WHY DID SRT BECOME SO HOT DURING THE PAST YEARS

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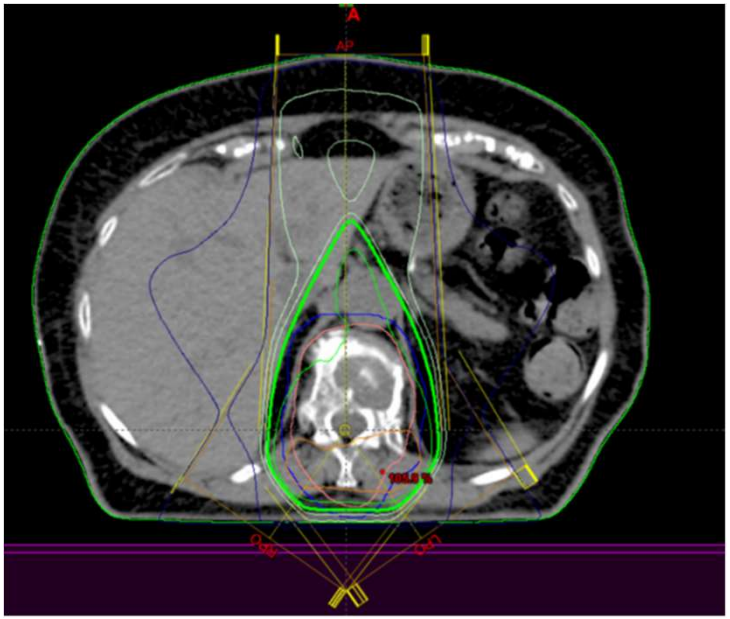
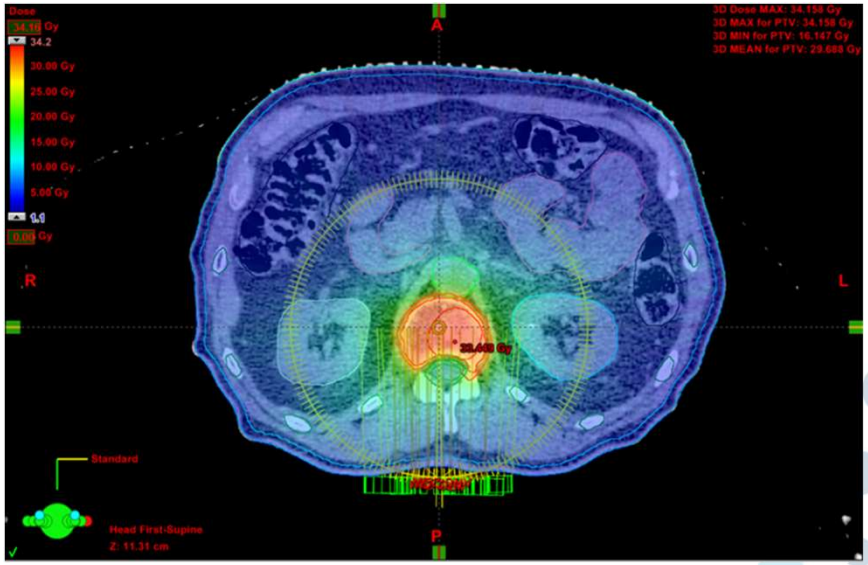
netwerk iridium
Topzorg in radiotherapie

All RT is equal?

