Challenger or Trailblazer?

How MR-Guided Radiotherapy is Shaping Prostate Cancer Treatment

Oct, 2024

Chengzhu Zhang

RUTGERS

The rationale of IGRT

Management of Target Delineation

Contour OAR
(reduce adverse effect)

Define Boundary
(radiation therapy)

Management of Precision

Image-guided Setup
(image registration)

Re-Simulation
(ineffective)

Management of Onboard Motion

4D-CBCT
(gating)

kV/MV Fiducial [1,2]
(Sequential acquisition)

Cine Imaging*
(sparsely sampled in time)

The rationale of MRgRT

Management of Target Delineation

Better delineation of CTV
(manual or automatic)

Soft-tissue OAR
(Phase II ERECT)

See GTV
(Phase III FLAME)

Management of Anatomy Change

Onboard MRI
(Interfractional Change)

Adaptive Planning
(Adapt to position/shape)

Management of Onboard Motion

Cine Imaging
(Intrafractional adaptive)

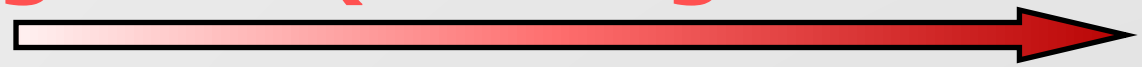
4D-MRI monitoring
(gating, tracking)

The Goal

- ***To understand the current treatment paradigm for local stage prostate cancer***

- ***To understand the role of MRgRT***

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)					
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			✓	✓

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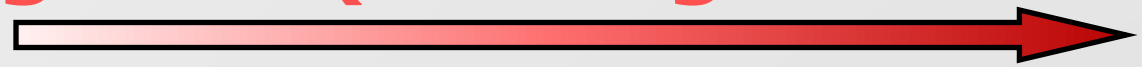

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Rx Diagram I – all risk groups

Traditional IMRT

50~60~70 Gy

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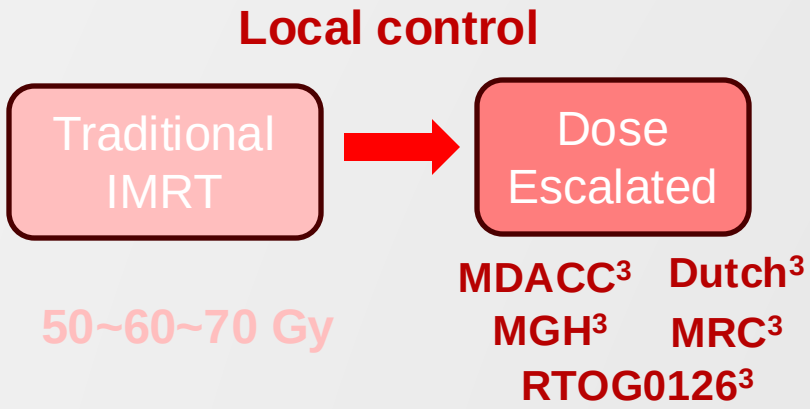

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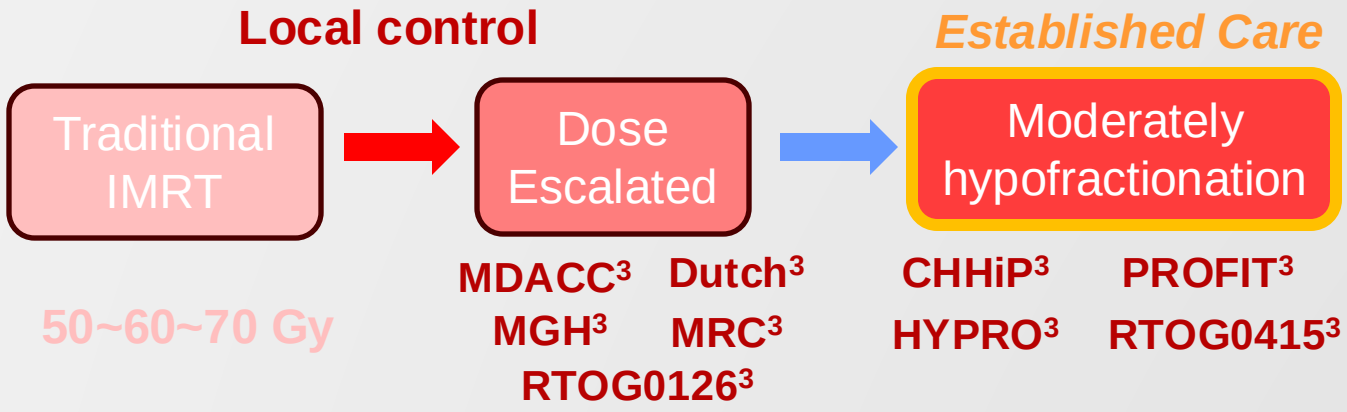

