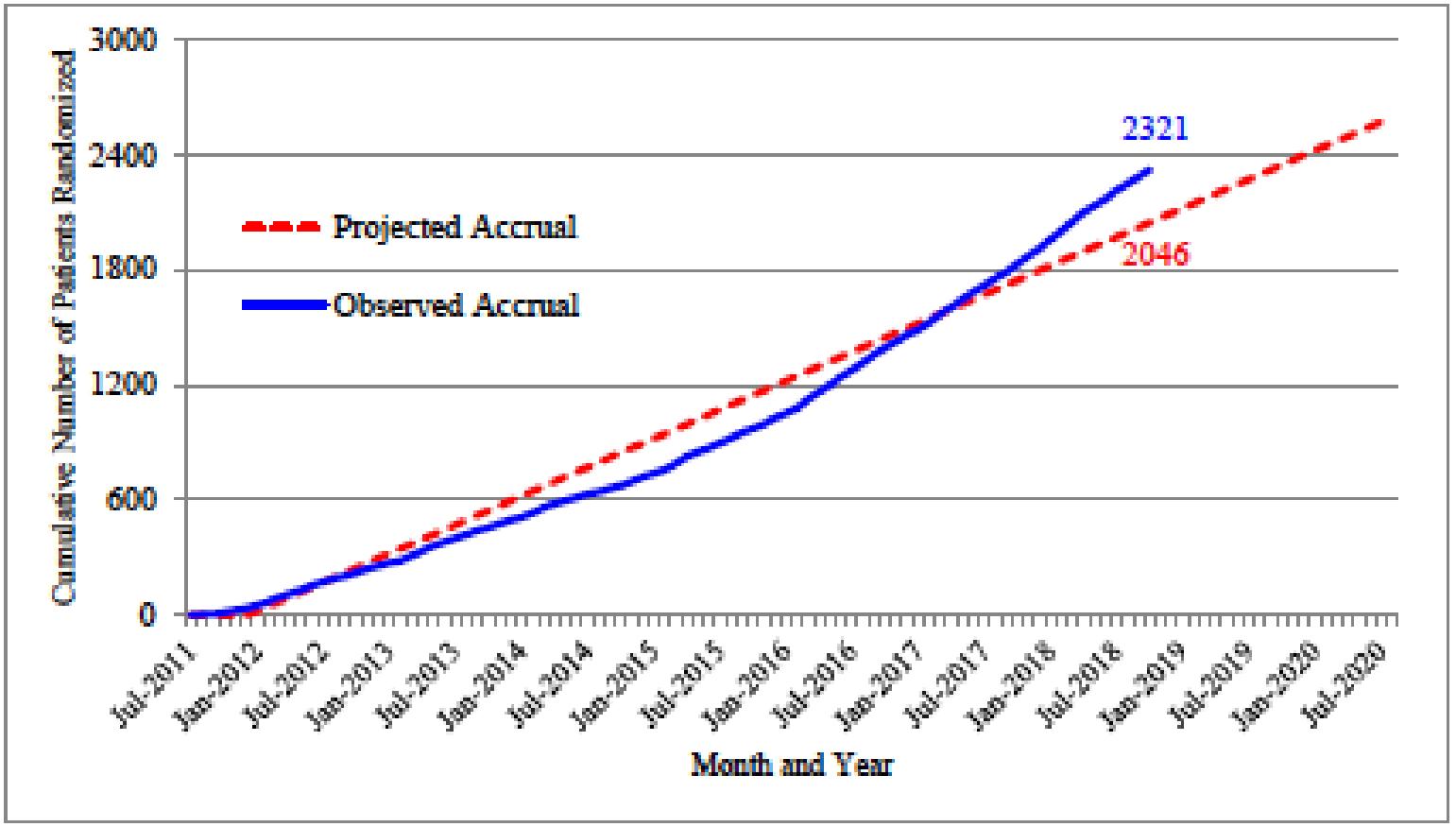
Figure 1
Cumulative Accrual for RTOG 0924 - Data as of 10/31/2018



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Research

JAMA Oncology | Original Investigation

Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer

The MIRAGE Randomized Clinical Trial. Kishan et al. Published online Jan. 2023

PRIMARY OBJECTIVE:

1. … whether (MRI)-guided stereotactic body radiotherapy (SBRT) improves acute physician-scored genitourinary (GU) toxicity when compared with standard computed tomography (CT)-guided SBRT for prostate cancer (PCa). Acute GU toxicity will be assessed by the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 scale.