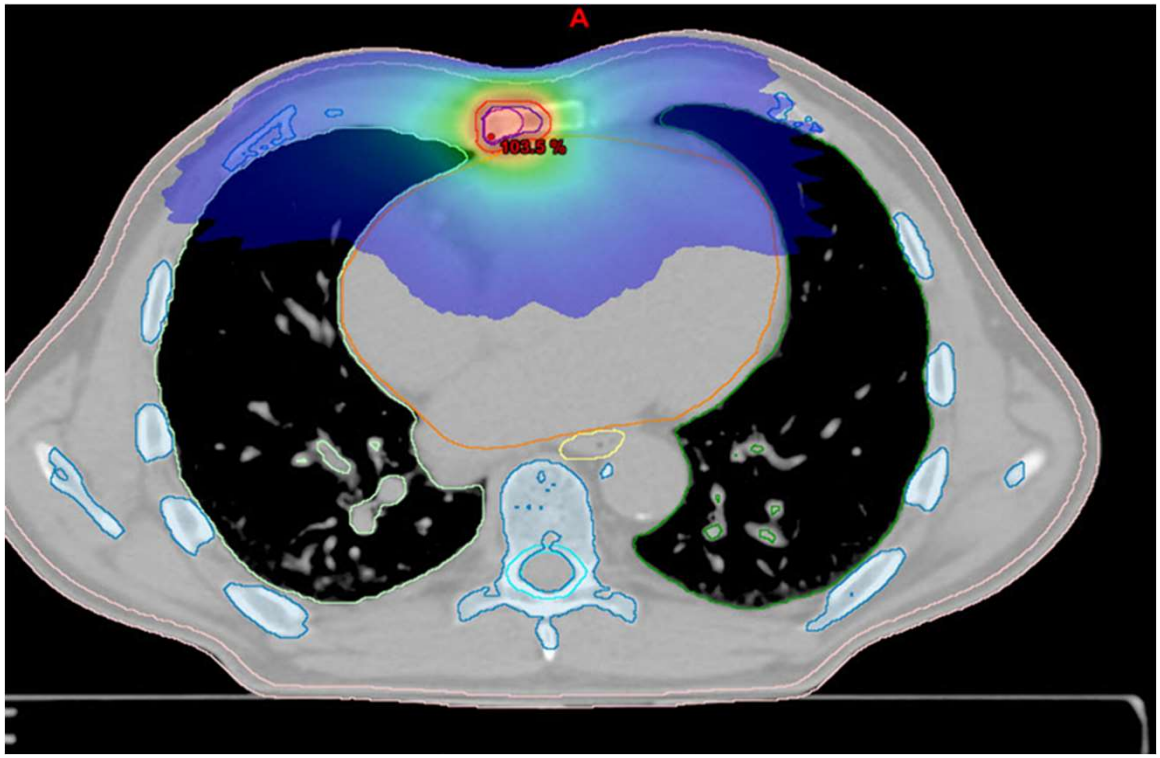
10x 3.0 Gy with 3D-CRT



3x 10.0 Gy with SBRT



Steretoactic (body) radiation therapy



1. GTV delineated on innovative imaging (MRI and/or PET)

2. No or limited CTV

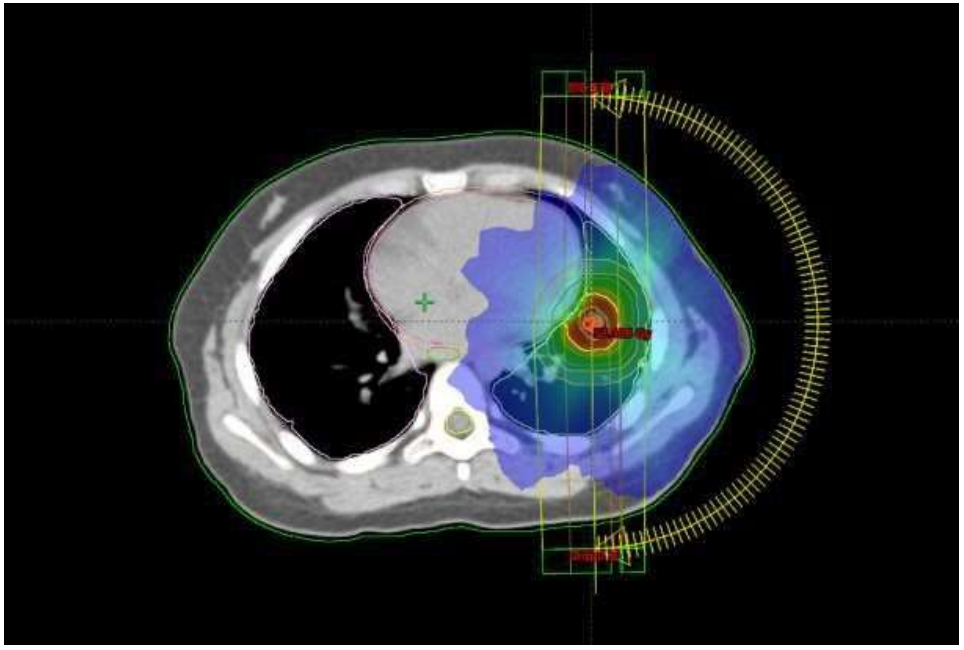
3. PTV margins < 3-5 mm

4. High-quality daily IGRT

5. Extremely hypofractionated

Two success stories of modern RT

Lung SBRT

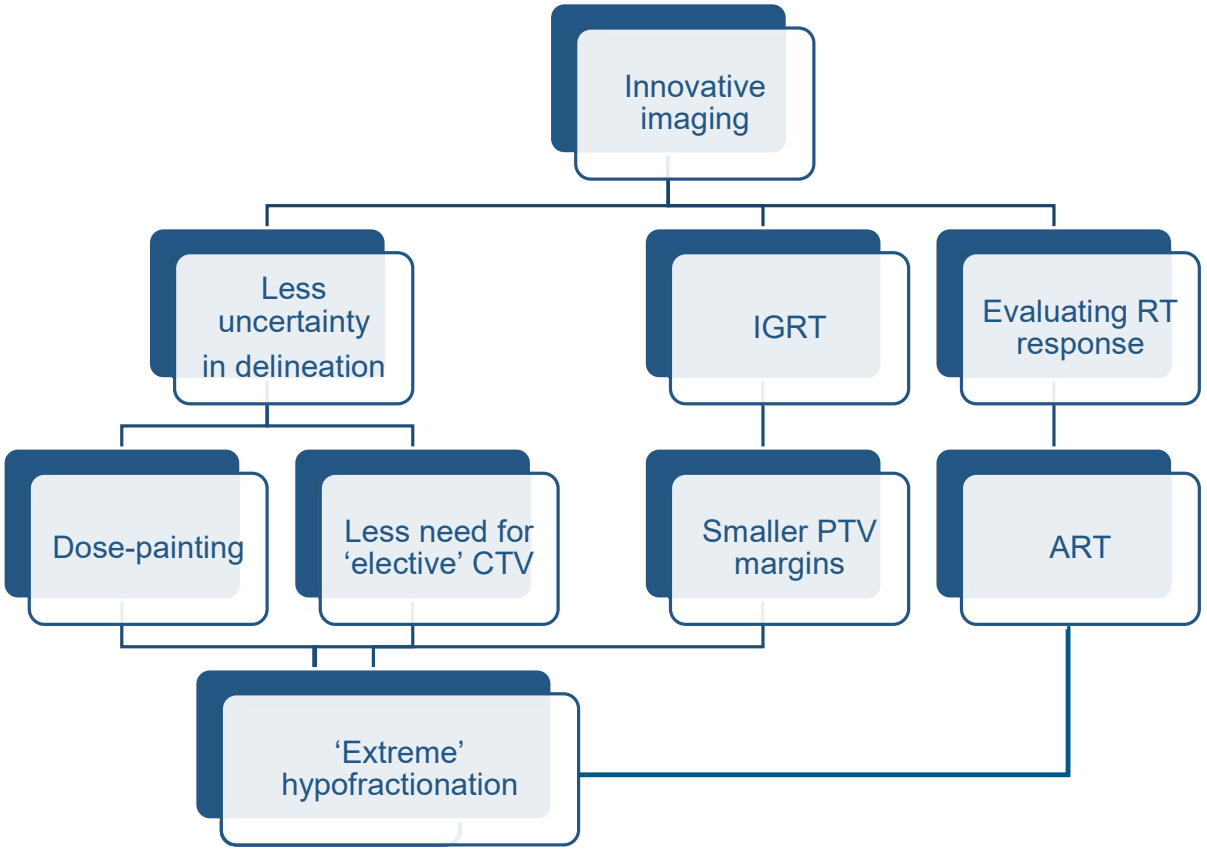


IGABT of the cervix

Technique or approach?

