Amsterdam UMC
Universitair Medische Centra

Radiation Oncology

MR-guided Stereotactic Radiation Therapy (MRgRT)

for prostate cancer

Frank Lagerwaard/Anna Bruynzeel/Miguel Palacios
Amsterdam UMC – location VUmc


inspire 2 live

MRgRT: the patient perspective

1. What is (adaptive) MRgRT, as performed in Amsterdam UMC ?
2. What are the benefits of MRgRT ?
3. What does MRgRT mean for the patient ?
4. What are the outcomes with regards to toxicity ?
5. What are the initial outcomes with respect to tumor control ?
6. Future (potential) perspectives

Clinical MRgRT @Amsterdam

From May 4th 2016-Aug 15th 2018:

MRIdian Co-system

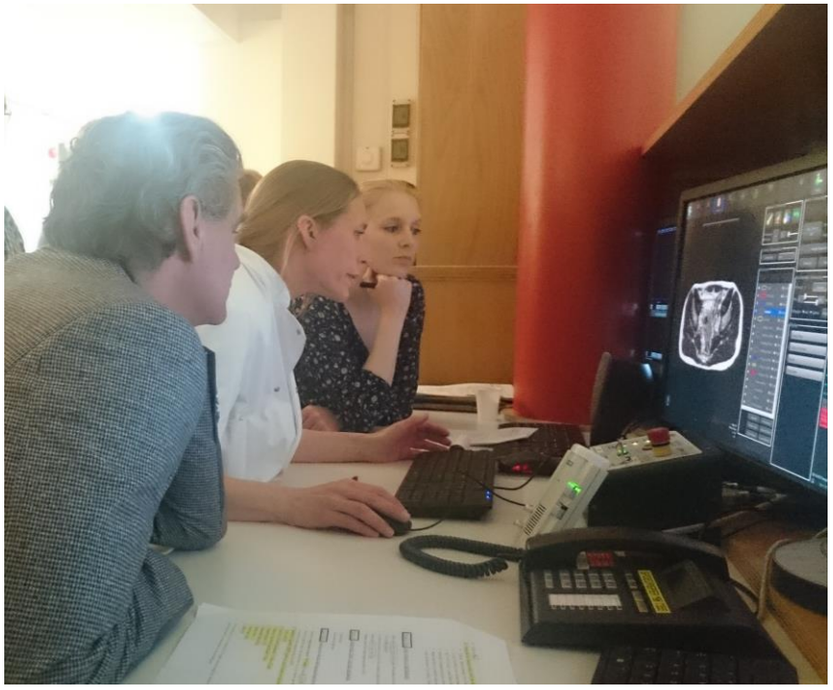
- 0.35 Tesla MRI
- IMRT delivery
- Three Co-60 sources

From April 18th 2018 onwards:

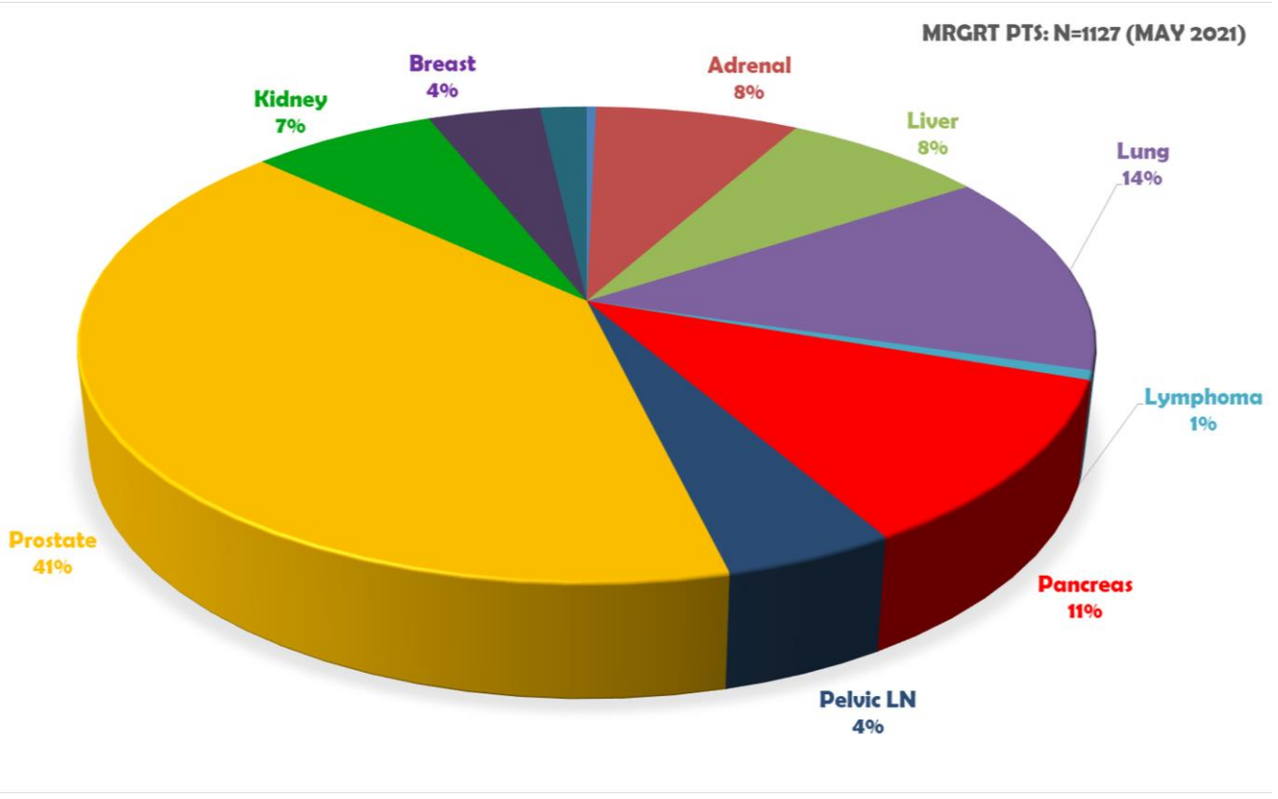
MRIdian Linac system (x2)

- 0.35 Tesla MRI
- IMRT delivery
- 6 MV, FFF

MRgRT @Amsterdam UMC/VUmc



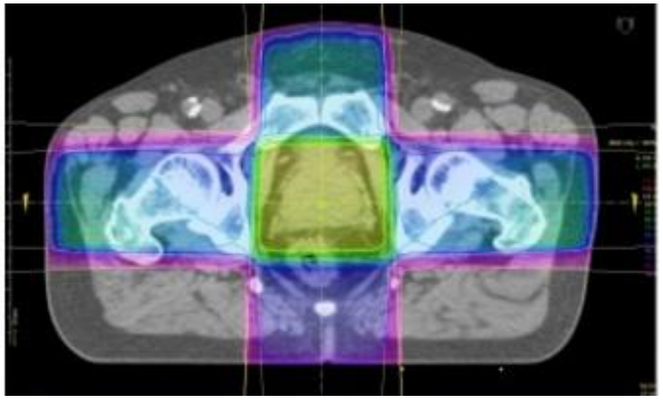
May 4th 2016

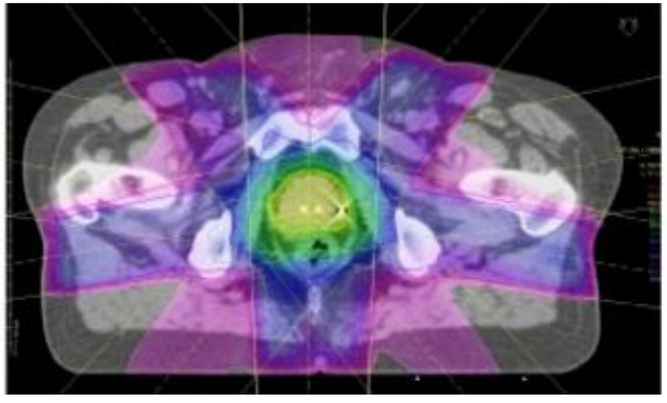


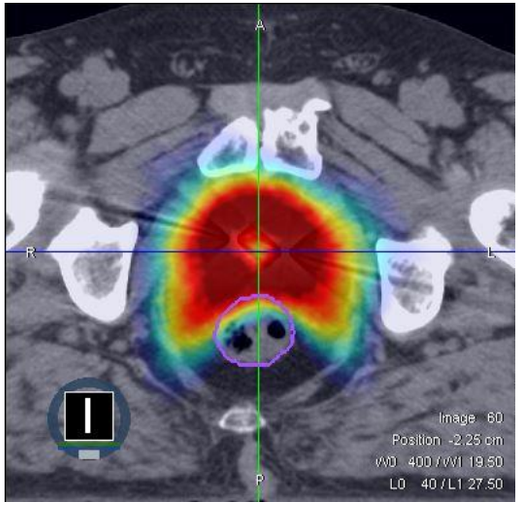
Since May 2016:

- More than 1200 pts treated with MRgRT
- More than 6000 (adaptive) fractions delivered
- Main indications: prostate-, lung-, pancreas-, kidney ca & oligomets

Evolution in RT techniques for prostate cancer







3D-conformal RT

Intensity modulated RT

Hypofractionation

Ultra-hypofractionation/SBRT

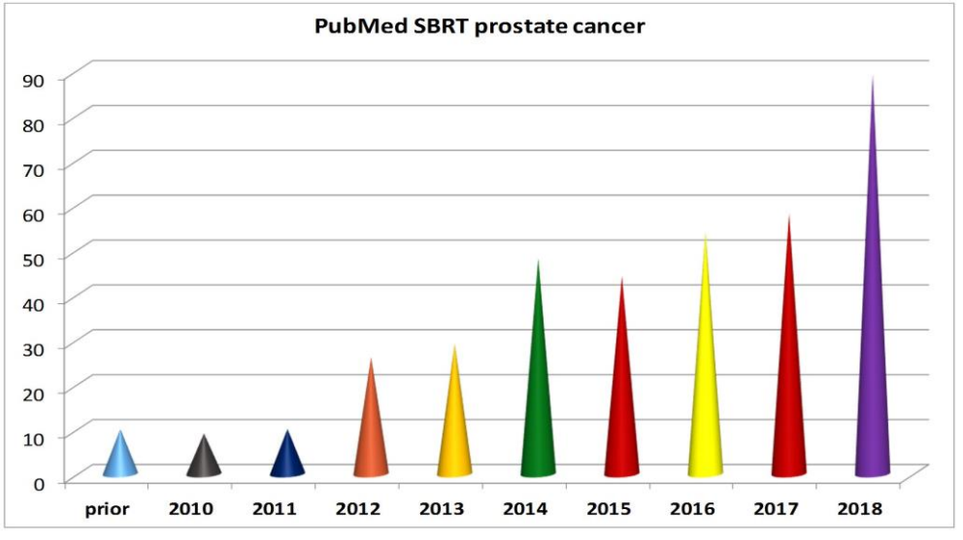
MR-guided (adaptive) SBRT

SBRT for prostate cancer is hot…

ASTRO/ASCO/AUA 2018: SBRT (≥500 cGy) for prostate cancer:

- for **low-risk** patients: it may be offered as an alternative to CFRT
- for **intermediate-risk** disease: it may be offered, but the expert panel **strongly encourages ……** within **clinical trial or multi-institutional registry**
- for **high-risk disease**, the panel ….. in context **of a trial or registry**

….European guidelines and recommendations more liberal….