INTERVENTIONS … randomized 1:1 to SBRT with CT guidance (control arm) or MRI guidance. Planning margins of 4mm (CT arm) … 2mm (MRI arm) … 40 Gy in 5 fractions.

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Research

JAMA Oncology | Original Investigation

Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer

The MIRAGE Randomized Clinical Trial. Kishan et al. Published online Jan. 2023

RESULTS … trial was closed to accrual early. … acute grade 2 or greater GU toxic effects was significantly lower with MRI vs CT guidance (24.4 vs 43.4%; P = .01), as was the incidence of acute grade ≥ 2 gastrointestinal toxic effects (0.0 vs 10.5%; P = .003). … a significantly smaller percentage of patients with a 15-point or greater increase in IPSS at 1 month (6.8 vs 19.4%; P = .01) and … a clinically significant (12-point) decrease in EPIC-26 bowel scores (25.0 vs 50.0%; P = .001) at 1 month.

CONCLUSIONS AND RELEVANCE … randomized clinical trial, compared with CT-guidance, MRI-guided SBRT significantly reduced both moderate acute physician-scored toxic effects and decrements in patient-reported quality of life …

Both sets of PTVs defined on 3T MR

Actually, <u>fiducial guidance vs MR guidance* w/o fiducials</u>

How much better is a 0.35T MR

than a transabdominal Ultrasound?

* Automatic beam hold adjustments initiated

"If greater than 10% of the prostate volume moved outside a 3-mm gating boundary …"

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"Thought Experiment" identical MR linacs with different margins

2mm margins
70.55cc irradiated

4mm margins
102.1cc irradiated

Would more side effects prove inferior technology?

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“Thoughts Experiment”: MR vs CT Linac?

2mm margins
70.55cc irradiated

Longer: 1133 secs

beam hold adjustments initiated “If greater than 10% of the prostate volume moved outside a 3-mm gating boundary …”. *

4mm margins
102.1cc irradiated

shorter: 232 sec

*** How often, how determined and interobserver variability?**

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Research

JAMA Oncology | Original Investigation

Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer
The MIRAGE Randomized Clinical Trial. Kishan et al. Published online Jan. 2023

Higher than typical doses & potential imbalances:

- **… doses recommended exceeded those used in ~90% of pts in a systematic review/meta-analysis of n>6000 (Jackson et al.).**
- **… allowed the investigators to use even higher doses, at their "discretion" delivering "… a simultaneous integrated boost to the dominate intraprostatic lesion (42 Gy 5 fractions) and … boost to a pelvic node … ".**
- **Given more high-risk patients on the CT arm, and a higher absolute number of risk factors likely to impact GI toxicity, could create bias favoring the MRI arm.**

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Table 1
Imbalances in factors that might impact toxicity (from E4 Table 1) [1]

Characteristic*	CT % (n=77)	MRI (n=79)	Comments
High or Very High Risk	39% (30)	25% (20)	Might favor MRI group due to target volumes drawn
No Rectal Spacer Use	58% (45)	53% (42)	Might favor MRI group due to more spacer use
Baseline GI comorbidity	23% (18)	15% (12)	Might favor MRI group due to lower baseline GI co-morbidity
total no. potentially adverse factors*	**93**	**74**	Combination of factors could cause biased results

***Patients may have had more than one factor; 1 Roach, Ling and Coleman submitted JAMA 2023**

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CMAJ RESEARCH

Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors

Methods: … systematic review of randomized clinical trials with both blinded and nonblinded assessment of the same measurement scale outcome.

Results: … meta-analysis included 16 trials (… 2854 patients) with subjective outcomes. … treatment effect was more beneficial when based on nonblinded assessors … exaggerated the pooled effect size by 68% (95% CI 14 - 230%).

Interpretation: … empirical evidence for observer bias in randomized clinical trials with subjective measurement scale outcomes. A failure to blind assessors of outcomes in such trials results in a high risk of substantial bias.