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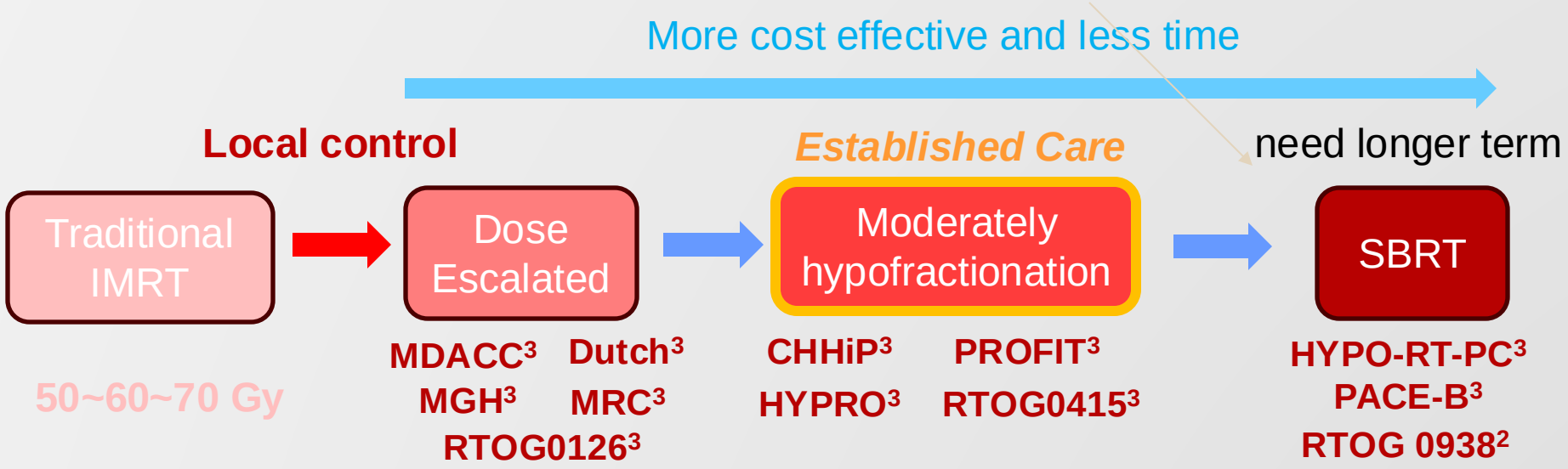

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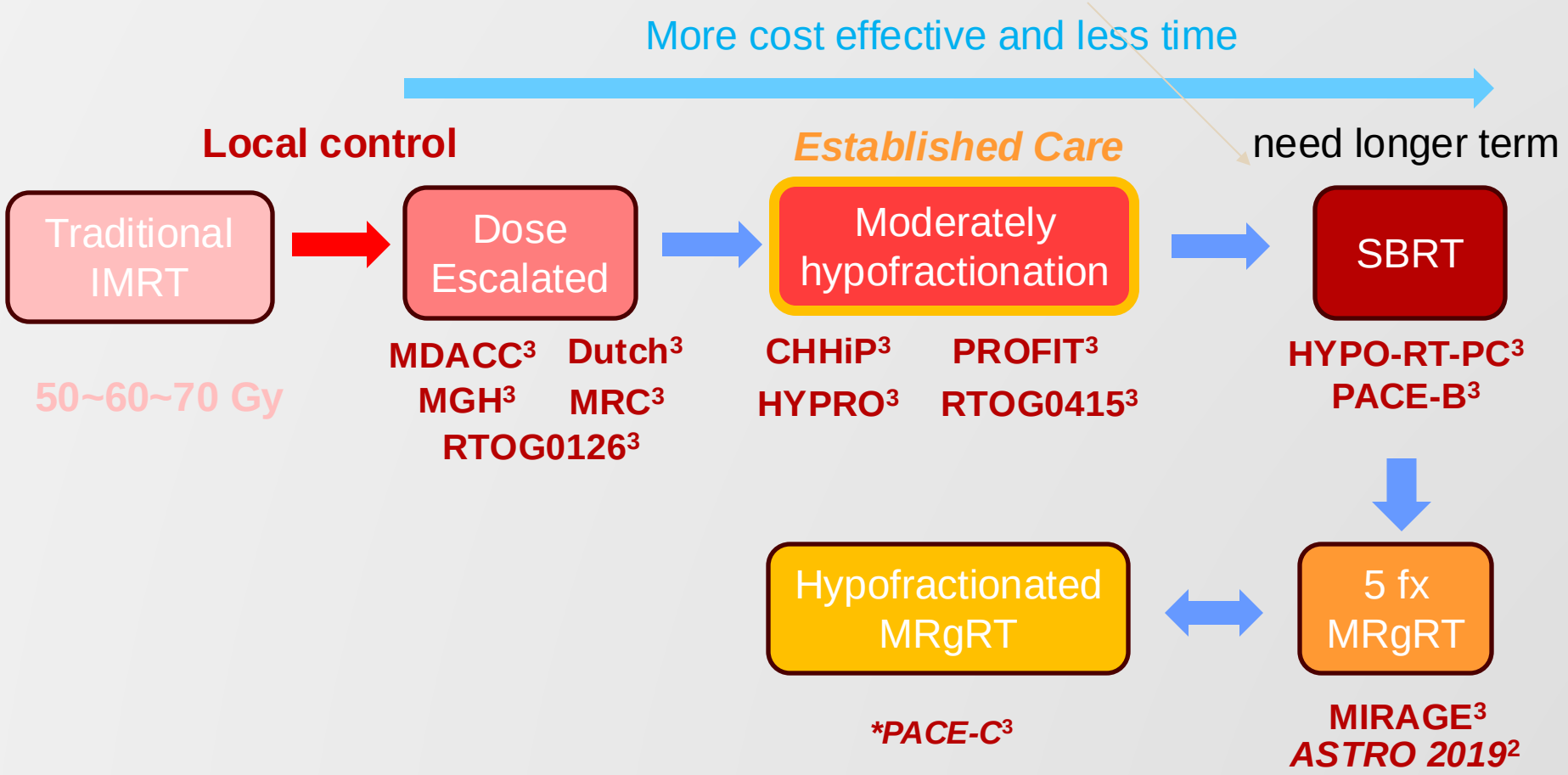