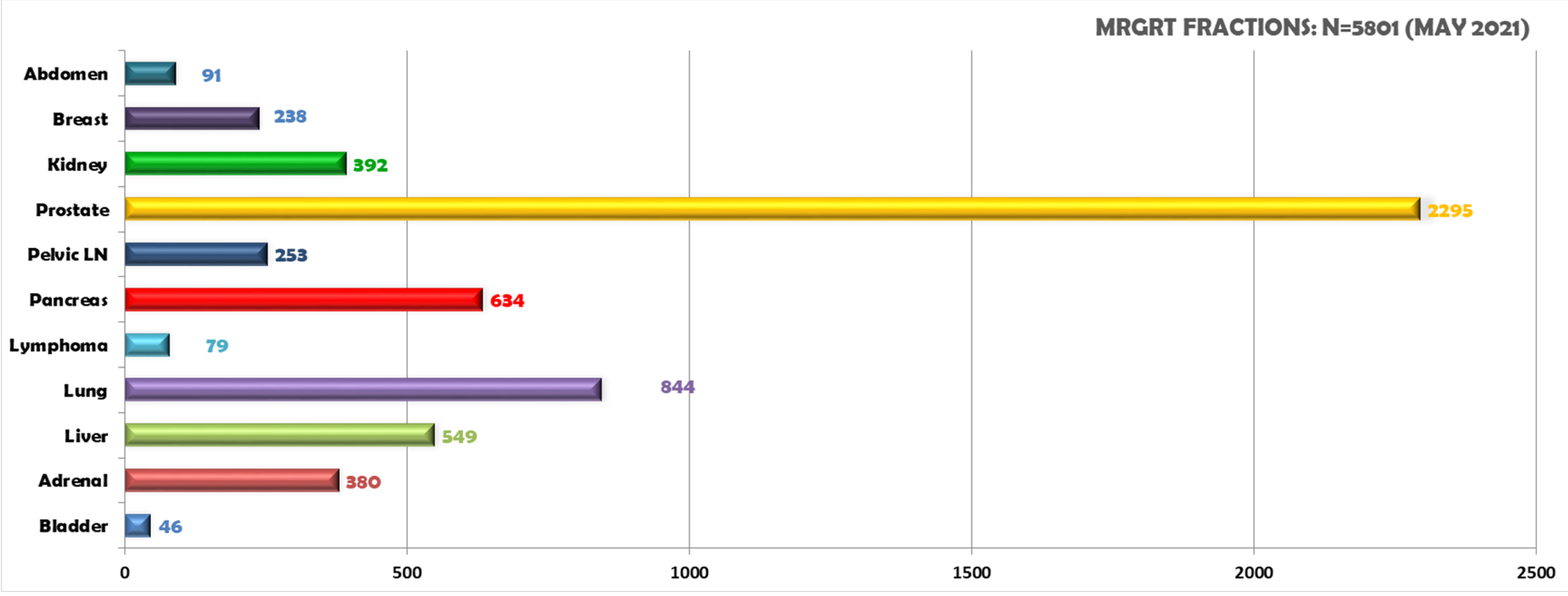


September 26, 2018 / Cancer Care

SBRT: Why More Men Should Know About This Treatment for Prostate Cancer

It stacks up well against conventional therapies

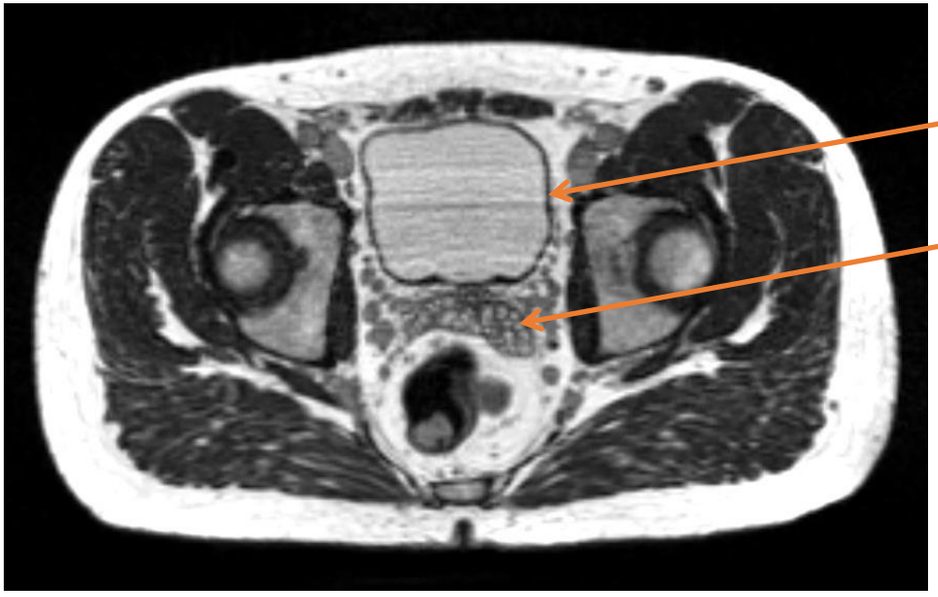
MRgRT @Amsterdam UMC/VUmc



Since May 2016:

- 2500+ adaptive fractions in 500+ PC patients
- Completed phase II prospective toxicity study in 101 patients
- Interim outcome results in the first 284 patients

