Brigham and Women's Hospital
Founding Member, Mass General Brigham

Phase I Trial: Dose Escalation Using Hypofractionated Radiation Therapy in RPS

Katie Lee, MD, PhD
Elizabeth Baldini, MD, MPH
Chandrajit Raut, MD, MS
Miranda Lam, MD, MBA

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Background

- Use of pre-operative RT in RPS remains an area of active study
- **STRASS**: Unplanned subgroup analysis showed a trend towards improved local control with preoperative RT for WDLPS and low-grade RPS
- Role of RT in locally recurrent RP LPS is being investigated
- Currently, the standard regimen for pre-operative RT for RPS has been a prescription of 50-50.4 Gy in 1.8-2 Gy per daily fraction delivered over 5-6 weeks

Hypofractionated Radiation Therapy

- Hypofractionation defined
  - Larger doses of RT per fraction delivering a full course of treatment over a shorter period of time compared to conventional fractionation
  - Interest in hypofractionation has increased given shorter and more convenient treatment schedule for patients

- Many malignancies, including breast, rectum, and prostate CA, are utilizing hypofractionated regimens of RT as standard of care with comparable toxicity and cancer outcomes

- Rectal cancer: 5 Gy x 5 fraction regimen pre-operatively

- MDACC: prospective trial in STS of extremities and trunk has shown excellent local control and wound complication rates with hypofractionated RT*

*Guadagnolo et al, *Lancet Oncol* 2022

MDACC: Hypofractionation in STS (HYPORT-STS)

- Single-arm, open-label, phase 2 trial of 120 patients
  - Hypofractionated preop RT: **2.85 Gy x 15 fractions (~3 weeks)** = **42.75 Gy**
  - Surgery 4 – 10 weeks following RT (median 5.7 weeks)
  - Primary endpoint: Major wound complication within 120 days of surgery

- Major wound complication rate
  - Hypofractionated regimen = **31%** [95% CI, 24-40%]
  - Comparable to historical major wound complication rate of conventional RT (35%)

- Local control
  - **5% LR** at median 16 mo postop
  - 30-mo actuarial **LRFS 93%** [95% CI, 86%-97%]