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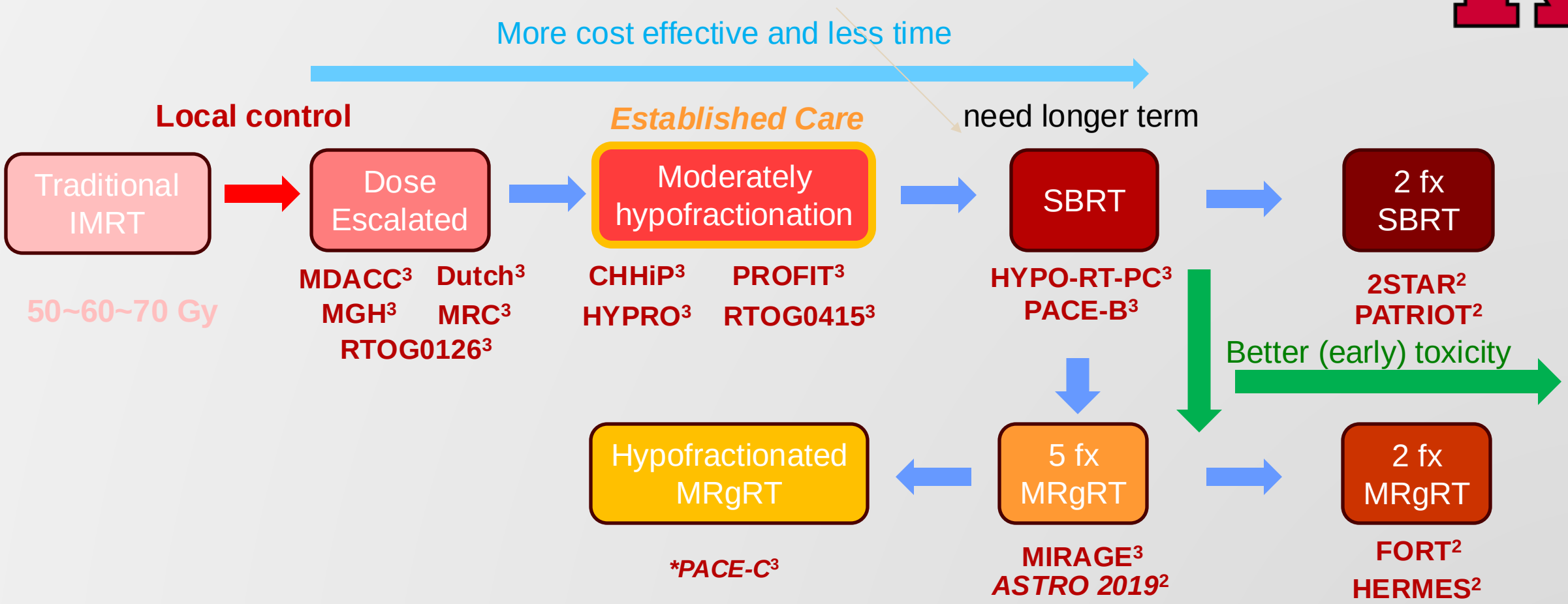