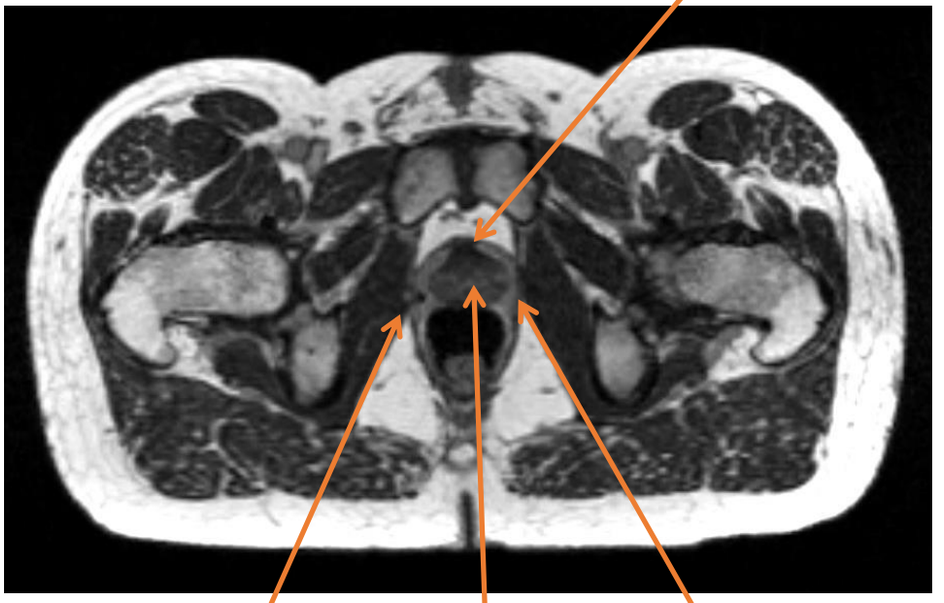
0.35T MR quality – TRUFI sequence



Bladder wall

Vesicles

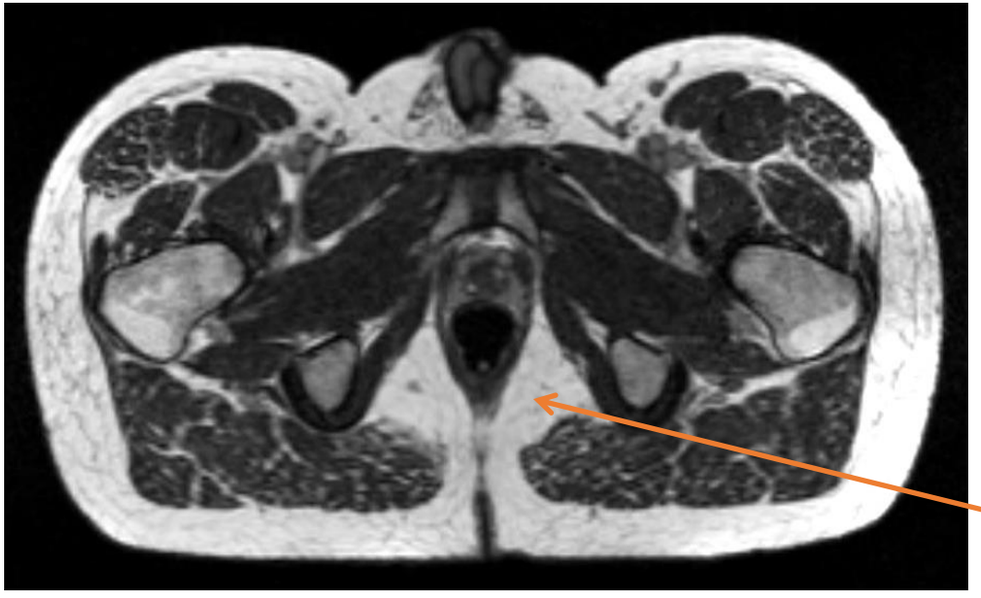
Fibromuscular zone



Marginal zone

Neurovasc bundle

Peripheral zone

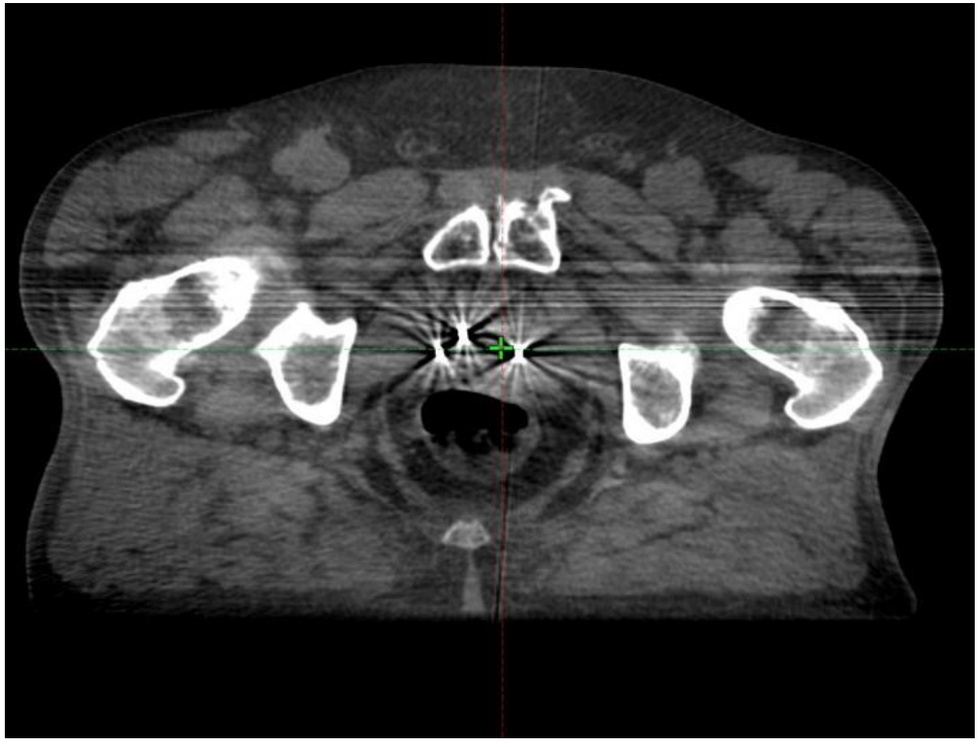


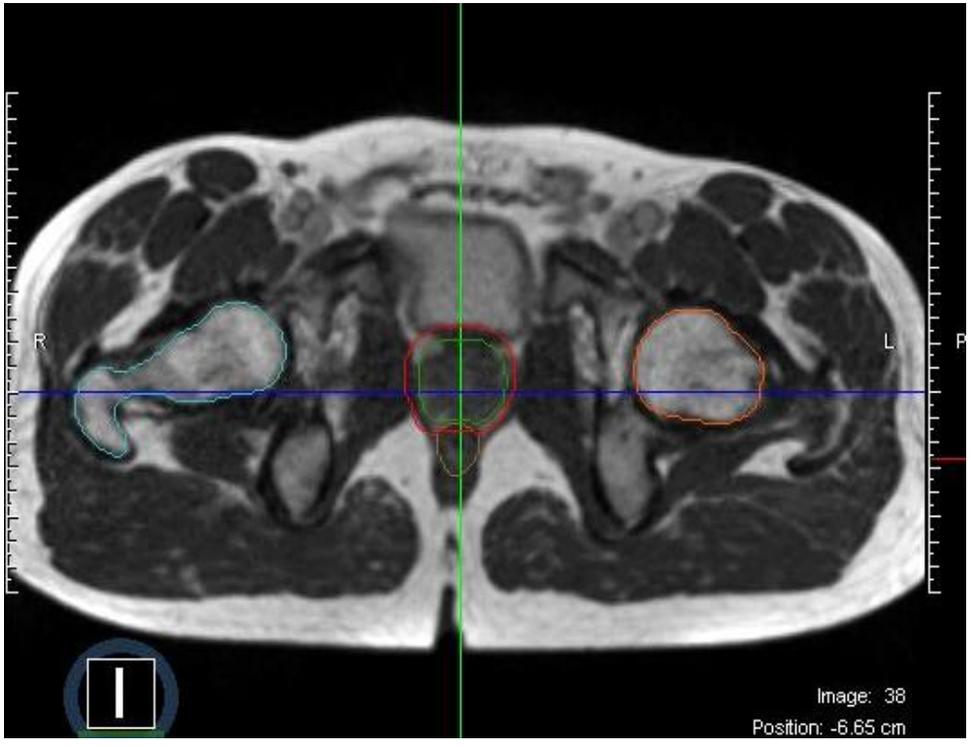
Ischiorectal fossa

Benefits of MRgRT (1): non-invasive

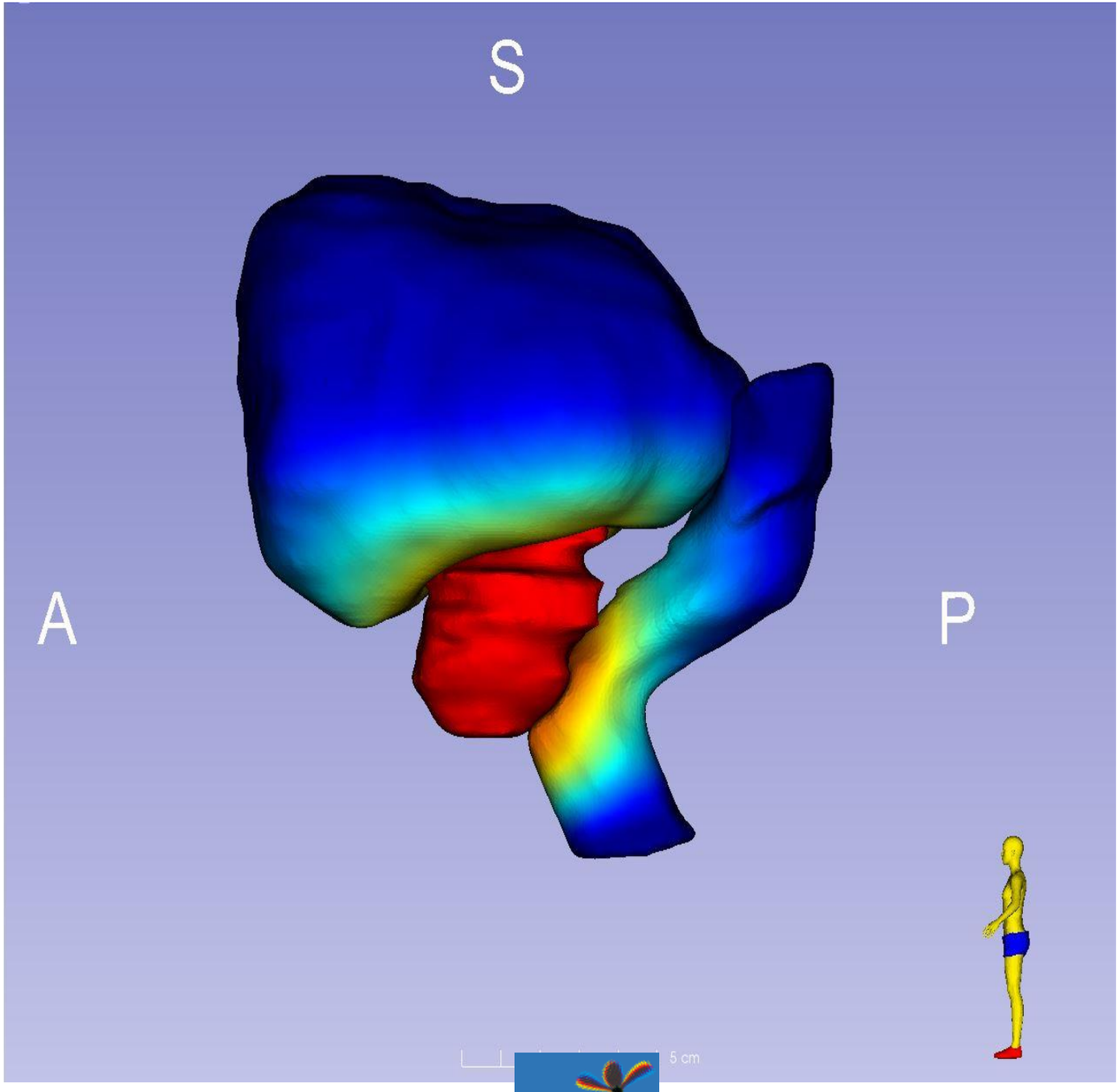
MR-based setup instead of CBCT

No need for implanted fiducials

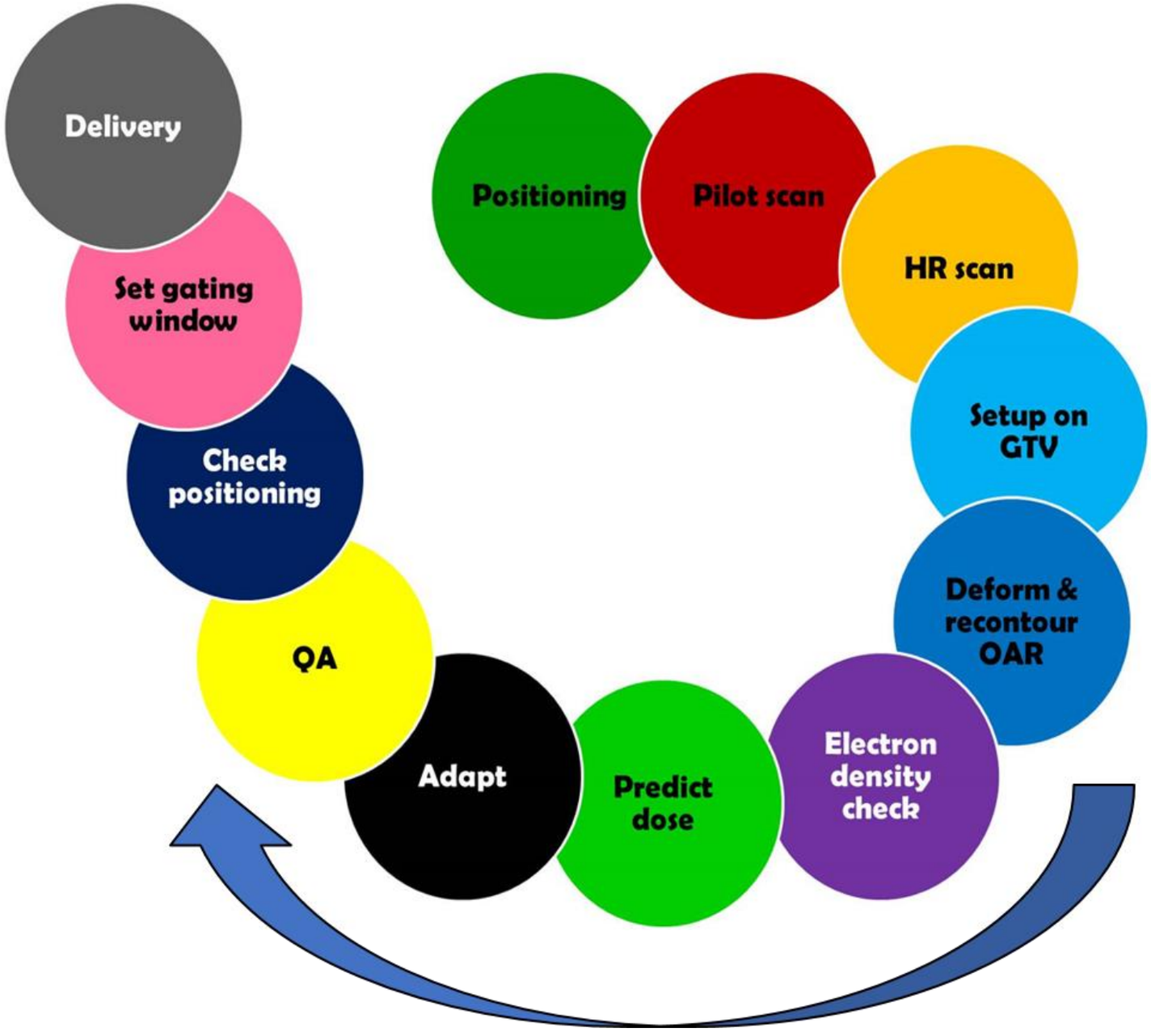




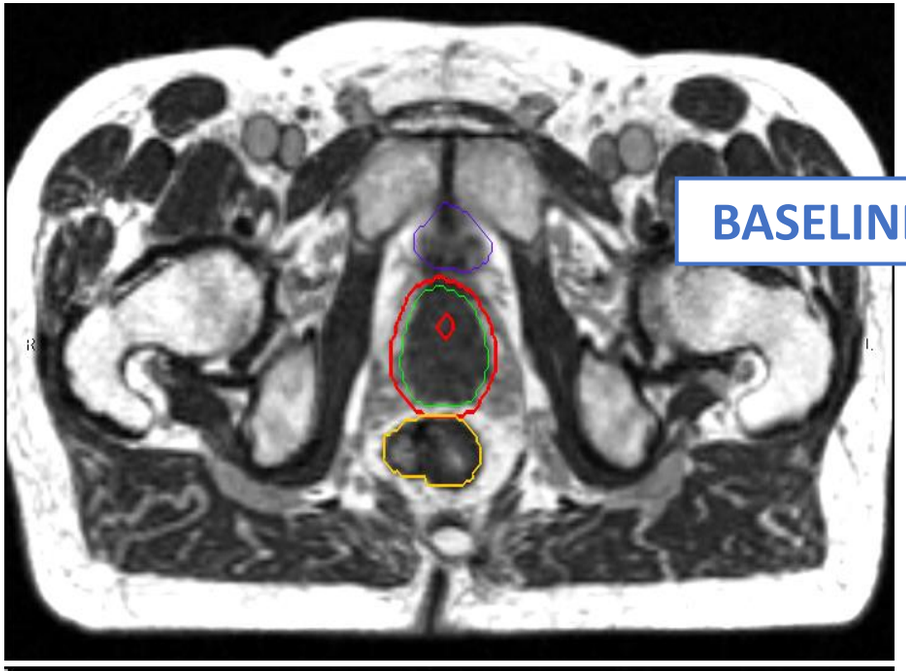
Benefits of MRgRT (2): Plan re-optimisation



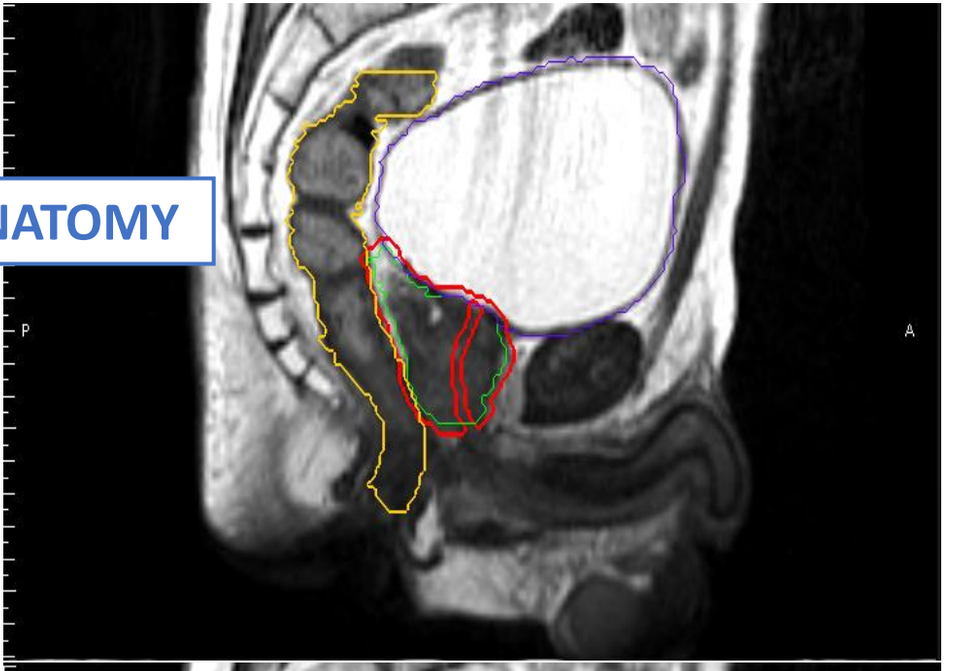
Adaptive MRgRT for prostate cancer: workflow