Hróbjartsson et al. CMAJ, March 5, 2013, 185(4)

Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors

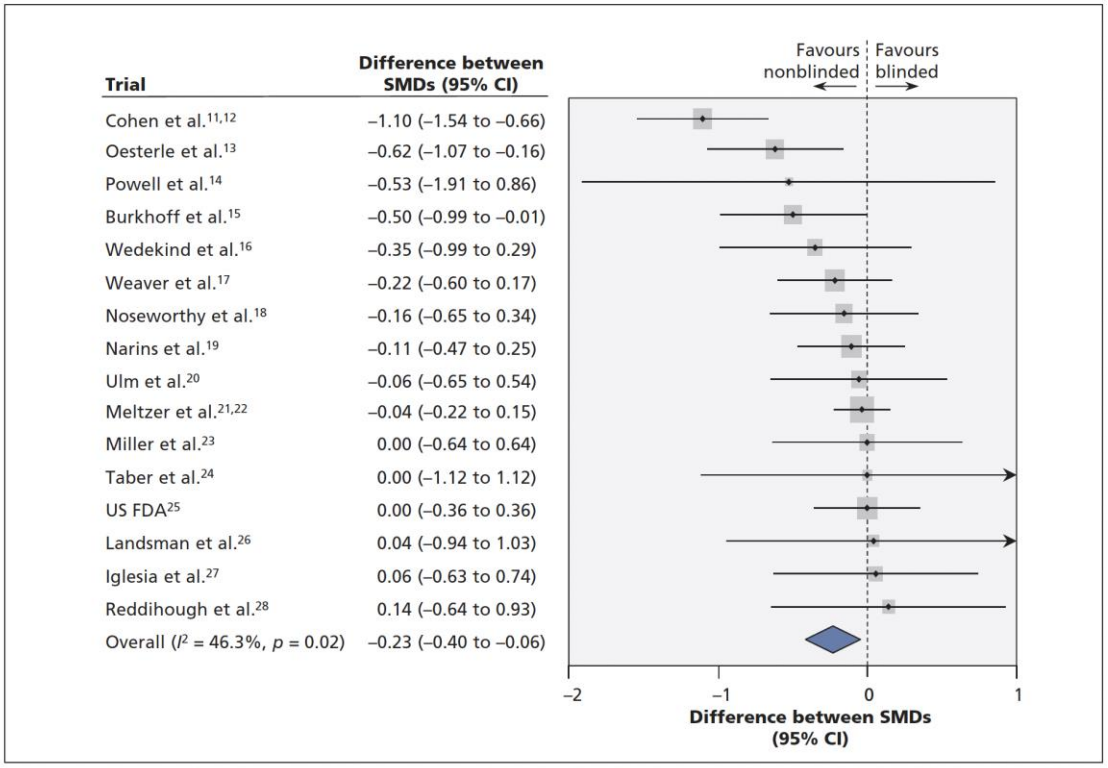

Figure 3: The effect of nonblinded assessors on estimated treatment effects in randomized clinical trials with subjective measurement scale outcomes. Weights were calculated using random effects analysis. CI = confidence interval, SMD = standard mean difference, US FDA = US Food and Drug Administration.

Hróbjartsson et al. CMAJ, March 5, 2013, 185(4)

Patient- versus physician-reported outcomes in prostate cancer patients receiving hypofractionated radiotherapy within a randomized controlled trial. Rammant et al. Strahlenther Onkol (2019) 195:393–401