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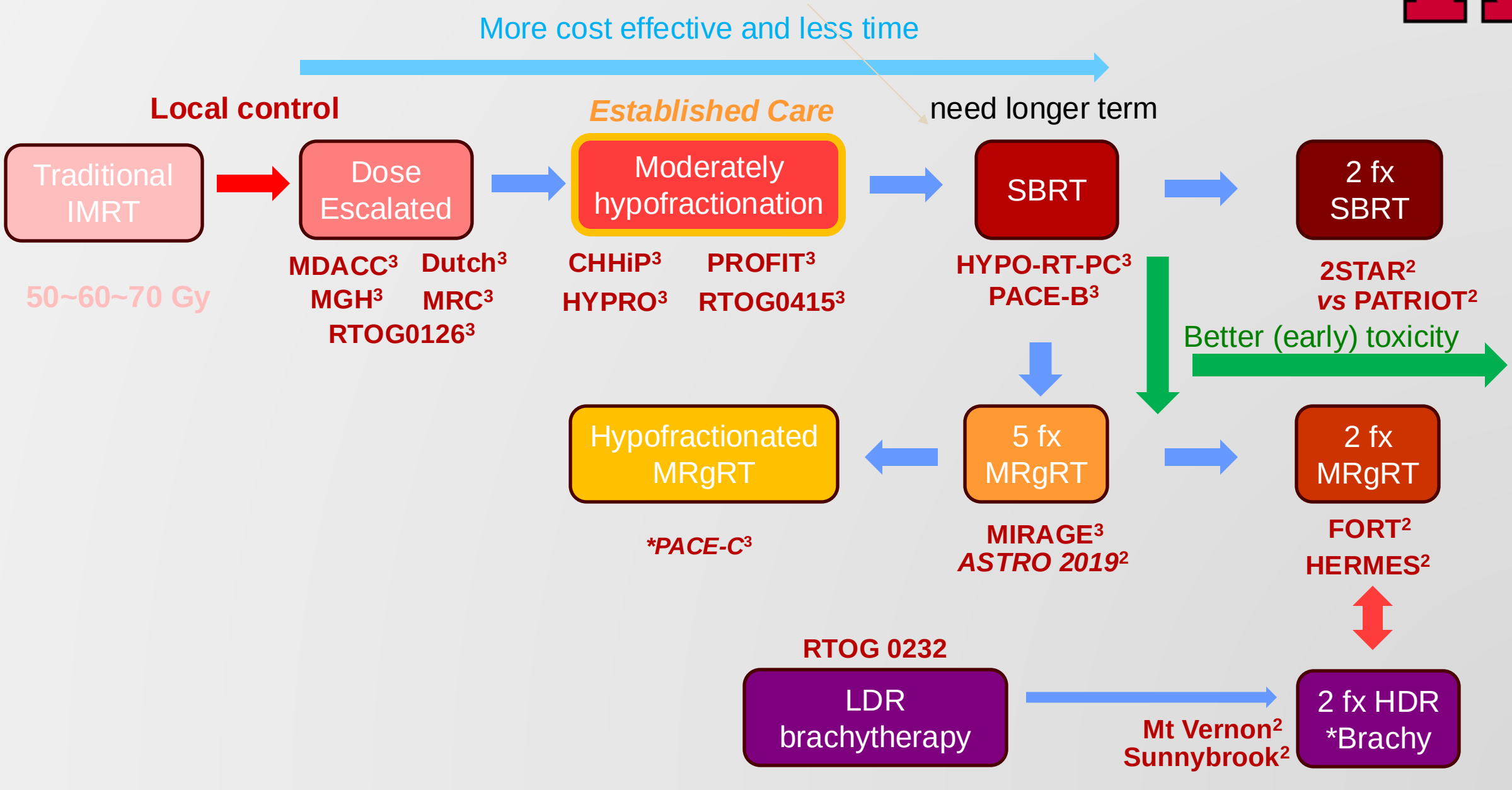