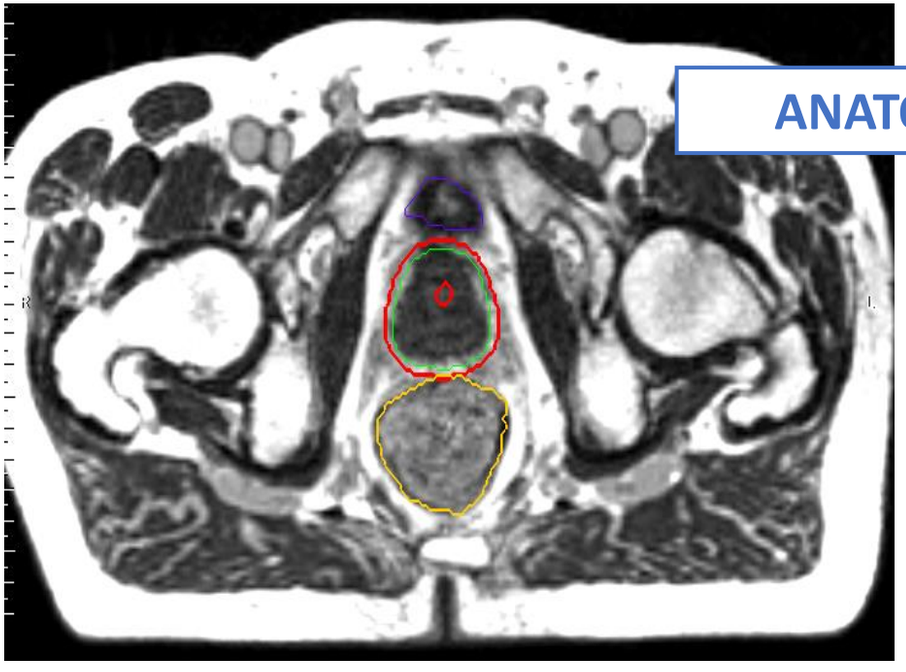


Why daily adaptation? Rectum filling

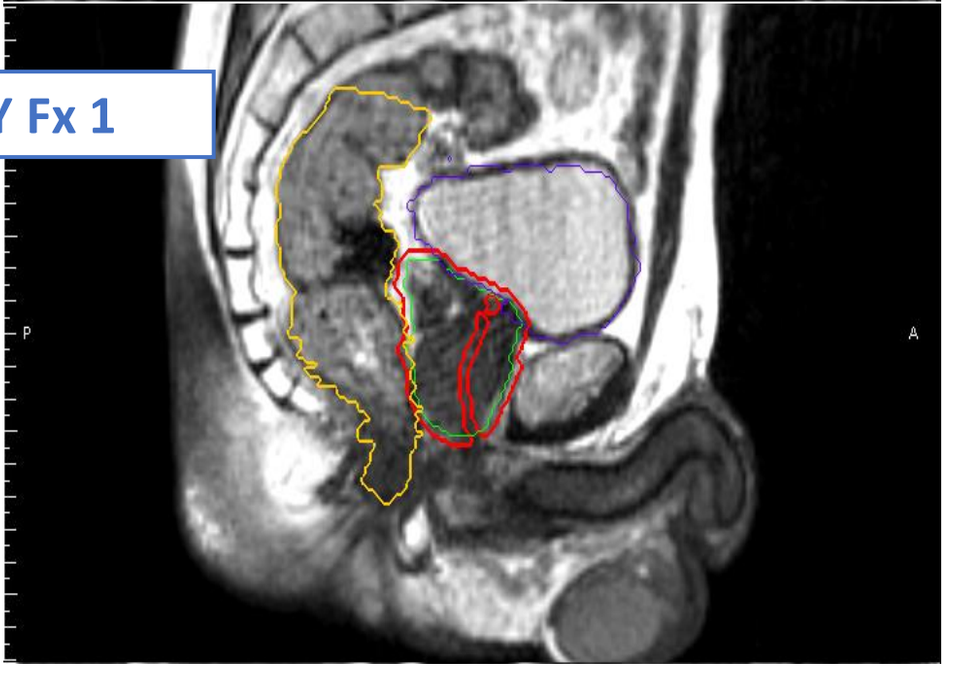


BASELINE ANATOMY

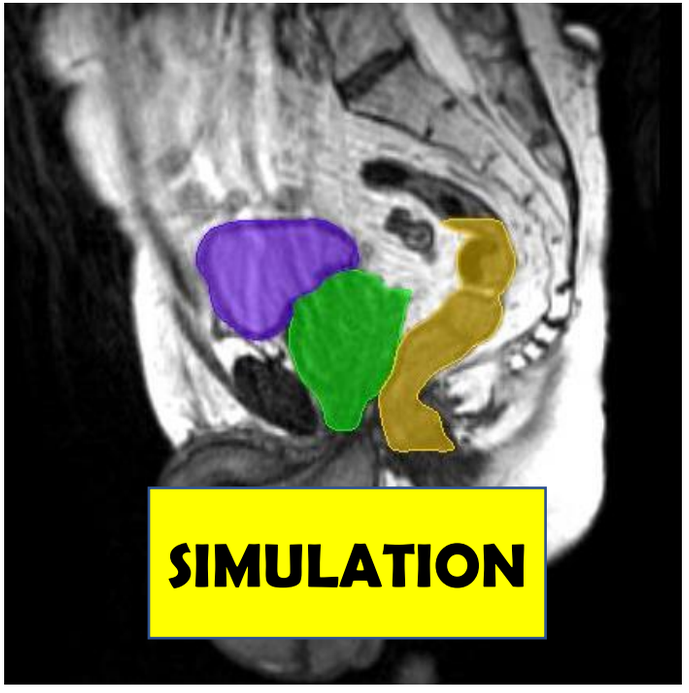


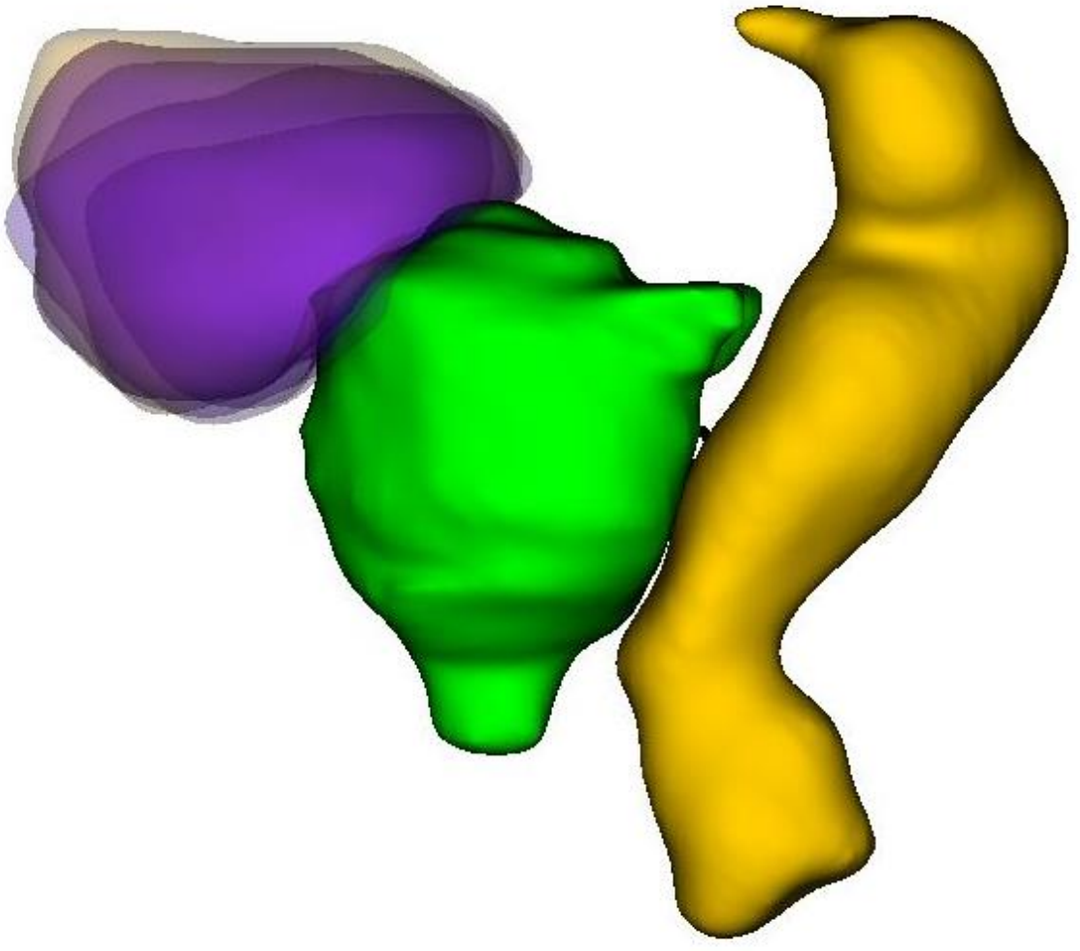


ANATOMY Fx 1



Why daily adaptation? Bladder filling

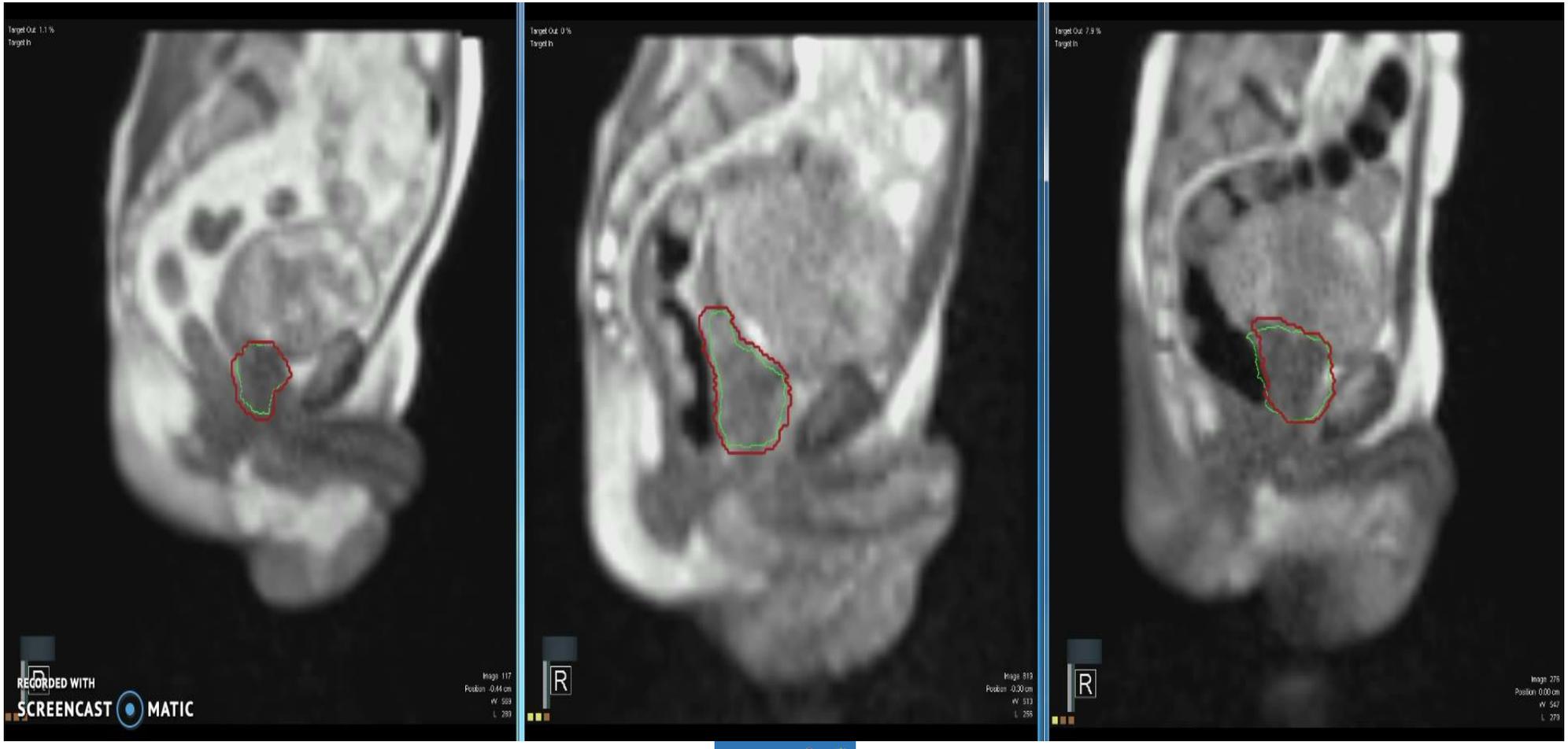




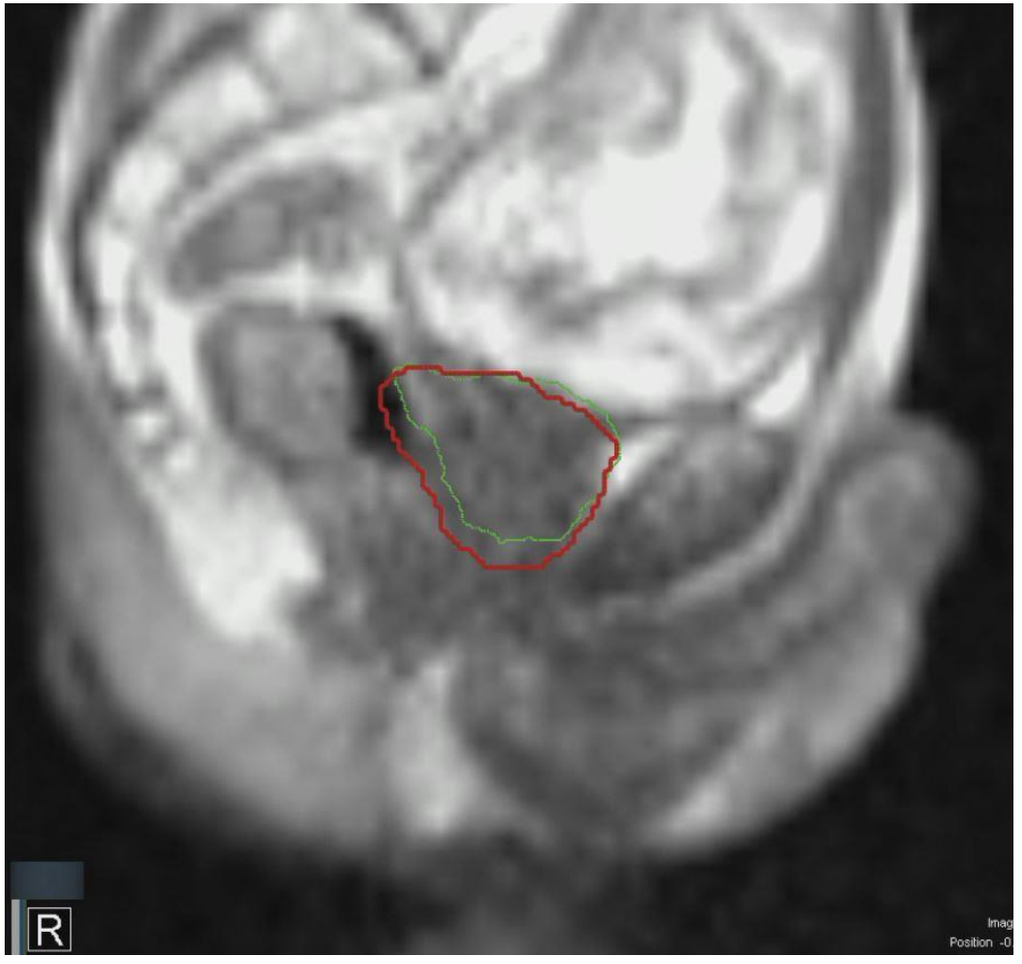
Benefits of MRgRT (3): gated delivery

Real-time target monitoring and automated gated delivery

Delivery using (only) 3 mm safety margins



Is gating important (with 3 mm margins) ?



#interup	No	1x	2x	3x	4x	5x	6x
1	304						
1,1		122					
1,2			40				
1,3				10			
1,4					3		
2	294						
2,1		109					
2,2			39				
2,3				4			
2,4					1		
2,5						1	
2,6							1
3	292						
3,1		124					
3,2			47				
3,3				19			
3,4					2		
4	291						
4,1		116					
4,2			41				
4,3				14			
4,4					3		
5	290						
5,1		112					
5,2			40				
5,3				12			
5,4					2		
5,5						1	
5,6							1
2335	1471	583	207	59	11	2	2
(%)	63	25	9	3	0	0	0

Adjustments during delivery in 30.7% of 2335 fractions

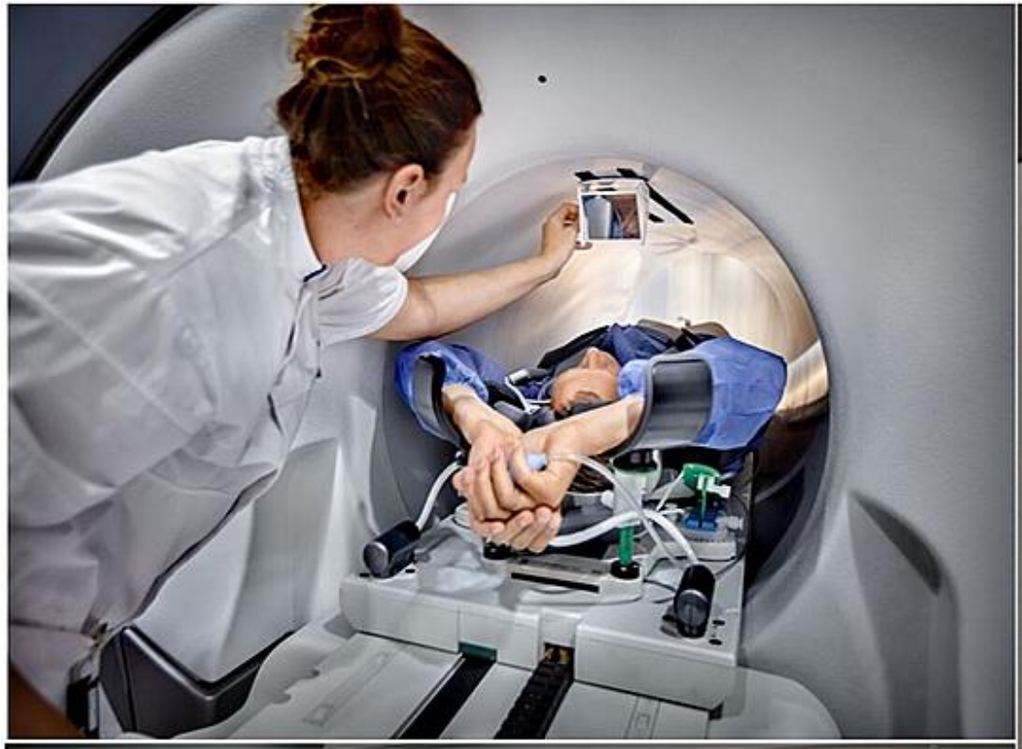
Summary of MRgRT benefits for patients

- **Full non-invasive procedure (no markers)**
- **5 fractions in two weeks treatment time (six hospital visits)**