- “High-tech” delivery techniques:
  - Conventional/3D-conformal/IMRT/VMAT/S(B)RT
  - MR-Linac, C-arm linac, O-ring linac
  - Photons/Protons/Carbon-ions
  - LDR/PDR/HDR BT
  - …
- What do we want?
  - 100% cure, 0% toxicity, 100% quality of life
- Treatment approach:
  - Spatial control of the dose distribution
  - Inhomogeneous dose distribution
  - Based on 3D tumor-characteristics
  - Individualized treatment

Modern radiation therapy

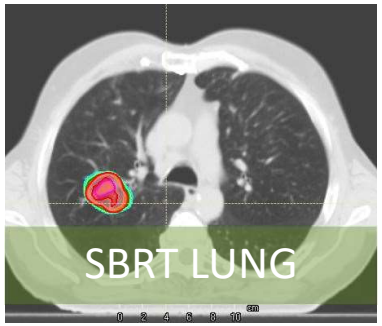


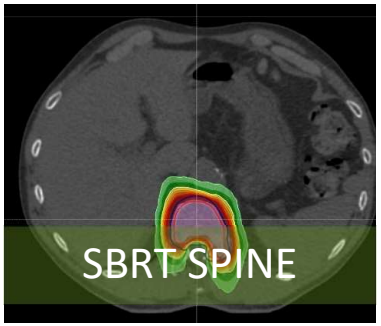
From moderate to extreme hypofractionation

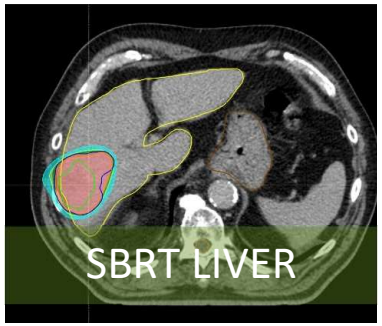
Target	Standard fractionation	Moderate hypofractionation	Extreme hypofractionation
Brain	30x 2,0 Gy	15x 2,67 Gy	SRS
Breast	25x 2,0 Gy	15x 2,67 Gy	5x 5,2 Gy
Lung	33x 2,0 Gy	20x 2,75 Gy	1x 34,0 Gy
Rectal	25x 1,8 Gy		5x 5,0 Gy
Prostate	37x 2,0 Gy	20x 3,0 Gy	5x 7,25 Gy
Bladder	33x 2,0 Gy	20x 2,75 Gy	6x 6,0 Gy
Metastases	10x 3,0 Gy	5x 4,0 Gy	1x 16,0 Gy
…			

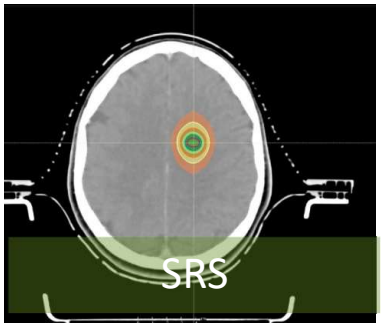
Dedicated STX-SBRT unit

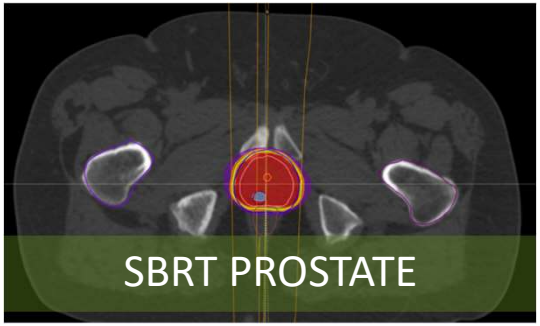
SRT programs at Iridium











Scientific focus at Iridium

Clinical:

1. GU, prostate (P. Ost)
2. GYN, breast (M. Machiels)

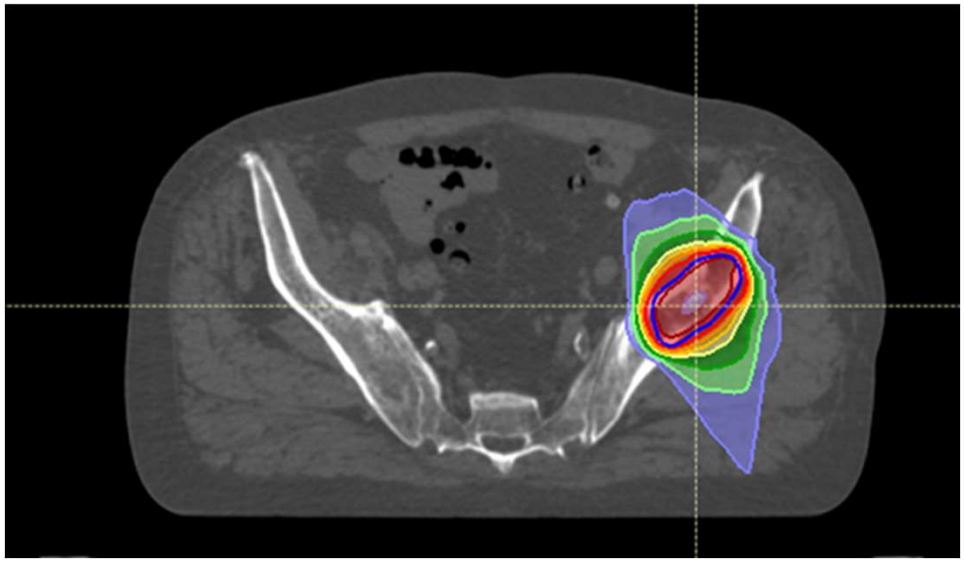
Technical:

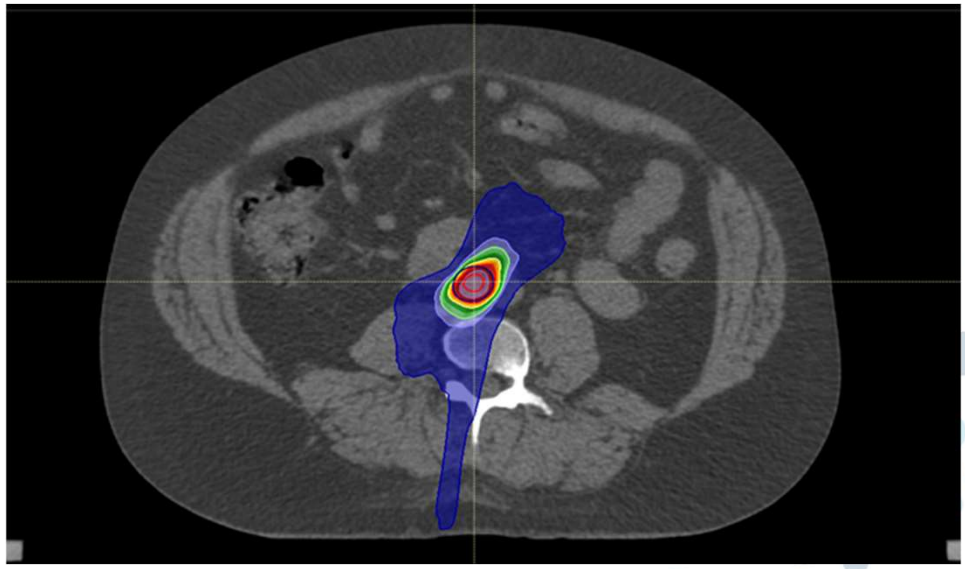
1. **SRT (Ch. Billiet)**
2. Ultra-high dose-rate (UHDR or FLASH) radiation therapy (Ph. Poortmans)

