Is MR-Linac the competitor to brachytherapy?

- advancement in MR-Linac for Prostate Cancer

Sep, 2024

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RUTGERS

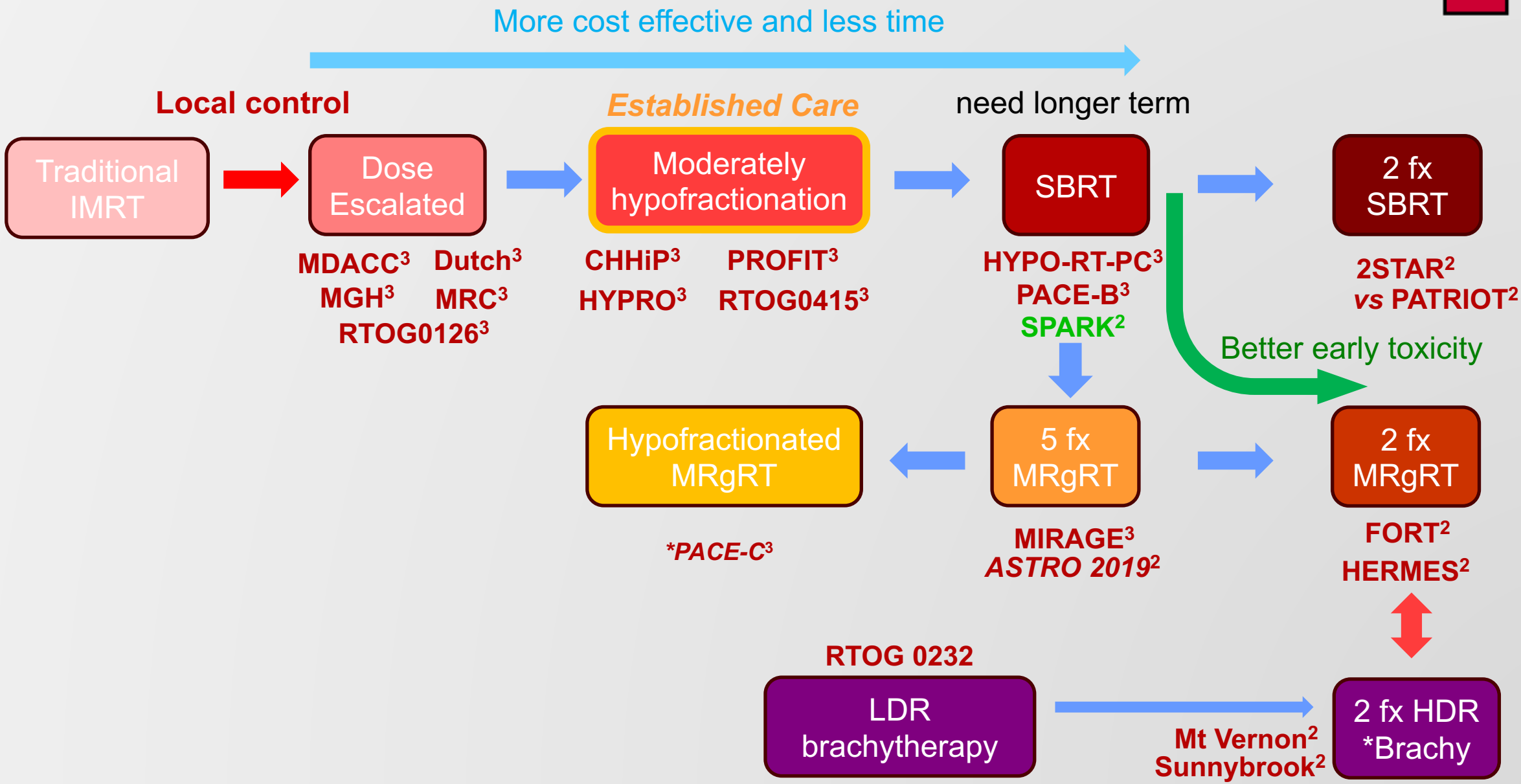
The rationale of IGRT

- Provide information to target delineation
  - Define boundary – radiation therapy
  - Contour OAR – reduce adverse effect
- Management of Anatomy Change
  - Daily CBCT – Halcyon Ethos
  - Daily MR – MR-Linac
  - Resim - ineffective
- Management of Motion – onboard imaging
  - Surrogate (Gating, Real time)
  - kV/kV Fiducial (Sequential acquisition)
  - Cine Imaging (sparsely sampled in time)