- **Minimal safety margins: less dose to rectum and bladder**
- **Treatment re-optimized to the anatomy of the day**

Each fraction is the best achievable for that day

(instead of a single plan for all fractions)

“Costs”of MRgRT (1): treatment within bore



Selection of prostate cancer patients for MRgRT

- **"Absolute" MR-contraindications**
  - Pacemaker, ICD
  - MR-conditional: untested for prolonged duration with 0.35T
  - Severe claustrophobia

- **IPSS > 19 (or 90 cc on TRUS)**
  - General SBRT advice (early toxicity)
  - Prolonged delivery with (half) full bladder

- **Artificial hip implant(s):** not an MR-CI, avoidance of beams

- **Prior TURP:** not an MR-CI, provided >6 weeks interval

"Costs"of MRgRT (2): MR-related side effects

- **Patient-reported outcome questionnaire after MRgRT**
- **N=150 patients (of which almost half prostate cancer pts)**
- **Some-considerable anxiety in 22% of pts**

	Yes	Considerable
Noise	60% (N = 90)	17% (N=26)
Cold	29% (N = 44)	10% (N = 15)
Paresthesia	28% (N = 42)	6% (N = 9)
Dizziness	11% (N = 16)	1% (N = 2)
Local heat sensations	9% (N = 13)	1% (N = 2)
Metallic taste	2% (N = 3)	-
Light flashes	2% (N = 3)	-

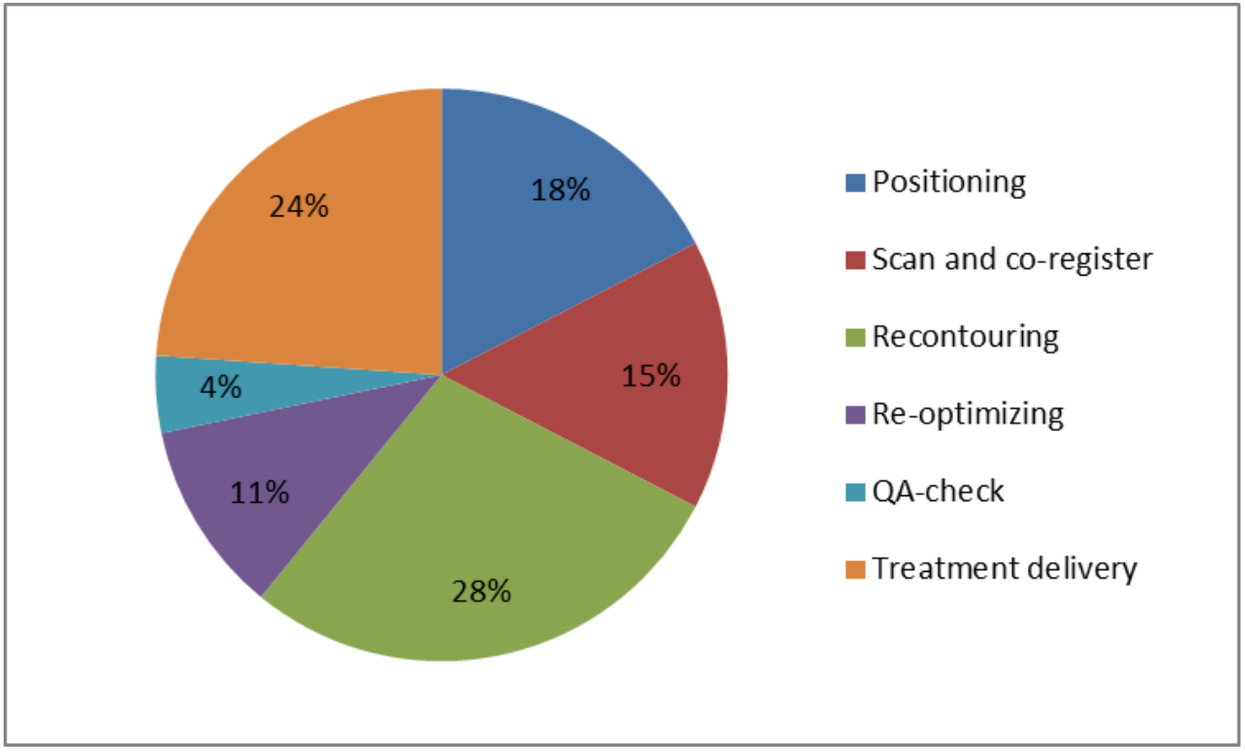
Table 3: MR-related Complaints
MR: magnetic resonance; N: number