Investigator-initiated trials (IIT)

Name	Phase	Focus	PI	Multicentric	Status
DESTROY	I	**SRT**	P. Dirix	no	published
ROBOMET	III	**SRT**	P. Dirix	yes	published
ULTIMO	III	Breast	M. Machiels	no	completed
SAVE	II	Prostate	P. Dirix	yes	completed
SABR-MESCC	III	**SRT**	Ch. Billiet	yes	accruing
THUNDER	III	Prostate	P. Ost	yes	accruing
TORPEDO	II	**SRT**	I. Joye	yes	accruing
PRADA-2	III	Breast	M. Machiels	yes	accruing
HERMES	III	**SRT**	Ch. Billiet	yes	accruing

A phase I dose-escalation trial of stereotactic ablative body radiotherapy for non-spine bone and lymph node oligometastases (NCT03486431)

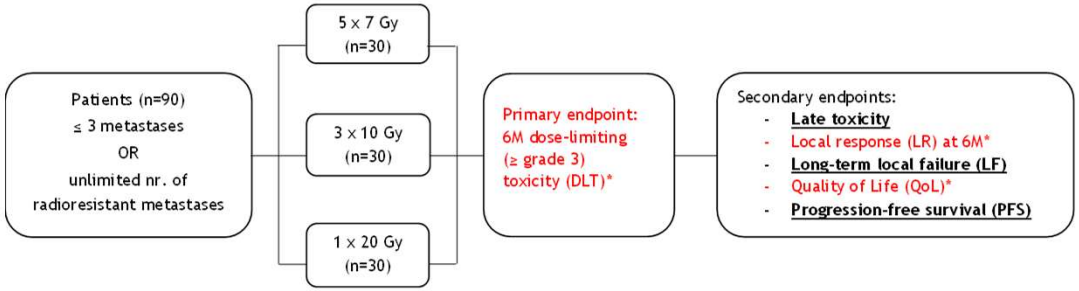




Outline

Table 2 Fractionation schedules

Level	Fractions	Interval	Dose/fraction	Total	BED_{10Gy}	EQD_{2Gy}
1	5	48 h	7	35	59.5	78.75
2	3	48 h	10	30	60.0	90
3	1	NA	20	20	60.0	110

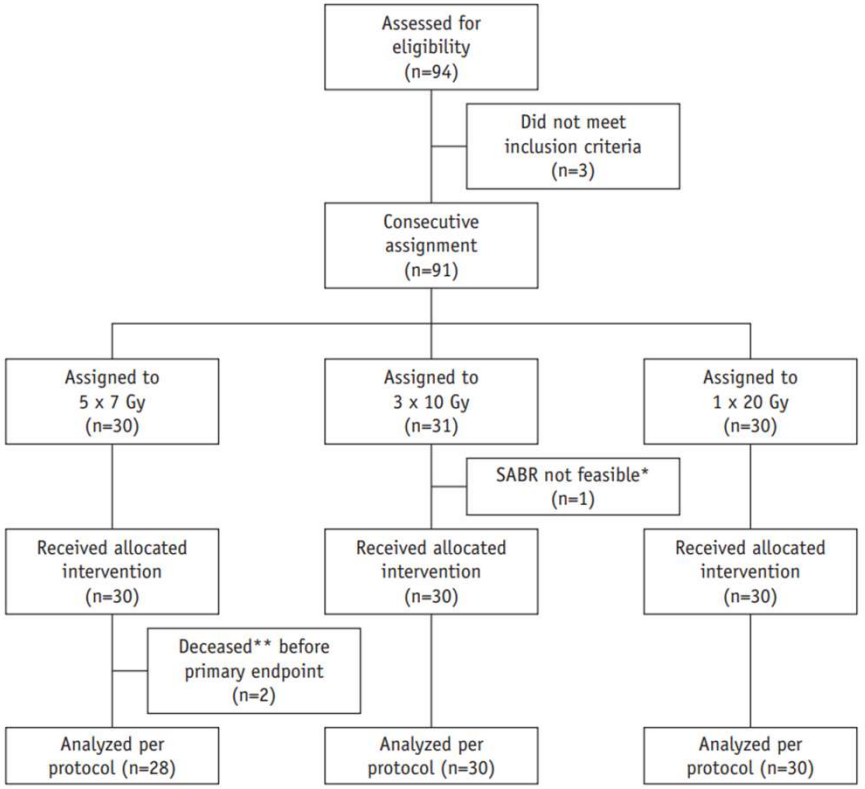


Toxicity: Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03

Local response & local failure: Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Quality of Life: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire

SBRT could be combined with standard of care systemic treatment



*Centrally located mediastinal lymph node
**Rapid distant disease progression

Fig. 1. Consolidated Standards of Reporting Trials diagram.

Mercier et al. Radiat Oncol 2018.