Rx Diagram I - Risk group breakdown

Moderately hypofractionation

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

SBRT

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

5 fx MRgRT

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

Rx Diagram II – boost for UFR and HR

Starting Plan

45 Gy ± SV ± WPRT

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Starting Plan

45 Gy ± SV ± WPRT

+

DE-IMRT

Prostate ± SV

RTOG-0924

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45 Gy ± SV ± WPRT

+ SIB

DE-IMRT

Prostate ± SV

RTOG-0924

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45 Gy ± SV ± WPRT

+

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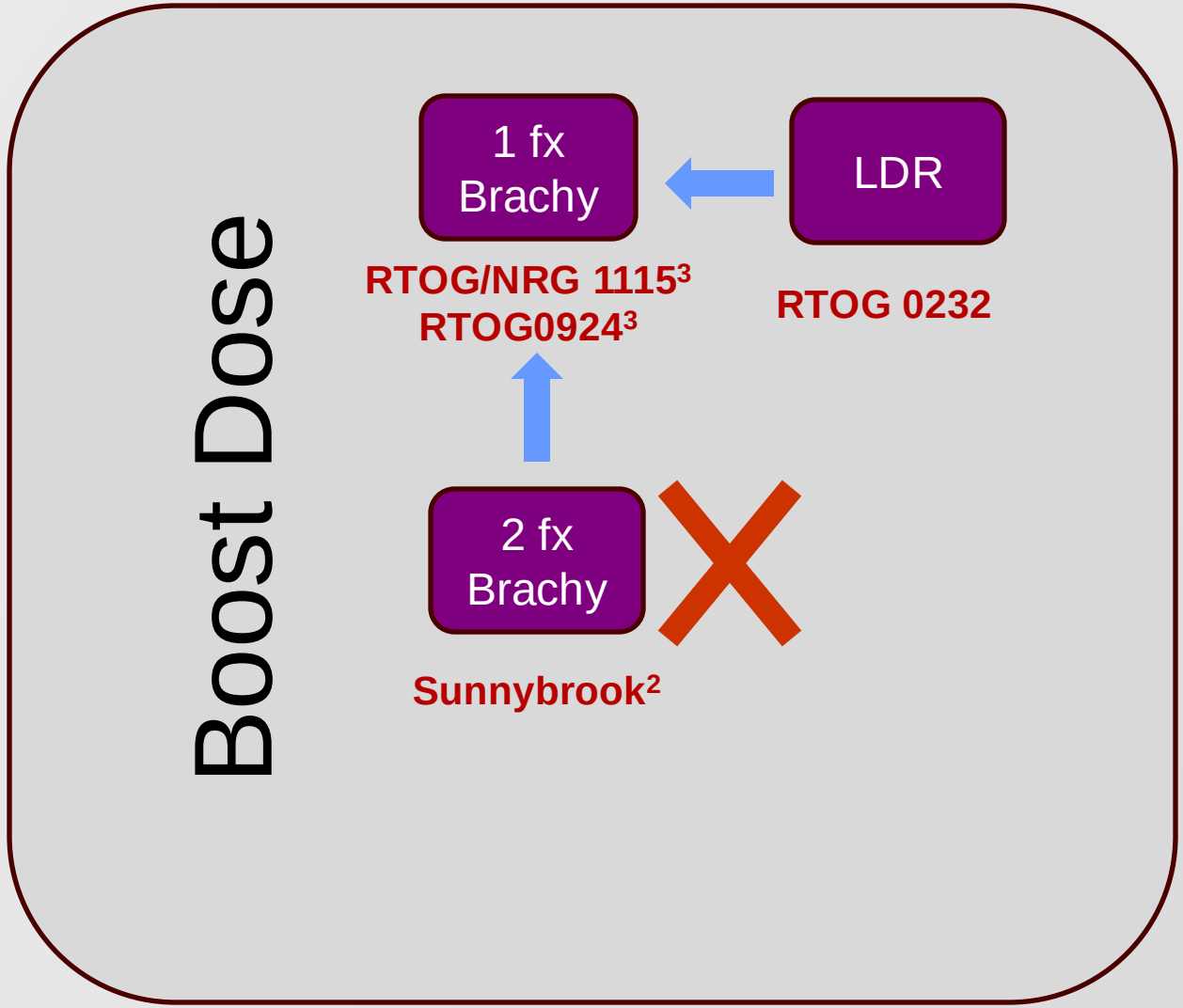
RTOG0924[3]