The rationale of MRgRT

- MRgRT ProvideS information to CTV, OAR, GTV
  - Better delination of CTV (manual vs automatic)
  - Soft-tissue OAR NVB delineation *(Phase II ERECT)*
  - See GTV, enabling focal boost *(Phase III FLAME)*
- Management of anatomy change
  - Daily onbard-MR, interfractional adaptive planning
- Management of motion – onboard imaging
  - 4D-MRI monitoring, gating, and tracking
  - Intrafractional adaptive planning

Rx Chain I – all risk groups



Rx Chain I - Risk group breakdown

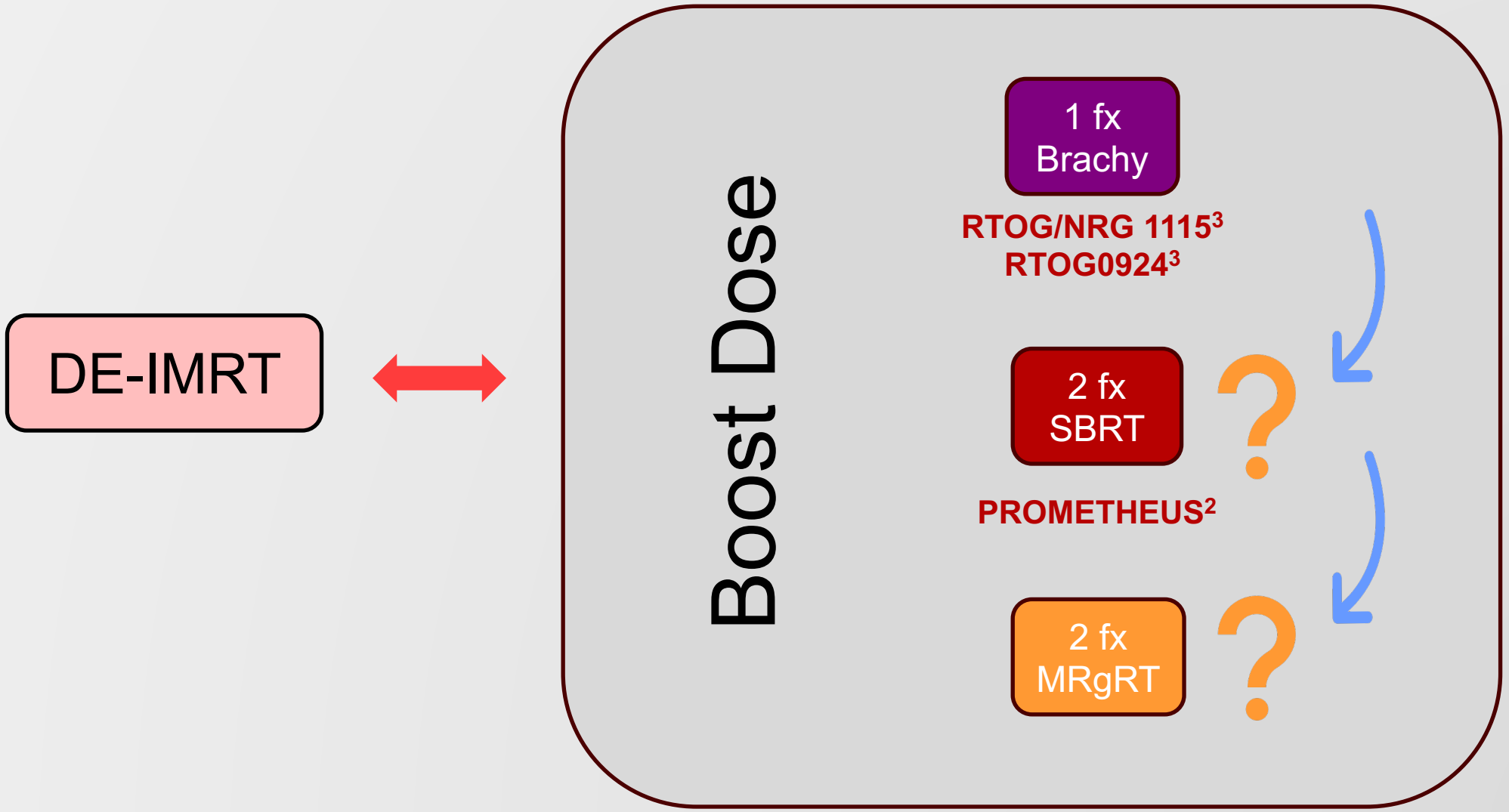
Moderately hypofractionation → SBRT → 5 fx MRgRT