Summary

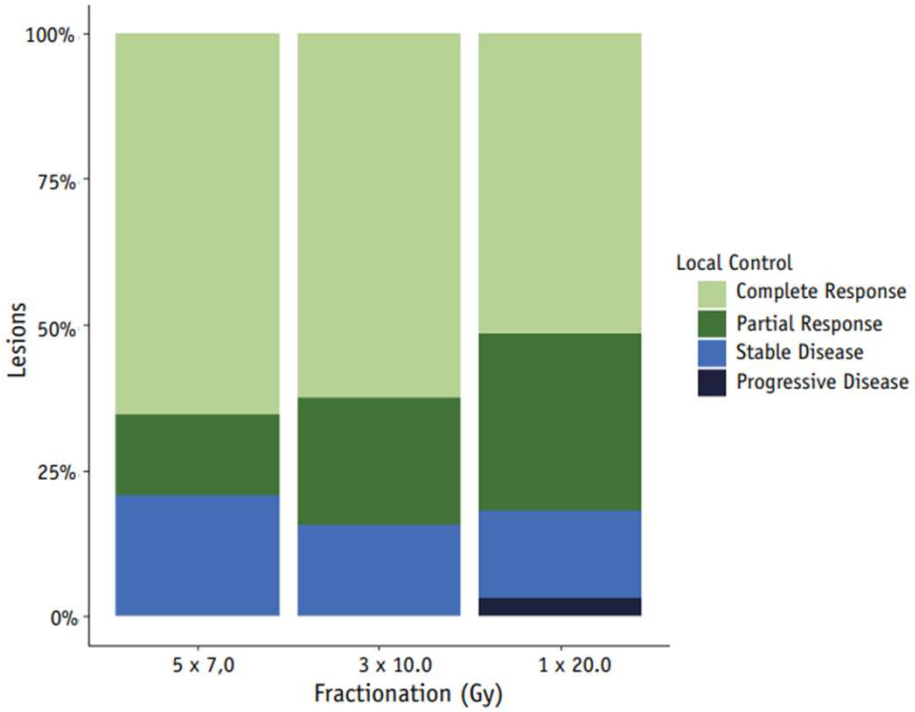
- Accrual opened in July 2017 and was completed in December 2018
- **Ninety patients** received SBRT to **101 metastases**
- Median age was 69 (IQR 62-75) and the majority of patients (74%) were male
- The most common primary tumour types were **prostate (58%), breast (14%)** and lung (9%)
- The three groups were **well-balanced** for patient and tumour characteristics

Table. Baseline characteristics

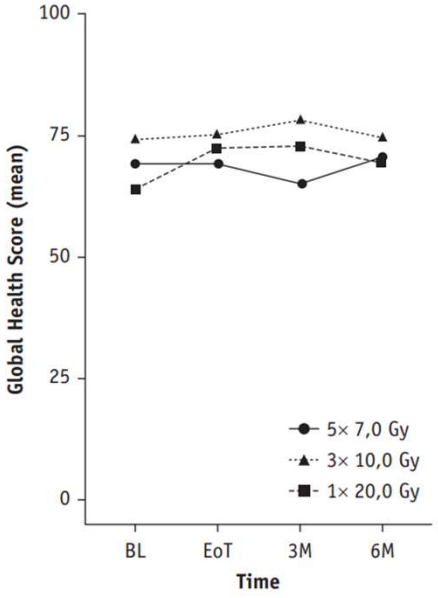
Characteristic		5 x 7 Gy (n=27)		3 x 10 Gy (n=28)		1 x 20 Gy (n=28)		*P-value*
Age (years)								*0,54*
	Median (IQR)	69	63-78	70	62-73	70	65-77	
Sex								*0,74*
	Men	21	78%	21	75%	19	68%	
	Women	6	22%	7	25%	9	32%	
Site of original primary tumour								*0,67*
	Prostate	17	63%	17	61%	16	57%	
	Breast	2	7%	5	18%	6	21%	
	Other	8	30%	6	21%	6	21%	
Time from diagnosis of primary tumour to inclusion (years)								*0,26*
	Median (IQR)	5,8	(1,6-12,5)	2,8	(0,5-4,6)	3,5	(0,4-4,4)	
Timing of metastatic diagnosis								*0,41*
	Synchronous	2	7%	5	18%	6	21%	
	Metachronous	25	93%	23	82%	22	79%	
No. of non-spine bone and lymph node metastases per patient								*0,36*
	1	25	93%	25	89%	22	79%	
	2	2	7%	3	11%	6	21%	
Type of metastases (n=94 lesions)								*0,31*
	Bone	13/29	45%	19/32	59%	21/33	64%	
	Lymph Node	16/29	55%	13/32	41%	12/33	36%	
Anatomic location								*0,9*
	abdomen	4/29	14%	6/32	19%	6/33	18%	
	axilla	1/29	5%	0/32	0%	1/33	3%	
	femur/hip	1/29	3%	3/32	9%	3/33	9%	
	humerus/shoulder	0/29	0%	2/32	6%	2/33	6%	
	pelvis	15/29	52%	14/32	44%	13/33	39%	
	thorax	8/29	28%	7/32	22%	8/33	24%	
Lesion volume								*0,47*
	Median (IQR)	4,18	(1,67-13,6)	4,72	(2,46-6,43)	6,86	(3,62-12,00)	

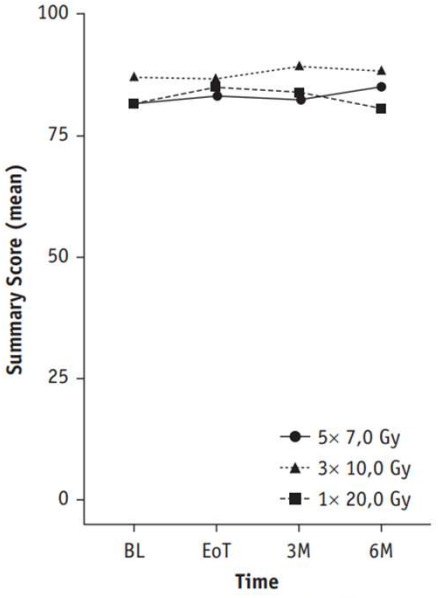
Initial analysis

- Median follow-up of 17.2 months
- Local response (LR) at 6M:



- **Dose-limiting toxicity (DLT) at 6M: none**
- Quality of Life (QoL):





Mercier et al. Int J Radiat Oncol Biol Phys 2021.