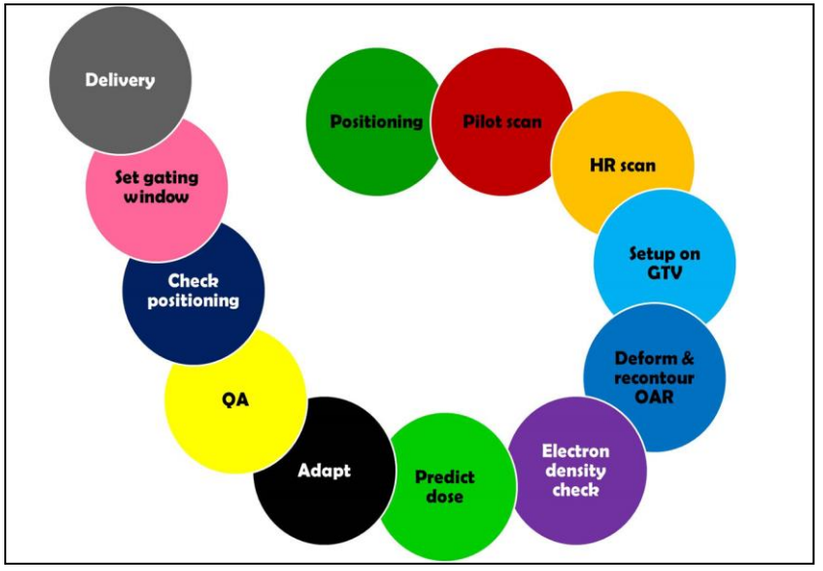
Tetar, Bruynzeel et al. Cureus 2018

“Costs”of MRgRT (2): Time per fraction

2018: Duration uneventful fx avg. 45 min

2021: Duration uneventful fx avg. 35 min





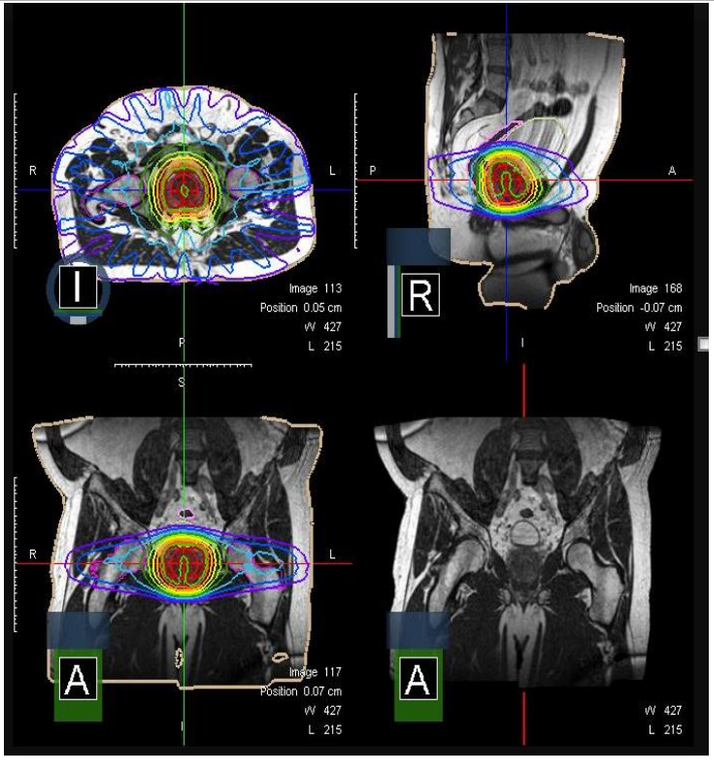
- **Too long for full bladder trtm**
- **Burdensome for last fx’s**

Adaptive MRgRT for prostate ca: "worth" the cost and effort?

PROTOCOL: SMART localized prostate cancer

(**S**tereotactic **M**R-guided **A**daptive **R**adiation **T**herapy for **L**ocalized **P**rostate **C**ancer)

Stereotactic MR-guided Adaptive Radiation Therapy (SMART) for localized prostate cancer; a phase II study



- **Prospective single arm phase II study**
- **101 pts cT1c – cT3b localized prostate cancer**
- **IPSS ≤ 19; prostate volume ≤ 90 cc**
- **5 fx of 7.25 Gy in 3 fx per week**

PI: Dr. Anna Bruynzeel, Dr. Frank Lagerwaard, Prof. Jeroen van Moorselaar (Urology dep)

MRgRT prostate ca: prospective phase II study

Study goal:

- To investigate the potential clinical 'benefit' of adaptive MRgRT (labour intensive and costly)

Endpoints of the study:

- Clinician-reported toxicity (focus on rectal and urinary symptoms) (CTCAE v. 4.03)
- Patient-reported outcomes (EORTC QoL C30 and PR-25 questionnaires, IPSS)

Baseline characteristics study patients

Table 2 Baseline patient characteristics (N = 101)

	n	%
Age, y		
Median	72	
Range	55-88	
Gleason score		
6	18	17.8
7	51	50.5
8	15	14.9
9	16	15.8
10	1	1.0
Baseline PSA (ug/L)		
<10	39	38.6
10-20	3.4	33.7
>20	28	27.7
Risk classification*		
Low	4	4.0
Intermediate	37	36.6
High	60	59.4
Hormonal treatment		
Yes	83	82.2
No	18	17.8
Baseline GU symptoms (IPSS)		
Mild	56	55.4
Moderate	45	44.6
Severe	-	-
Prior TUR prostate		
Yes	14	13.9
No	87	86.1
CTV, cm^3		
Median		56.3
Range		12-155

Abbreviations: CTV = clinical target volume; GU = genitourinary; IPSS = International Prostate Symptoms Score; PSA = prostate-specific antigen; TUR = Transurethral resection.

* According to AUA/ASTRO/SUO 2017 criteria.

Risk classification (AUA/ASTRO/SUO 2017)

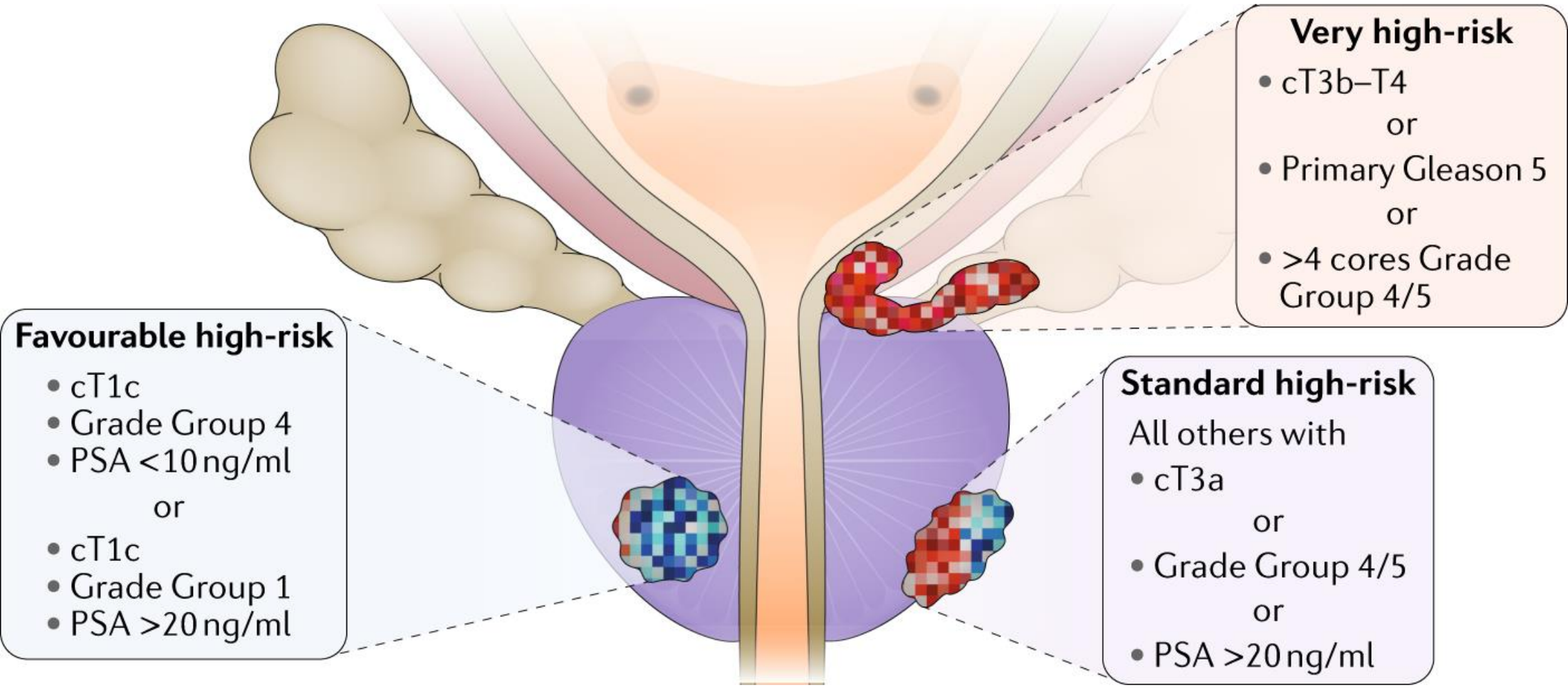
Low risk	**4.0%**
Intermediate risk	**36.6%**
High risk	**59.4%**

***indicates including BOV in contouring**

ADT in 82.2% of patients (mostly 6 months)