- CHHiP trial (73% IR, 12% HR),
- PROFIT trial (all IR),
- HYPRO trial (26% IR, 74% HR)
- RTOG0415 (LR)

- HYPO-RT-PC (89%IR, 11% HR)
- PACE-B (9.3%LR, 90.7% (F)IR)
- PACE-C* (IR, HR)

- MIRAGE (All risks)
- ASTRO (IR, HR)
- HERMES (IR)
- FORT (LR, IR)

Rx Chain II – boost for UFR and HR



Radiation therapy regimen (NCCN guidelines)

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High
EBRT					
Moderate Hypofractionation	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7	✓	✓	✓	✓
Brachytherapy Monotherapy					
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy	✓	✓		
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓		
Boost Brachytherapy or SBRT with EBRT (2.5 Gy × 15 fx = 37.5 Gy or 1.8 Gy × 25 fx = 45 Gy)					
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost			✓	✓

First Question I: is MRgRT better than standard hypofractionation or SBRT

- Early toxicity results comparing 5 fx
  - Phase II, single-arm (ASCO GU 2019), view-ray – early toxicity better than HYPRO arm
  - Phase III, MIRAGE (ASCO GU 2022), view-ray – reduced margin (2 mm) better than PACE-B arm (4 mm), but have a lower Rx.

- Dose MRgRT offer better biochemical control?
  - Not data yet, but included in MIRAGE objective IV w 5 yr followup

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EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost			✓	✓

Question II: Can MR-Linac take LR and FIR group patients from Brachytherapy?

- Brachy-monotherapy treats this risk group.
- Does standard hypofractionation/SBRT treat this group?
  - **Yes endorsed by NCCN, and supported by this meta-analysis***
- Does SBRT provide non-inferior outcome?
  - Is hypofractionation a strong competitor*? **Yes (RTOG0415)**
  - Is SBRT a strong competitor*? **Yes (PACE-B)**
  - Can MR-Linac replace hypofractionation/SBRT? **Yes (MIRAGE, ASTRO2019), but noninferiority needed.**

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EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost			✓	✓

Question III: Can MR-Linac take HR group patients from brachytherapy boost?

- ***Which boost*** is better, EBRT or Brachy
  - **Answered by ASCENDE-RT, biochemical failure halved but toxicity higher in brachy.**

- ***Which boost*** is better, SBRT or Brachy?
  - brachytherapy GU↑, GI↓; SBRT GU↓; **no prospective data.**

- ***<u>Can MR-Linac boost patents?</u>***
  - *No data yet, rely on evidence from PROMETHEUS*