Long-term toxicity

- Long-term follow-up through September 2022
- Median follow-up of **50 months**
- No new safety signals, **no late grade 3-5 toxicities**
- Rates of grade 2 SBRT-related acute or late toxicity were 13%,7 % and 10% in cohort 1 through 3, respectively (p=.9)

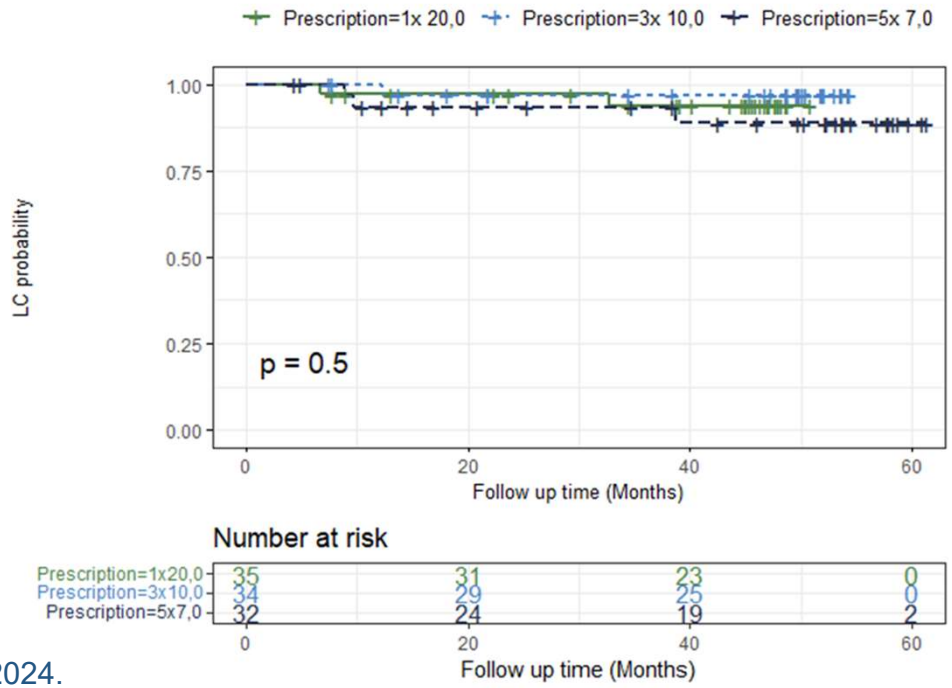
Treatment-related grade 2 adverse events

	Grade 2 adverse event	5 x 7.0 Gy	3 x 10.0 Gy	1 x 20.0 Gy	*P value*
Acute	Pain flare	2/30 (7%)	1/30 (3%)	0/30 (0%)	
	Gastrointestinal	2/30 (7%)	0/30 (0%)	1/30 (3%)	
	ALL	4/30 (13%)	1/30 (3%)	1/30 (3%)	*.36*
Late	Gastrointestinal	0/30 (0%)	1/30 (3%)	0/30 (0%)	
	Fracture	0/30 (0%)	0/30 (0%)	1/30 (3%)	
	Plexopathy	0/30 (0%)	0/30 (0%)	1/30 (3%)	
	ALL	0/30 (0%)	**1/30 (3%)**	2/30 (7%)	.8
Acute + Late	ALL	4/30 (13%)	2/30 (7%)	3/30 (10%)	.9

Mercier et al. Int J Radiat Oncol Biol Phys 2024.

Long-term lesion control

- LF occurred in 9% vs 3% vs 6% of lesions for the first, second and third cohort, respectively (p=.5)
- Overall estimated **4-year local control rate was 93%**
- There was no difference in local control rates between schedules:



Mercier et al. Int J Radiat Oncol Biol Phys 2024.

Long-term disease control

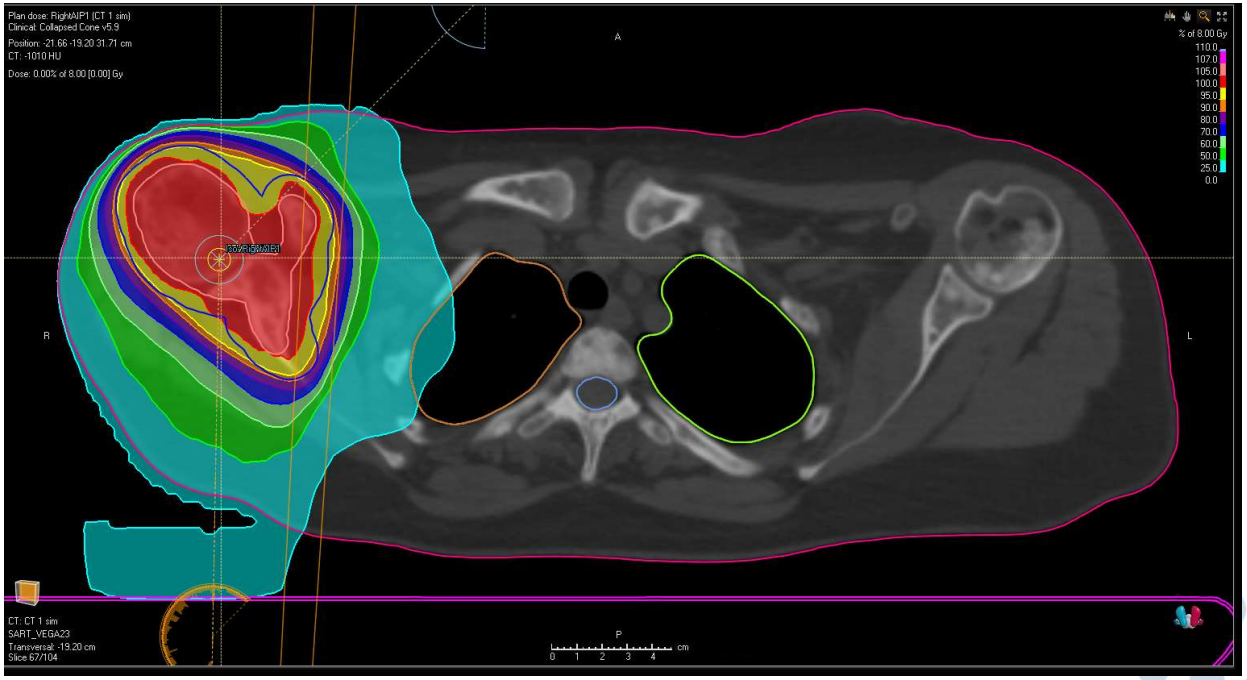
- Progression-free survival (PFS)
  - **Median PFS was 16.5 months** (95% CI 9.8 - 21.5)
  - 4-year PFS was 21% (95% CI 14 - 32)

- Disease control:
  - Twenty-one patients (23%) remained long-term disease-free
  - Thirty-three (37%) patients were oligoprogressive (≤3 new lesions) at first recurrence
  - Thirty-six (40%) developed a polymetastatic relapse

- Overall survival (OS):
  - Median OS not reached (95% CI 53 months – NA)
  - 4-year OS was 68% (95% CI 59 – 78)

Mercier et al. Int J Radiat Oncol Biol Phys 2024.