Prior transurethral resection in 13.9%

One (of many) risk classifications for PC



Nature review Oncology 2019

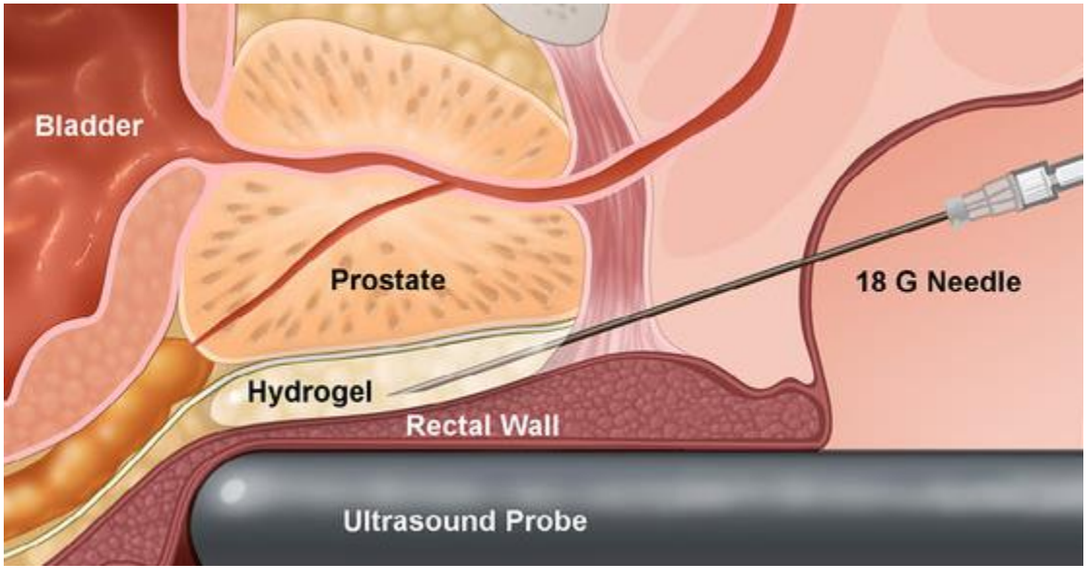
Clinician-reported trial outcomes

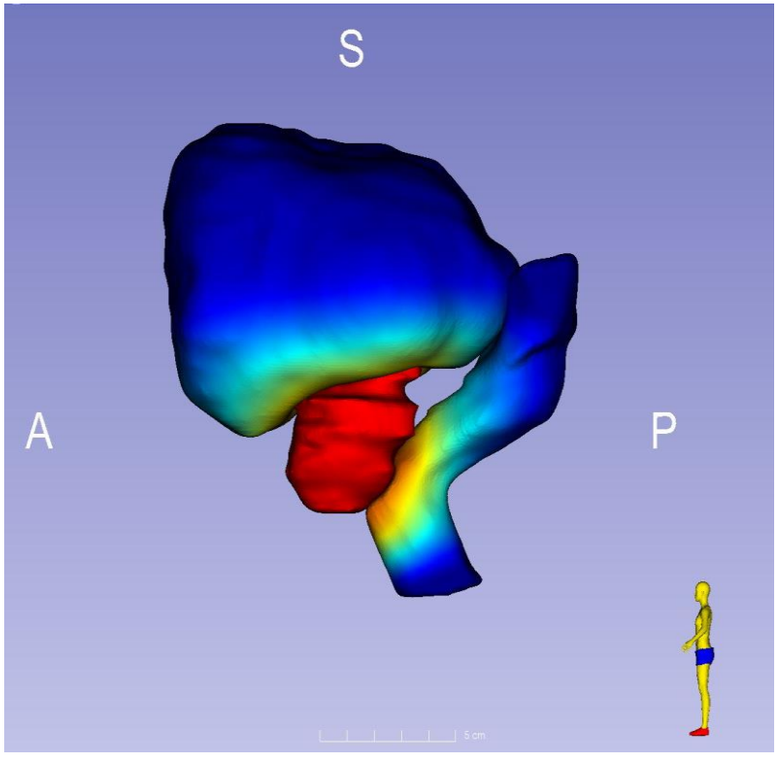
	GI toxicity (Grade ≥2)	GU toxicity (Grade ≥2)
Baseline	0.0%	1.0%
End of MRgRT	3.0%	21.8%
6 weeks	1.0%	7.0%
3 months	1.0%	4.0%
6 months	0.0%	3.1%
9 months	0.0%	5.1%
1 year	0.0%	3.1%

- Very, very low gastrointestinal toxicity
- Acute (fast) urinary toxicity, quickly resolving

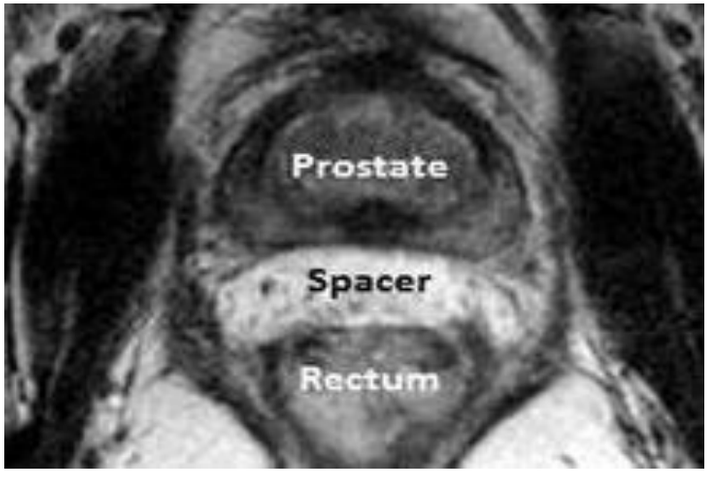
- **But patient-reported outcomes are more objective!**

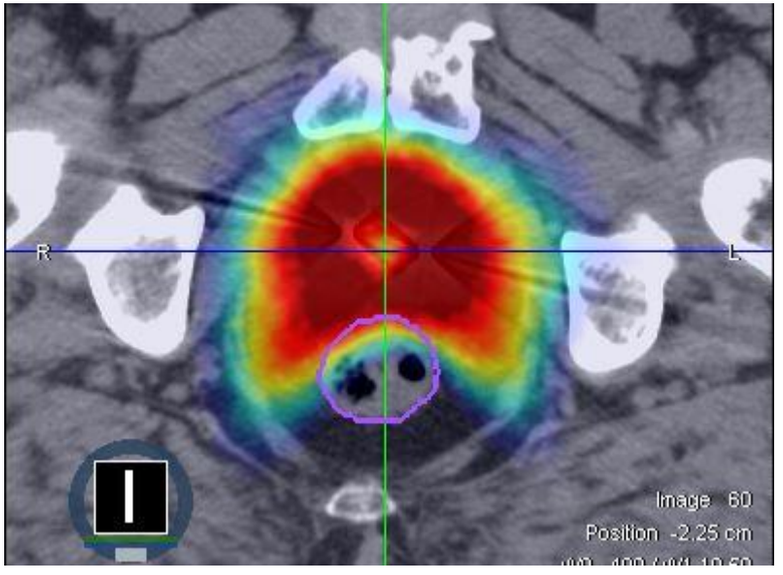
Benefits of MRgRT (4): no rectum spacers





Common international practice to insert hydrogel between prostate and rectum (for SBRT) for fear of rectal toxicity when using high dose/fraction





Patient-reported outcomes

Using standardized scoring systems from EORTC QoL-C30 & PR25 scoring:

- More objective and "reliable" than physician-based scoring
- Gives a clear insight on toxicity that matters to patients
- Patients filled in questionnaires without physician-guidance
- Overall response rate
  - ≥ 95% for C30 questions
  - ≥ 91% for PR25 questions
  - ≥ 33% for sexual domain questions

Comparison of 12-month outcome measures

Grade ≥2 (12 months)	Clinician reported	Patient reported
GU toxicity (ADL)	**0%**	**3.1%**
Dysuria	0%	2.1%
Leakage	1.0%	3.1%
Urgency 12 M Urgency BL	3.1% 0%	13.4% 12.0%
GI toxicity (ADL)	**0.0%**	**2.2%**
Diarrhea	0%	2.1%
Blood in stool	0%	0%
Incontinence	0%	0%
Constipation	0%	1.0%

Clinicians tend to "under"score the toxicity that patients experience

Patient-scoring of urinary toxicity (IPSS)

IPSS	helemaal niet	minder dan 1 van de 5 keer	minder dan de helft van de keren	ongeveer de helft van de keren	meer dan de helft van de keren	bijna altijd
Hoe vaak had u in de afgelopen maand het gevoel dat uw blaas nog niet leeg was nadat u had geplast?	0	1	2	3	4	5
Hoe vaak moest u in de afgelopen maand binnen 2 uur nadat u had geplast weer plassen?	0	1	2	3	4	5
Hoe vaak merkte u in de afgelopen maand dat tijdens het plassen de straal enkele keren stopte en weer begon?	0	1	2	3	4	5
Hoe vaak had u in de afgelopen maand moeite om het plassen uit te stellen?	0	1	2	3	4	5
Hoe vaak had u in de afgelopen maand een zwakke urinestraal?	0	1	2	3	4	5
Hoe vaak moest u in de afgelopen maand persen om de urinestraal op gang te brengen?	0	1	2	3	4	5
Hoe vaak moest u in de afgelopen maand gemiddeld per nacht het bed uit om te plassen?	nooit	1 keer	2 keer	3 keer	4 keer	5 keer

som IPSS-score:

kwaliteit van leven	gelukkig	plezierig	over het algemeen tevreden	gemengde gevoelens (om het even)	over het algemeen ontevreden	ongelukkig	verschrikkelijk
	0	1	2	3	4	5	6

score kwaliteit van leven:

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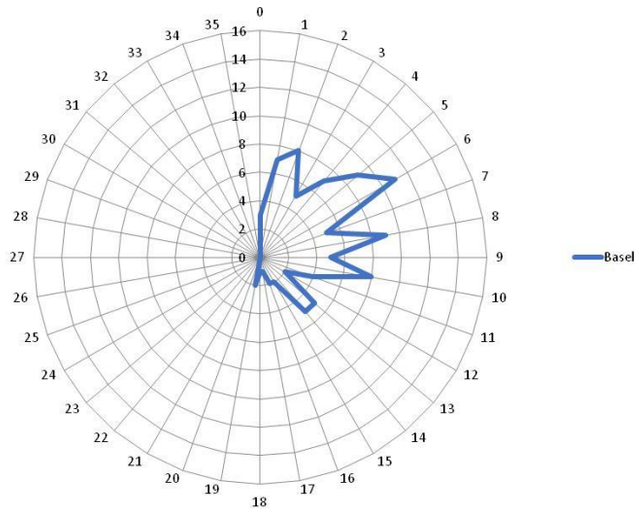
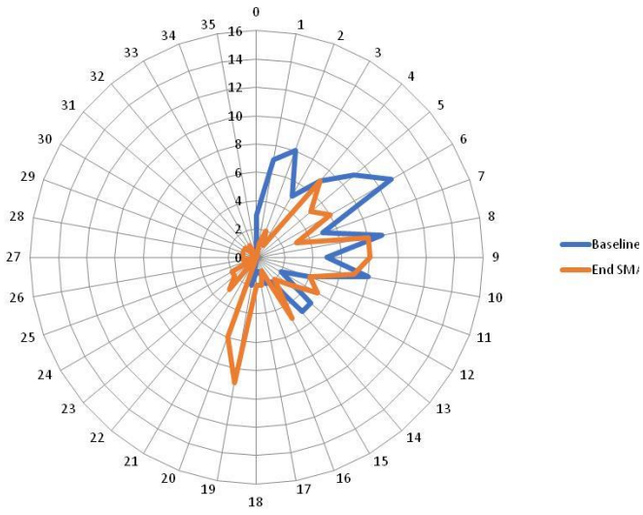
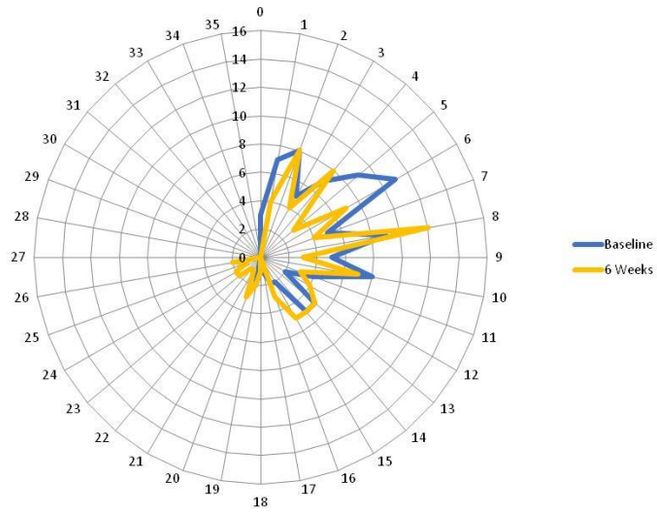
IPSS symptom scores