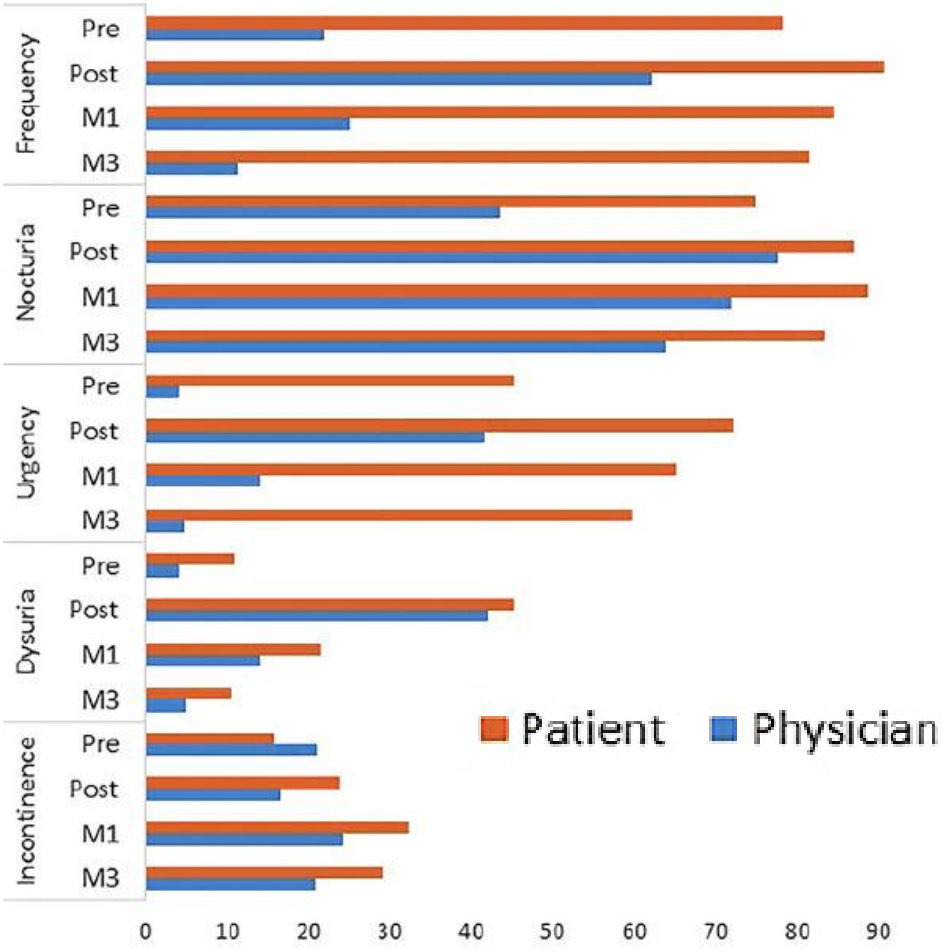

Fig.1 Urinary symptoms reported by patient and by physician. Patient-reported outcomes: score of ≥2 on the EORTC questionnaire; physician-reported outcomes: score of ≥1 on the CTCAE or RTOG

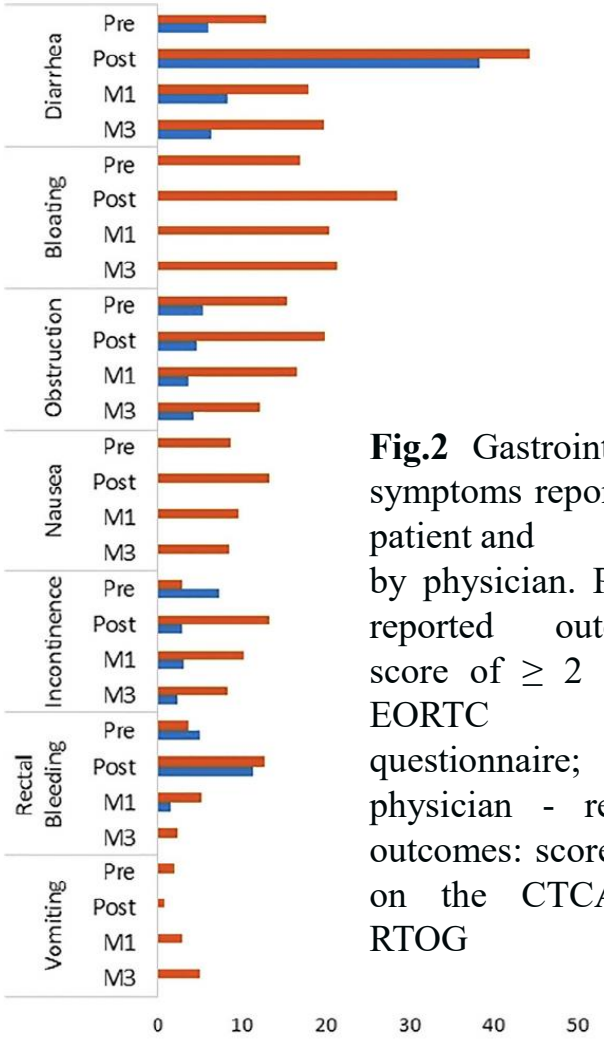

Fig.2 Gastrointestinal symptoms reported by patient and by physician. Patient-reported outcomes: score of ≥ 2 on the EORTC questionnaire; physician - reported outcomes: score of ≥1 on the CTCAE or RTOG

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MD reported:

Patient reported:

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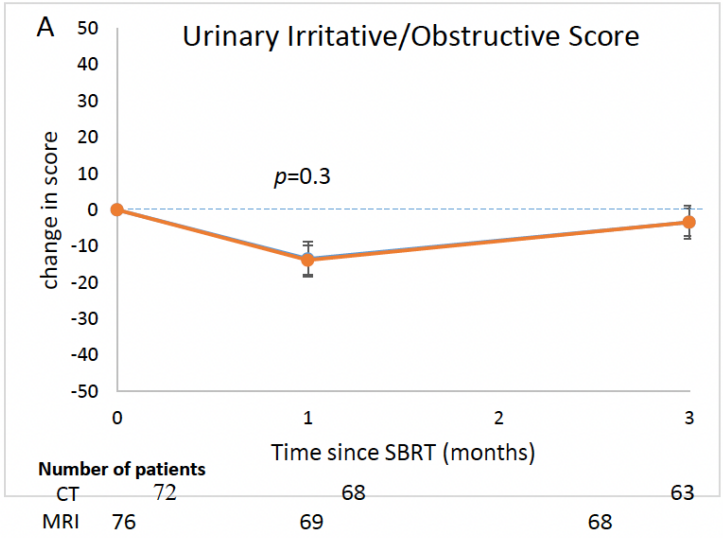
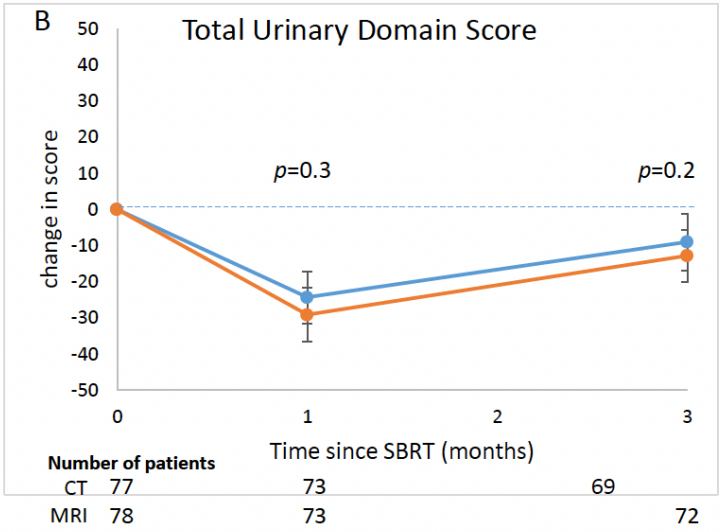
eTable 3. Sensitivity Analysis for Differences in Acute Genitourinary and Gastrointestinal Toxicity Including Patients Not Who Were Analyzed But Not Evaluable

	CT-guidance	MRI-guidance	*P* value
Grade ≥2 Genitourinary	42.7% (31-.6-54.7)	25.3 % (16.2-36.4)	0.02

eFigure 1. Longitudinal Changes in Urinary Irritative/Obstructive and Total Urinary Expanded Prostate Cancer Index Composite-26 (EPIC-26) Scores

P values determined by the Mann-Whitney test.





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Placebo Effects (examples)

University of Cincinnati study tested both blue and pink stimulants and sedatives on students … unbeknownst to the students, the stimulants and sedatives were placebos.

But the blue placebo sedatives were 66% effective, compared with 26% for the pink ones. Blue placebos were around 2.5 times more effective for relaxation that pink ones.

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Conclusions concerning MIRAGE Trial:

1. **Flawed design:**
   a) Rationale doses and discretionary choices.
   b) Arbitrary Margins
   c) Lack of motion adjustment data and potential for interobserver variability
   d) Fiducial guidance vs MR guidance without fiducials*
2. **Evidence of potential biases**
3. **Opportunities placebo effects**
4. **No clinical outcomes**
5. **Known higher cost**

* Which is more accurate?

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Conclusions concerning the SHIPP Trial:

1. **Well designed with centralized QA:**
   a) Rationale doses and discretionary choices.
   b) Consensus on Margins
   c) Motion adjustment data
   d) Fiducial guidance
2. **Minimize potential biases**
3. **Opportunities placebo effects**
4. **Clinical outcomes required**

“I skate to where the puck is going to be, not to where it has been”

– Wayne Gretsky

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