Dose-escalated stereotactic versus conventional radiotherapy for painful bone metastases (NCT03831243)



Outline

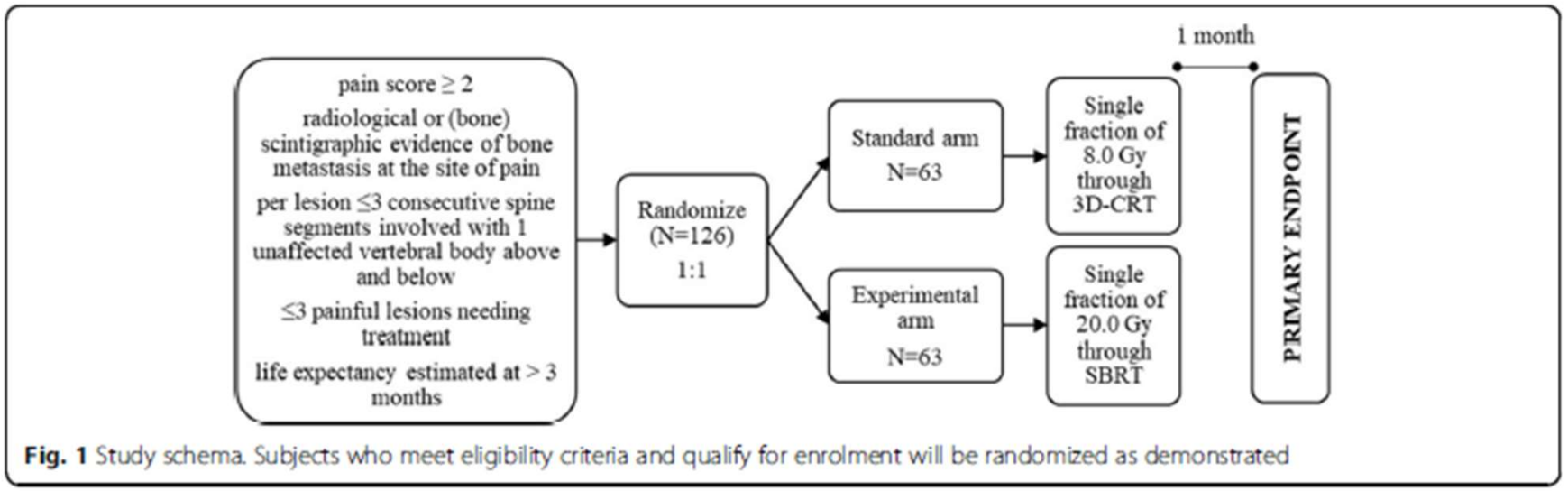


Fig. 1 Study schema. Subjects who meet eligibility criteria and qualify for enrolment will be randomized as demonstrated

Mercier et al. BMC Cancer 2019.

Results

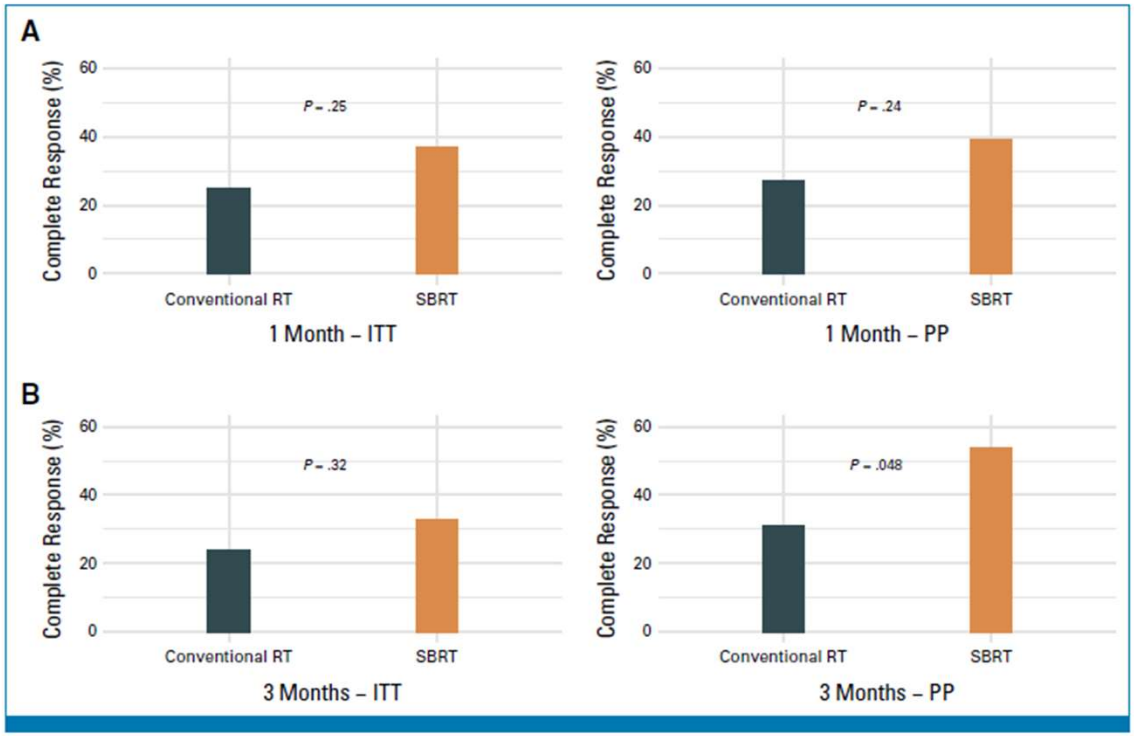


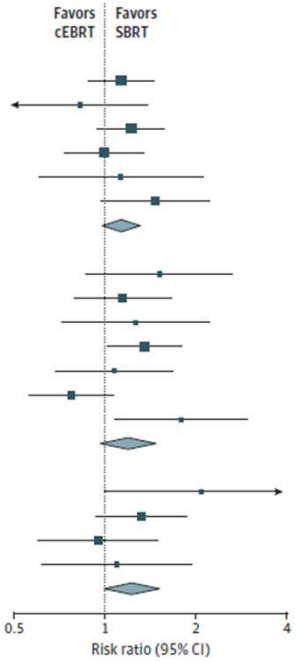
FIG 2. (A) Complete pain response after 1 month by ITT analysis and PP analysis. (B) Complete pain response after 3 months by ITT analysis and PP analysis. ITT, intention-to-treat; PP, per-protocol; RT, radiotherapy; SBRT, stereotactic body radiotherapy.