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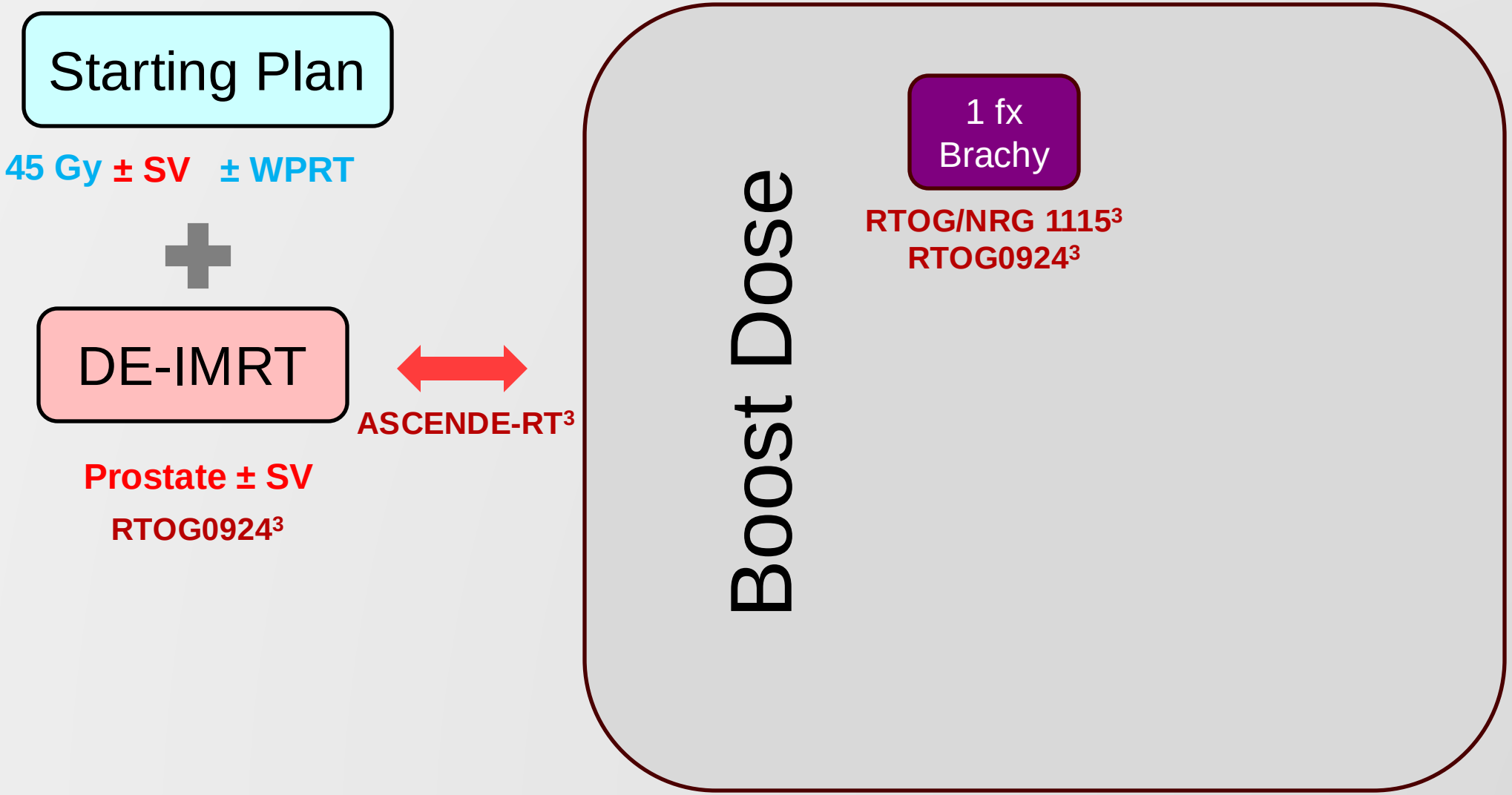

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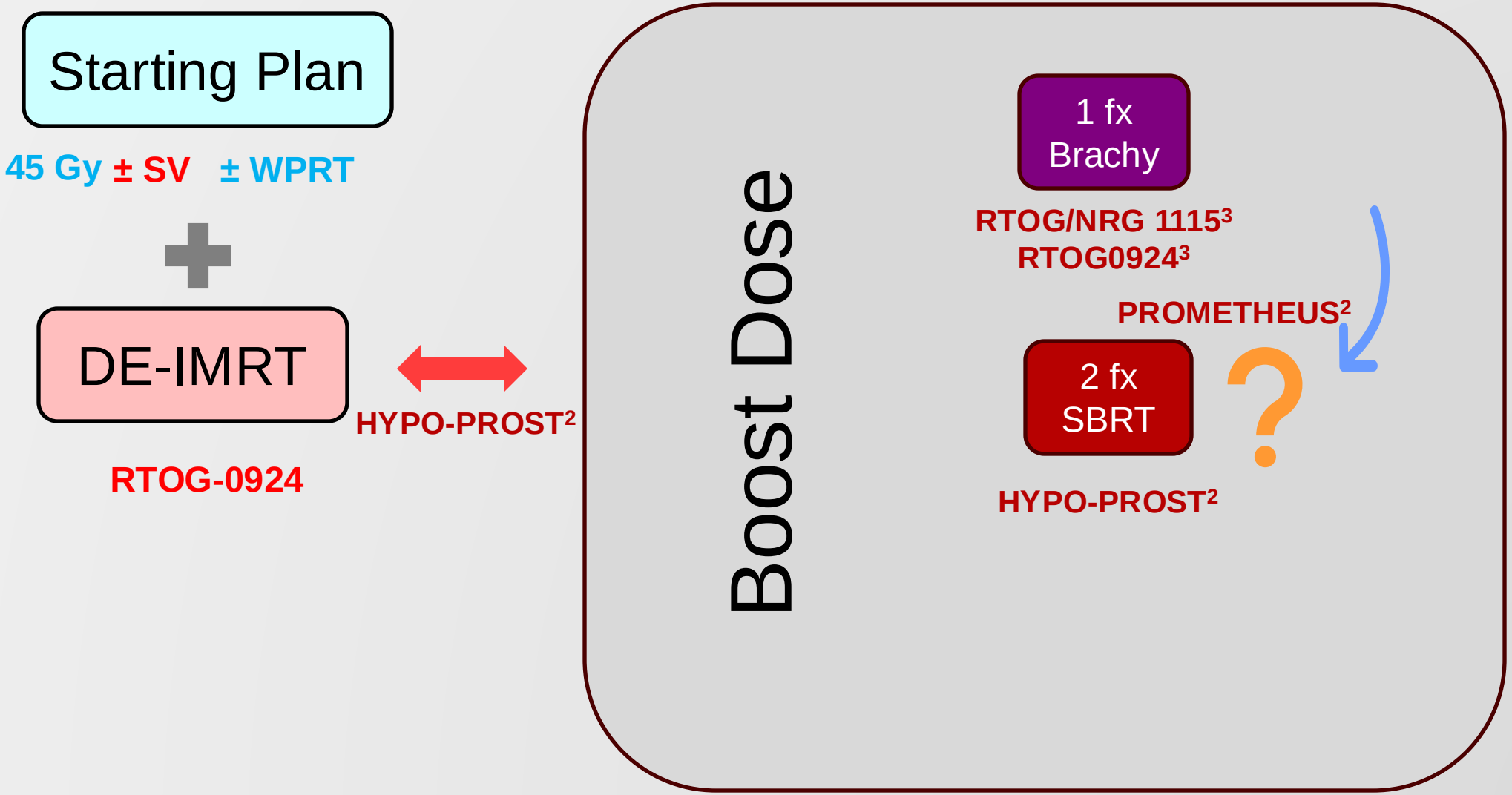