Advanced topics

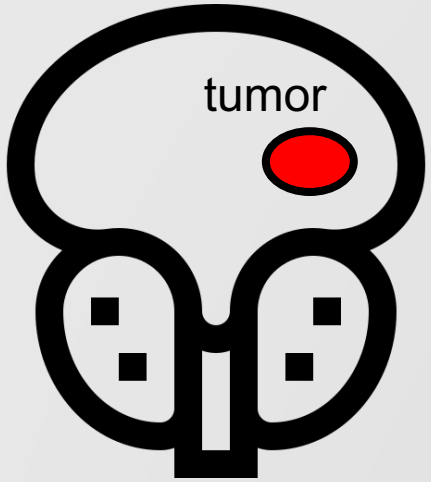
Local Primary

Hypofractionated

EBRT ± BT boost

SBRT & MRgRT

Focal Boost

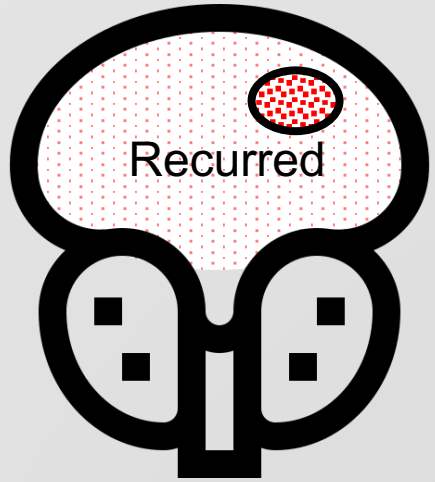


EBRT SIB

FLAME

DELINEATE

Focal Salvage



EBRT Salvage

GETUG, 2019 retro
MASTER, 2021 retro

HDR Salvage

Fsharp

*EBRT focal boost

- **Phase III Flame Trial**
  - A focal boost to the dominant intraprostatic lesion (DIL) showed improved biochemical disease-free survival (bDFS) with comparable toxicity to patients receiving no boost.
  - (85%HR, 15%IR, 4 LR) utilized a *conventional* fractionation scheme that delivered 77Gy in 35 fractions (2.2 Gy/fx) to the prostate with a SIB t to the DIL to 95Gy
- **Phase II HYPO-FLAME**
  - (25% IR and 75% HR) delivering 35Gy in 5 fractions, once-weekly with SIB to the DIL to 50Gy total. (HYPO 2.0, twice-weekly)
- **Phase II DELINEATE (hypo PSV)**
  - (IR, HR) report 5-year efficacy and toxicity of intraprostatic lesion boosting using 2Gy/fx and 3Gy/fx(CHHiP) radiation therapy.
  - DELINEATE Cohort E in 5 fx, similar to HYPO-FLAME & 2.0.

Question IV: Can MR-Linac treat focal boost?

- **Phase II MSK Boost trial**
  - 40 Gy in 5 fractions (**5 × 8**) to the prostate with 45 Gy to the dominant lesion
- **Phase II AFFIRM**
  - 35 Gy to the prostate with 50 Gy to the intraprostatic tumor in 5 fractions
- **Phase II HERMES**
  - 24 Gy in 2 fractions (12 × 2) to the prostate with an intraprostatic boost to 27 Gy in 2 fractions

Question V: Can MR-Linac treat focal Salvage?

- A major challenge in reirradiation is sparing cumulative toxicity in previously irradiated adjacent organs at risk.
- Feasibility: A systematic review and meta-analysis of local salvage therapies after radiotherapy for prostate cancer (MASTER).
- Concern: recurrence due to focal boost, instead of the whole gland
- ***MRgRT offers a solution* (a registry study)***

Summary: Patient Selection at local stages

- **Contradiction**
  - Patient size, limited by the bore
  - Longer treatment time (bladder filling, patient tolerance etc.)
  - Patients with metallic implants
- **Competing CT-based, conventional hypofractionation?**
  - **Yes, all risk groups, evidenced by two single-arm phase II trial to PACE-B**
- **Competing brachytherapy?**
  - Low risk group – Yes. 2 fx / 5fx MR-Linac
  - High risk group boost – PROMETHEUS trial → MR-Linac?
  - Locally advanced group – DELINEATE trial → MR-Linac?
  - Focal Boost - FLAME trial EBRT → no trial opened for brachy & MR-Linac
  - Focal Salvage – FSHARP trial Brachy → no trial opened for MR-Linac

Questions

- Existing trials did not show biochemical and local control data.
  - Too early. Usually early toxicity results are shown first in the interim study.
- MR-Linac has its own competitors such as kV monitoring, CBCT-guided etc.