Mercier et al. J Clin Oncol 2025.

Meta-analysis

Figure 2. Intention-to-Treat Meta-Analysis on Overall Pain Response (OPR) at 1, 3, and 6 Months After Radiotherapy of the 8 Included Randomized Trials

Study	Patients with cEBRT, No. OPR	Patients with cEBRT, No. Total	Patients with SBRT, No. OPR	Patients with SBRT, No. Total	EQD2 for SBRT, Gy	Risk ratio (95% CI)
1 mo						
Mercier et al,[20] 2023	39	63	44	63	50	1.13 (0.88-1.45)
Pielkenrood et al,[8] 2021	19	55	16	55	50	0.84 (0.49-1.46)
Sahgal et al,[9] 2021	53	115	64	114	44	1.22 (0.94-1.57)
Ryu et al,[19] 2023	44	136	70	217	42; 34.7	1.00 (0.73-1.36)
Berwouts et al,[29] 2015	8	15	9	15	34.7	1.12 (0.60-2.11)
Nguyen et al,[7] 2019	24	79	36	81	34.7; 22	1.46 (0.97-2.21)
($Q = 3.55$; $df = 5$; $P = .62$; $I^2 = 0.0\%$; $\tau^2 = 0.00$)						1.14 (0.99-1.30)
3 mo						
Sprave et al,[33] 2018	11	30	16	30	68	1.45 (0.82-2.59)
Mercier et al,[20] 2023	28	63	32	63	50	1.14 (0.79-1.65)
Pielkenrood et al,[8] 2021	14	55	18	55	50	1.29 (0.71-2.32)
Sahgal et al,[9] 2021	45	115	60	114	44	1.35 (1.01-1.79)
Sakr et al,[10] 2020	9	12	8	10	42.8	1.07 (0.68-1.67)
Ryu et al,[19] 2023	46	136	57	217	42; 34.7	0.78 (0.56-1.07)
Nguyen et al,[7] 2019	17	79	31	81	34.7; 22	1.78 (1.07-2.94)
($Q = 10.52$; $df = 6$; $P = .10$; $I^2 = 44.5\%$; $\tau^2 = 0.03$)						1.19 (0.96-1.47)
6 mo						
Sprave et al,[33] 2018	7	30	14	30	68	2.00 (0.94-4.25)
Sahgal et al,[9] 2021	36	115	47	114	44	1.32 (0.93-1.87)
Ryu et al,[19] 2023	25	136	38	217	42; 34.7	0.95 (0.60-1.50)
Nguyen et al,[7] 2019	17	79	19	81	34.7; 22	1.09 (0.61-1.94)
($Q = 3.11$; $df = 3$; $P = .37$; $I^2 = 0.0\%$; $\tau^2 = 0.00$)						1.22 (0.96-1.54)



The trials compared conventional external beam radiotherapy (cEBRT) with stereotactic body radiotherapy (SBRT). Studies were sorted based on the equivalent dose delivered in 2 Gy (EQD2) for SBRT, with the highest dose on top.

Bindels et al. JAMA Netw Open 2024.

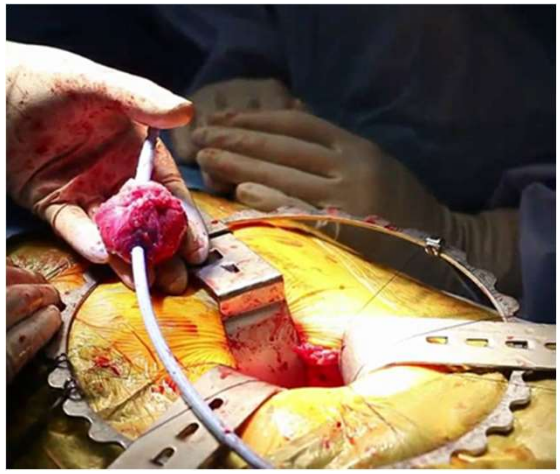
Conclusions

- What's in a name?
  - The future lies in extreme hypofractionation (5 or 3 fractions for large volumes, single fraction for smaller volumes)
  - Sometimes this is called S(B)RT, e.g. in prostate cancer, sometimes not, e.g. in breast cancer

- Ultimately, the distinction will become irrelevant as most, if not all, modern RT will involve:
  - Smaller target volumes with limited elective CTV and minimal PTV margins
  - High-end imaging to delineate, irradiate and follow the target
  - Extreme hypofractionation schedules

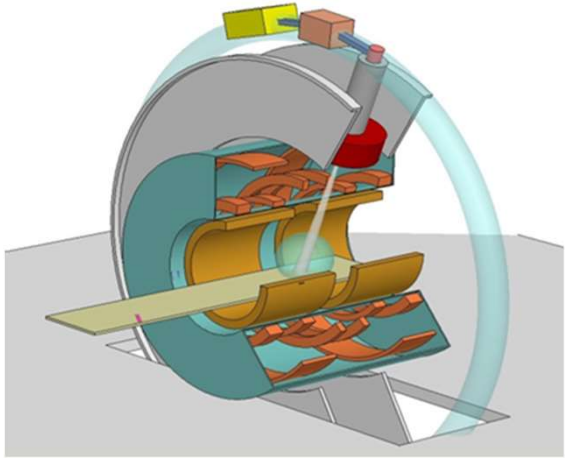
- Prospective trials clearly demonstrate the benefit of this **approach**:
  - To ablate disease
  - To improve HRQoL

RT is the natural evolution of cancer treatment



Open surgery

Robotic surgery



Non-invasive surgery