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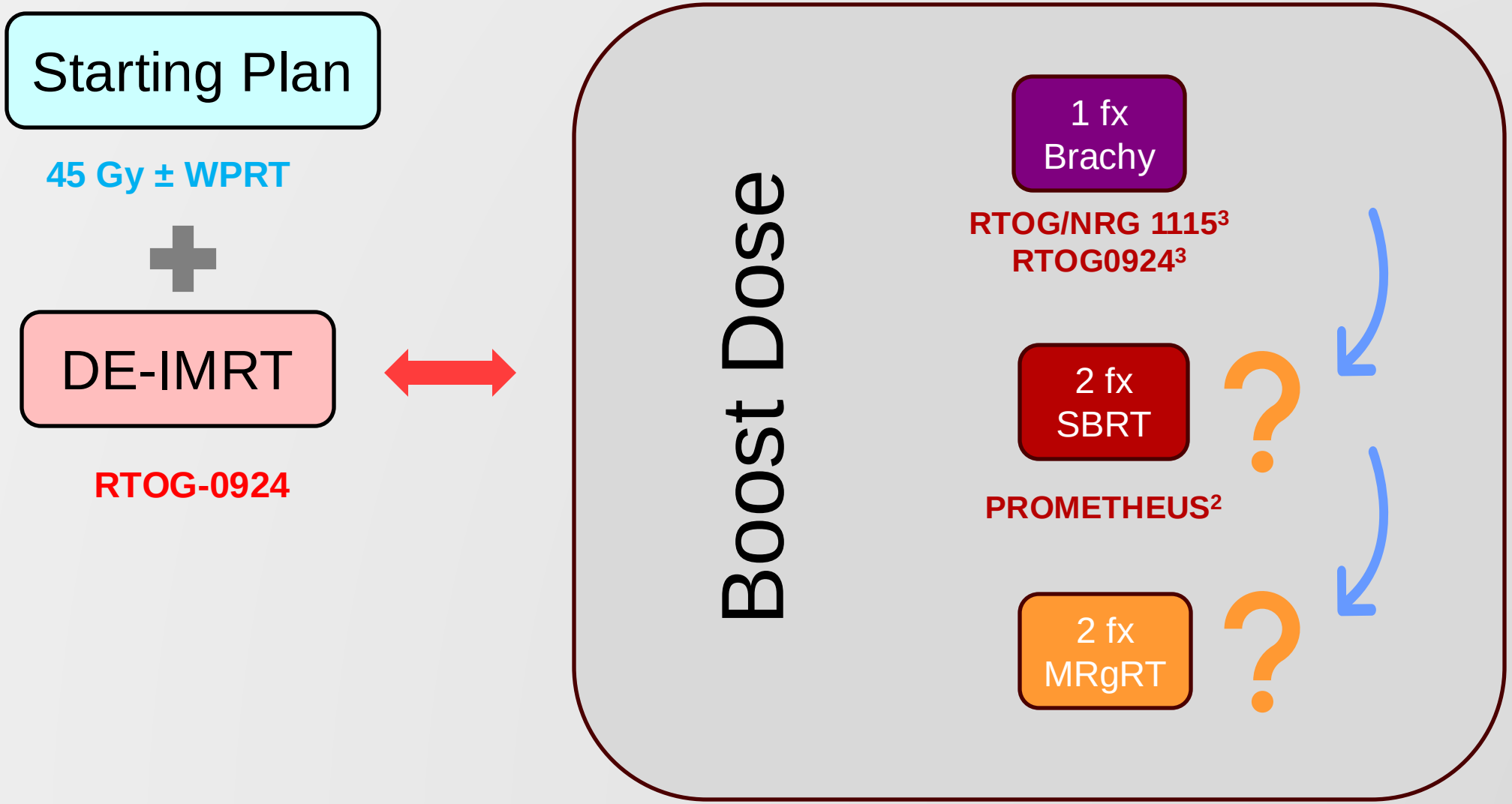