MRgRT trials

Trial	NCT	Device	Phase	Plan #	Primary outcome	Target Rx	Standard Rx	status
HERMES	04595019	Unity	II	46	Acute grade 2+ GU toxicity	24 Gy in 2 fractions to the prostate with an intraprostatic boost to 27 Gy in 2 fractions	36.25 Gy to the prostate in 5 fractions	Open
UltraHypo	05183074	Unity	II	50	Incidence of acute GU and GI toxicity	Not stated	NA	Open
ERECT	04861194	Unity	II	70	Erectile dysfunction over 3 years post SBRT	36.25 Gy in 5 fractions with sparing of the neurovascular bundle, IPA, corpora cavernosa, and penile bulb	NA	Open
Boost (MSK)	04997018	Unity	II	91	A reduction in posttreatment biopsy rates at 24 months	40 Gy in 5 fractions to the prostate with 45 Gy to the dominant lesion	NA	Open
AFFIRM	05373316	Unity	II	95	Acute GI and GU toxicity	35 Gy to the prostate with 50 Gy to the intraprostatic tumor in 5 fractions	NA	Open
2SMART	03588819	Unity	?	30	Quality of life using EPIC	26 Gy in 2 fractions to the prostate and the DIL dose of up to 32 Gy in 2 fractions delivered 1 week apart	NA	Open
iSMART	05600400	Unity	II	144	Change in quality of life function	27 Gy in 2 fractions to the prostate	Five every other day fractions of 8 Gy	Open
LEAD	01411319	ViewRay	I	25	Grade 2 or higher physician-reported treatment-related adverse events	12-14 Gy in 1 fraction to the mpMRI-defined GTV on day 1, followed by standard 38 fraction IMRT	N/A	Completed
FORT	04984343	ViewRay	II	136	Change in patient-reported GI symptoms using EPIC	37.5 Gy in 5 fractions to the prostate	25 Gy in 2 fractions to the prostate	Recruiting
SIBRT	03664193	ViewRay	?	30	Feasibility	35 Gy in 5 fractions to the prostate with prostate lesion SIB to 37.5, 40, 42.5, or 45 Gy	NA	Completed
EXCALIBUR	04915508	ViewRay	II	102	Change in patient-reported GI symptoms using EPIC	30-34 Gy in 5 fractions	N/A	Recruiting
SHORTER	04422132	ViewRay	II	134	Change in patient-reported GI symptoms using EPIC	32.5 Gy in 5 fractions	55 Gy in 20 fractions	Recruiting

MRgRT trials

Trial	Patients included	Design	Primary outcome	Projected study completion
MIRAGE	Low, intermediate, and high risk	Randomized 5 fraction SBRT of CT v. MRI	Incidence of acute grade ≥2 GU physician-reported toxicity	April 1, 2027
SMILE	Low and intermediate risk	Single arm 5 fraction SBRT on MRL	Any GU or GI grade ≥2 toxicity within 1 year after the start of RT	March 25, 2028
PROSEVEN	Low and intermediate risk	Single arm 5 fraction SBRT on MRL	Clinician reported grade 2 or more acute GI or GU toxicity up to 3 months	July 2029
HERMES	Intermediate risk	Randomized 5 vs 2 fraction SBRT on MRL	Proportion of patients experiencing grade 2+ GU toxicity from the start of radiotherapy up to 3 months posttreatment	April 30, 2028
FORT	Low and intermediate risk	Randomized 5 vs 2 fraction SBRT on MRL	Noninferiority of patient-reported urinary and bowel side effects at 2 years	December 31, 2027
SCIMITAR	Postoperative	Single arm 5 fraction SBRT on CTL or MRL	1. Efficacy of 5 fraction SBRT compared with historical control efficacy rates	November 1, 2023
EXCALIBUR	Postoperative	Single arm 5 fraction SBRT on MRL	2. Two-year change in patient-reported GI symptoms based on EPIC following 5 fraction SBRT	August 1, 2027
SHORTER	Postoperative	Randomized 20 vs 5 fractions on MRL	Change in the number of patient-reported GU and GI symptoms using the EPIC	December 31, 2025

Metastatic (recurrence) Settings

PostOp settings