*Guadagnolo et al, *Lancet Oncol* 2022

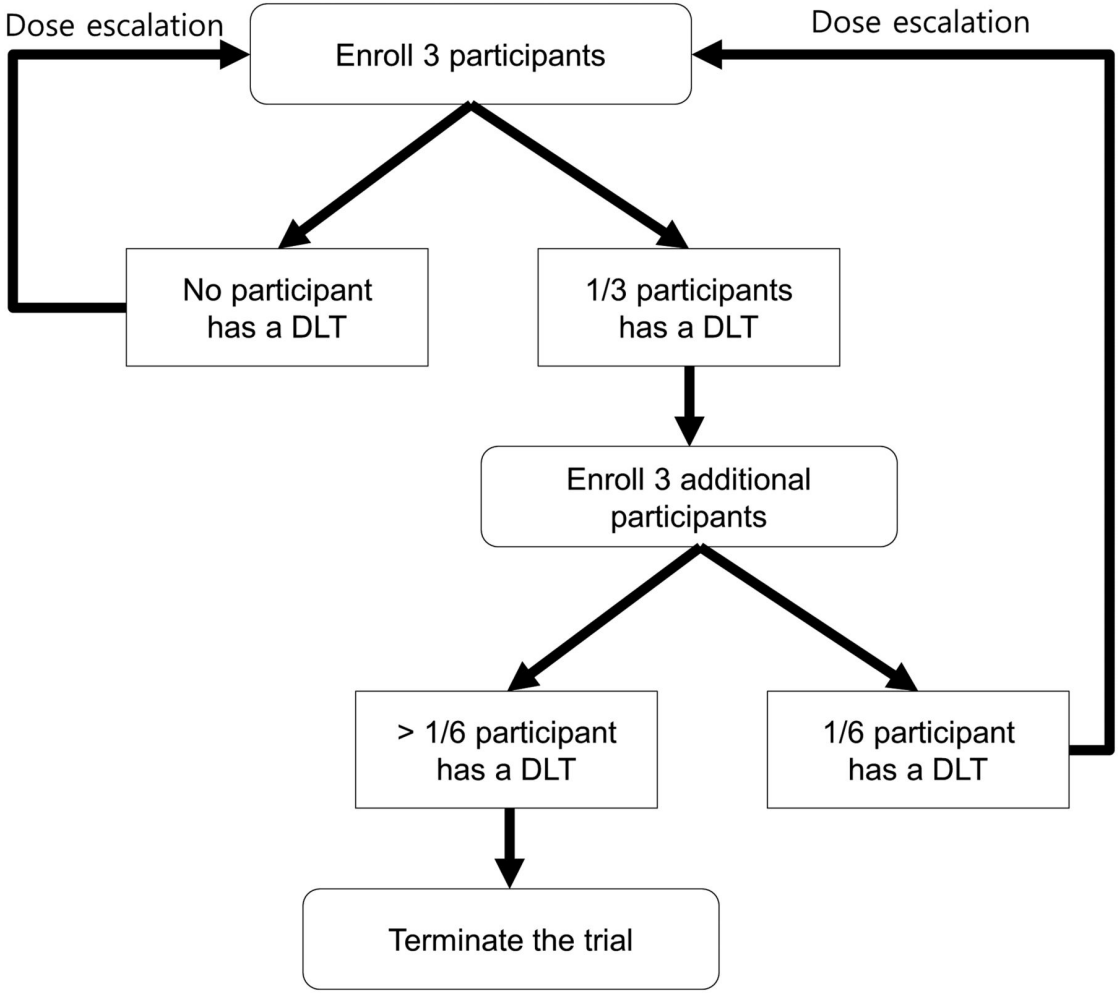
Study Design

- **Primary Objective**
  - Determine the maximum tolerated dose (MTD) of hypofractionated radiotherapy for primary and recurrent RPS using increasing dose per fraction and based on acute toxicity
- Two study arms: preop RT and RT alone
- Dose escalation plan: standard 3+3 design

Eligibility Criteria

- Must have a histologically confirmed STS of the retroperitoneal space or infra-peritoneal spaces of pelvis excluding GIST, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, aggressive fibromatosis, or sarcomatoid or metastatic carcinoma
- Must have radiologically measurable disease (RECIST 1.1)
- Participant may have primary, locally recurrent, or metastatic disease requiring treatment of the retroperitoneal mass
- Arm 1 (pre-op RT): Tumor must be suitable for RT and surgery (anticipated R0/R1 resection)
- Arm 2 (RT alone): Tumor must be suitable for RT and without plan for surgery