Question I: Is MRgRT better than standard hypofractionation or SBRT

- 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), reduced toxicity and improved QoL.

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- Early toxicity results comparing 5 fx
  - Phase II, single-arm (ASCO GU 2019), view-ray
  - Phase III, MIRAGE (ASCO GU 2022), view-ray

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

Question II: Can MR-Linac compete in the LR and FIR group against Brachytherapy?

- Brachy-monotherapy treats this risk group. (**RTOG0232**)
- Does standard hypofractionation/SBRT treat this group?
  - **Yes endorsed by NCCN, and supported by meta-analysis***

    Kishan JAMA 2019
- Does SBRT provide non-inferior outcome?
  - Is hypofractionation a strong competitor*? **Yes (RTOG0415)**
  - Is SBRT a strong competitor*? **Yes (PACE-B)**

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  - Is hypofractionation a strong competitor*? **Yes (RTOG0415)**
  - Is SBRT a strong competitor*? **Yes (PACE-B)**
  - Is MR-Linac better than “CT-Linac”? **Promising (MIRAGE, ASTRO2019), but noninferiority needed.**

Question III: Can MR-Linac compete in UIR & HR group against 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.**
  - *rely on evidence from PROMETHEUS*

- ***Can MR-Linac boost patents?***
  - *No data, rely on evidence from PROMETHEUS and MIRAGE*

Standard of Care

Local Primary

Hypofractionated

EBRT ± BT boost

SBRT

MRgRT

Focal Treatment

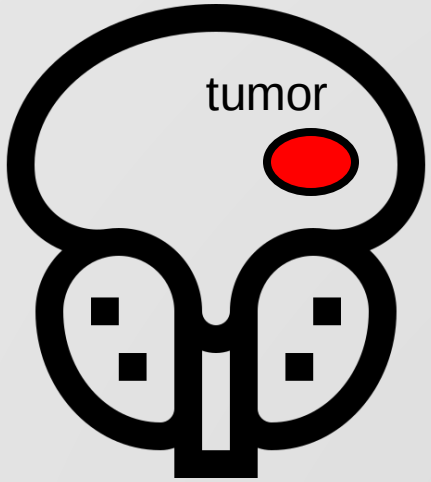
Local Primary

Hypofractionated

EBRT ± BT boost

SBRT & MRgRT

Focal Boost



EBRT SIB

FLAME

DELINEATE

*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 to the DIL to 95Gy

*EBRT focal boost

- **Phase III Flame Trial**

- **Phase III PIVOTALboost (DELINEATE)**
  - (IR, HR) report 5-year efficacy and toxicity of intraprostatic lesion boosting using the base of 3Gy/fx (CHHiP) radiation therapy to prostate + SV and 67 Gy to the intraprostatic lesion.

*EBRT SBRT focal boost

- **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 PIVOTALboost (DELINEATE)**
  - (IR, HR) report 5-year efficacy and toxicity of intraprostatic lesion boosting using the base of 3Gy/fx (CHHiP) radiation therapy to prostate + SV
  - DELINEATE Cohort E in 5 fx, similar to HYPO-FLAME & 2.0.

Question IV: Can MR-Linac treat focal boost?

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- **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

Discussions

- Existing trials did not show biochemical and local control data.
  - Too early. Early toxicity results are shown first in the interim study.

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- Existing trials did not show biochemical and local control data.
  - Too early. 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 (not comprehensive)

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

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 compared to PACE-B**
- **Competing brachytherapy?**
  - Low risk group – Yes. 2 fx / 5fx MR-Linac → tumor control?
  - High risk group boost – PROMETHEUS trial → MR-Linac?
  - Locally advanced group – DELINEATE trial → MR-Linac?
  - Focal Boost - FLAME trial EBRT → no trials opened for brachy & MR-Linac
  - Focal Salvage – FSHARP trial Brachy → no trial opened for MR-Linac