3+3 Dose Escalation



MTD = Previous Dose

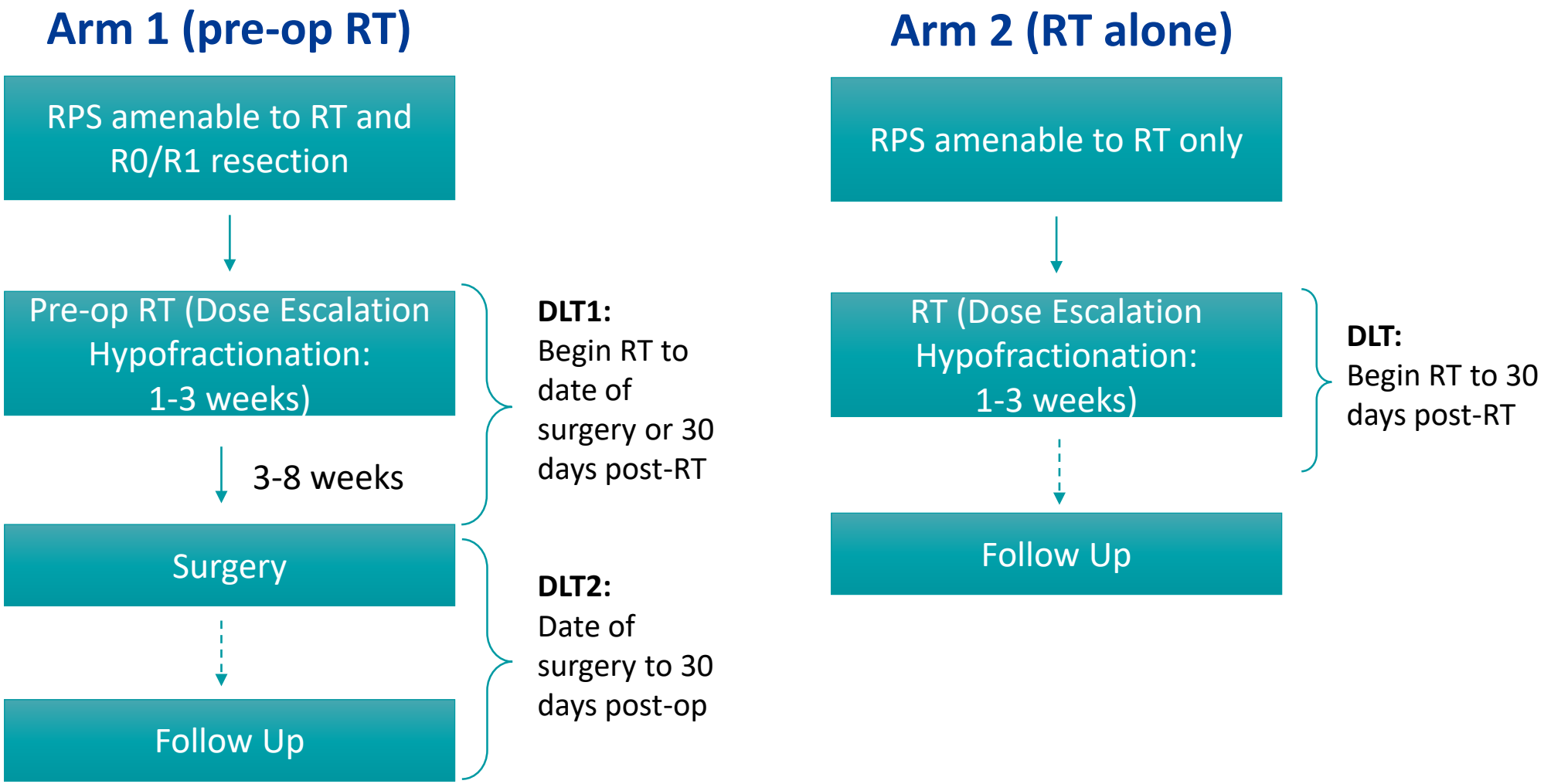
Cheon et al, *BMJ* 2018

Dose Escalation

Dose Cohort	Number of Participants	Dose of Radiation Therapy	Equivalent Dose in 2Gy Fractions (EQD2*)
		Current Standard 2 Gy x 25 fractions (50 Gy)	50 Gy
1	3 or 6, depending on toxicity	2.85 Gy x 15 fractions (42.75 Gy)	48.8 Gy
2	3 or 6, depending on toxicity	5 Gy x 5 fractions (25 Gy)	37.5 Gy
3	3 or 6, depending on toxicity	5.5 Gy x 5 fractions (27.5 Gy)	43.5 Gy
4	3 or 6, depending on toxicity	6 Gy x 5 fractions (30 Gy)	50 Gy

*$\alpha/\beta=4$

Schema


Arm 1 (pre-op RT)
RPS amenable to RT and R0/R1 resection
Pre-op RT (Dose Escalation Hypofractionation: 1-3 weeks)
3-8 weeks
Surgery
Follow Up
DLT1: Begin RT to date of surgery or 30 days post-RT
DLT2: Date of surgery to 30 days post-op
Arm 2 (RT alone)
RPS amenable to RT only
RT (Dose Escalation Hypofractionation: 1-3 weeks)
Follow Up
DLT: Begin RT to 30 days post-RT

Dose-Limiting Toxicity (DLT)

- Arm 1 (pre-op RT)
  - **DLT1**: Defined from start of radiation therapy to date of surgery or 30 days post-RT (whichever is soonest)
  - **DLT2**: Defined from 30 days post-RT to 30 days post-op
- Arm 2 (RT alone)
  - **DLT:** Defined from start of radiation therapy to 30 days post-RT
- CTCAE v5.0
  - Any unanticipated ≥ grade 3 non-hematologic or hematologic toxicity probably or definitely related to the dose-escalated radiation, seen either acutely during radiation or at subsequent pre-operative visit or post-operative visit; or
  - Any grade 4 non-hematologic toxicity; or
  - Any grade 4 neutropenia or thrombocytopenia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