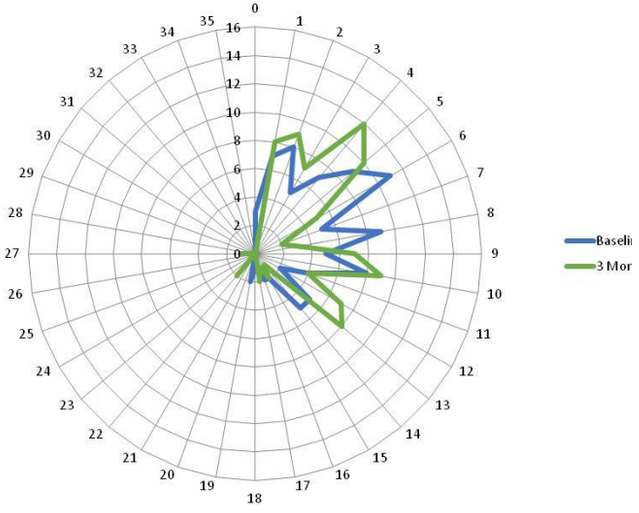
Baseline



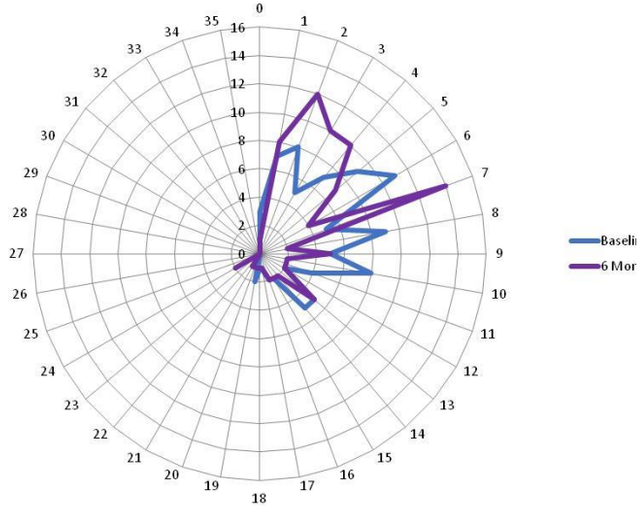
End MRgRT



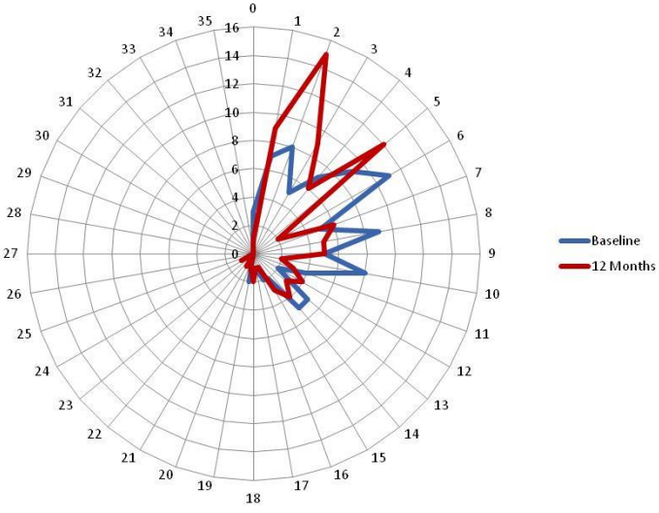
6 weeks



3 months



6 months



12 months

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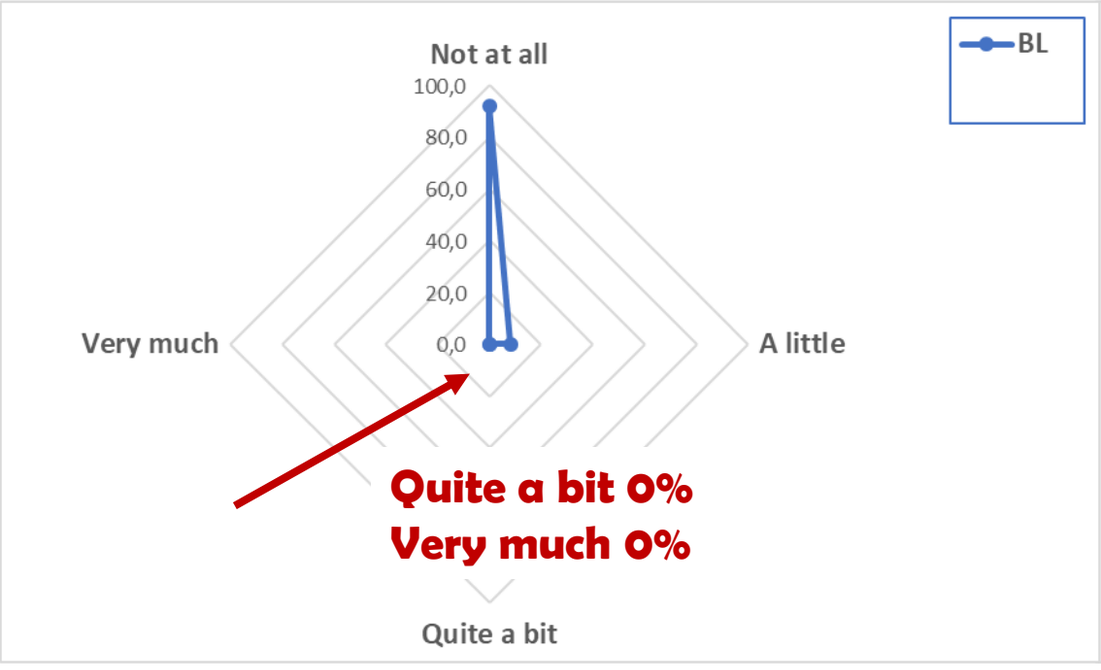
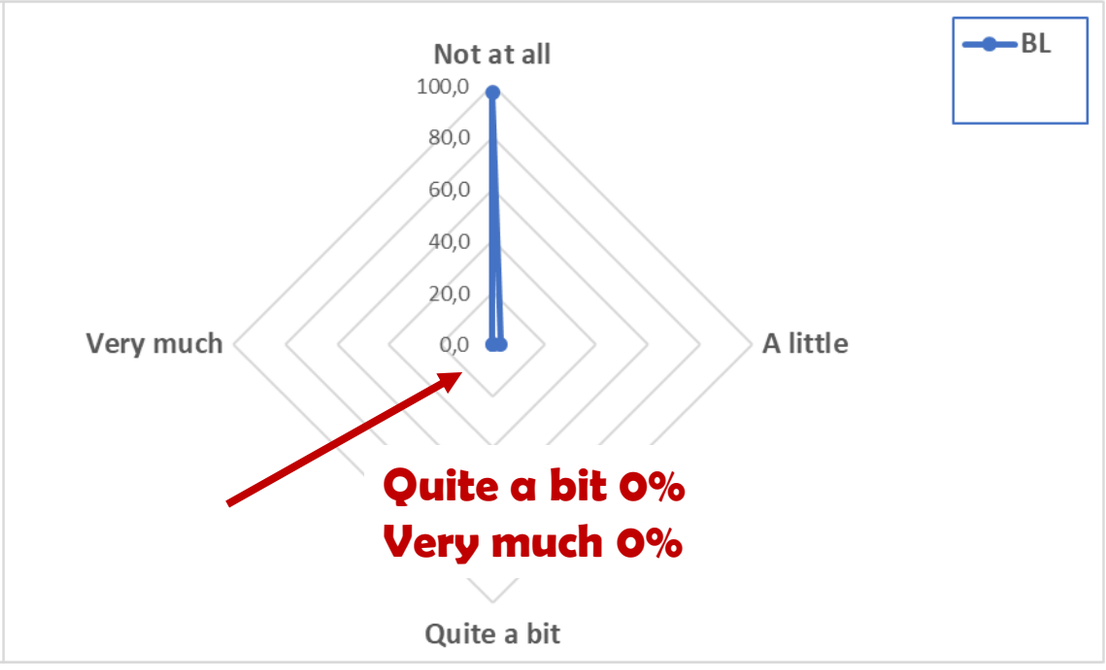
Impact on daily activities

Have your daily activities been limited by your urinary problems?

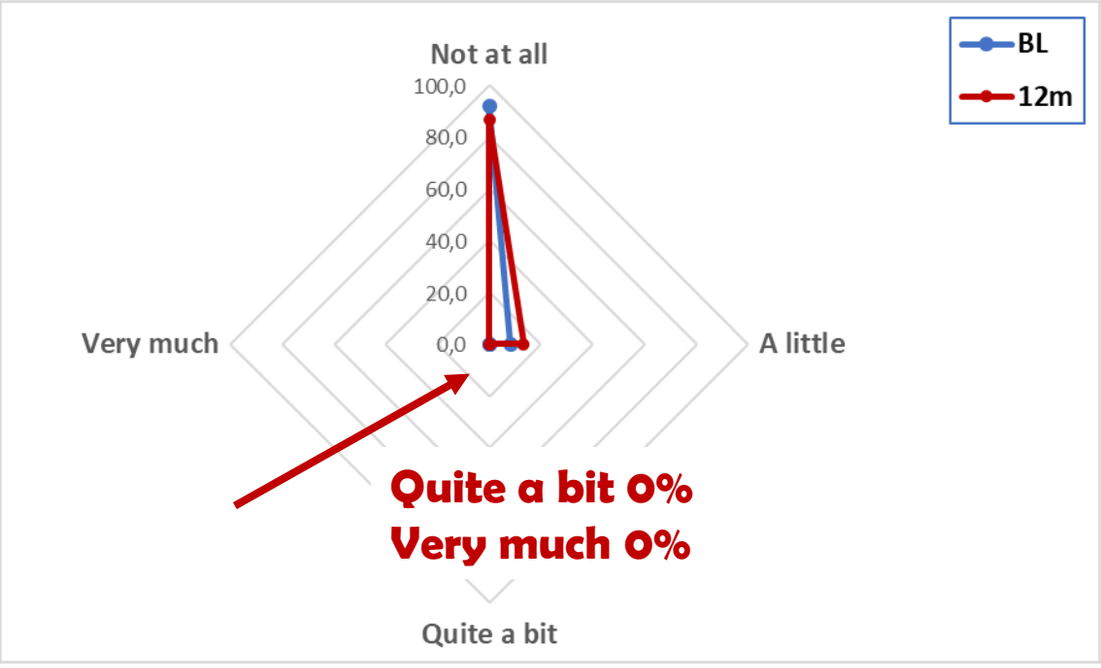


Have your daily activities been limited by your bowel problems?



Impact on daily activities

Have your daily activities been limited by your urinary problems?



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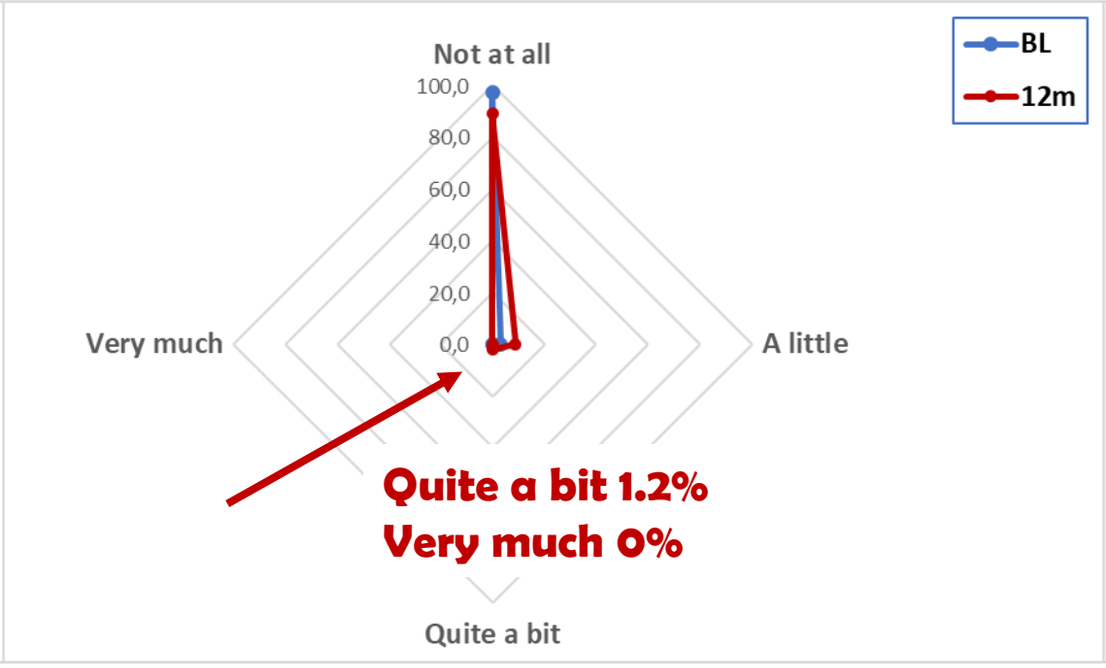


Early toxicity in the context of prior studies

	Early G≥2 GU (3 months)	Early G≥2 GI (3 months)
Arcangeli (2011) Hypofx arm	47%	35%
HYPRO study (2015) Hypofx arm	61%	42%
CHHiP (2016) Hypofx arm(s)	46%	38%
PROFIT study (2017) Hypofx arm	31%	17%
RTOG-0415 (2017) Hypofx arm	27%	11%
HYPO-RT-PC (2019) Hypofx arm	28%[1]	8%[1]
Pace-B (2019) SBRT arm	23%	10%
MRgRT study (2019) SBRT	24%	5%

- Clinician-reported outcomes, cumulative incidences at 3 months
- !! Different fractionation schemes (and mobility margins) !!
- !! Varying scoring systems & time points, some values estimated from graphs!!

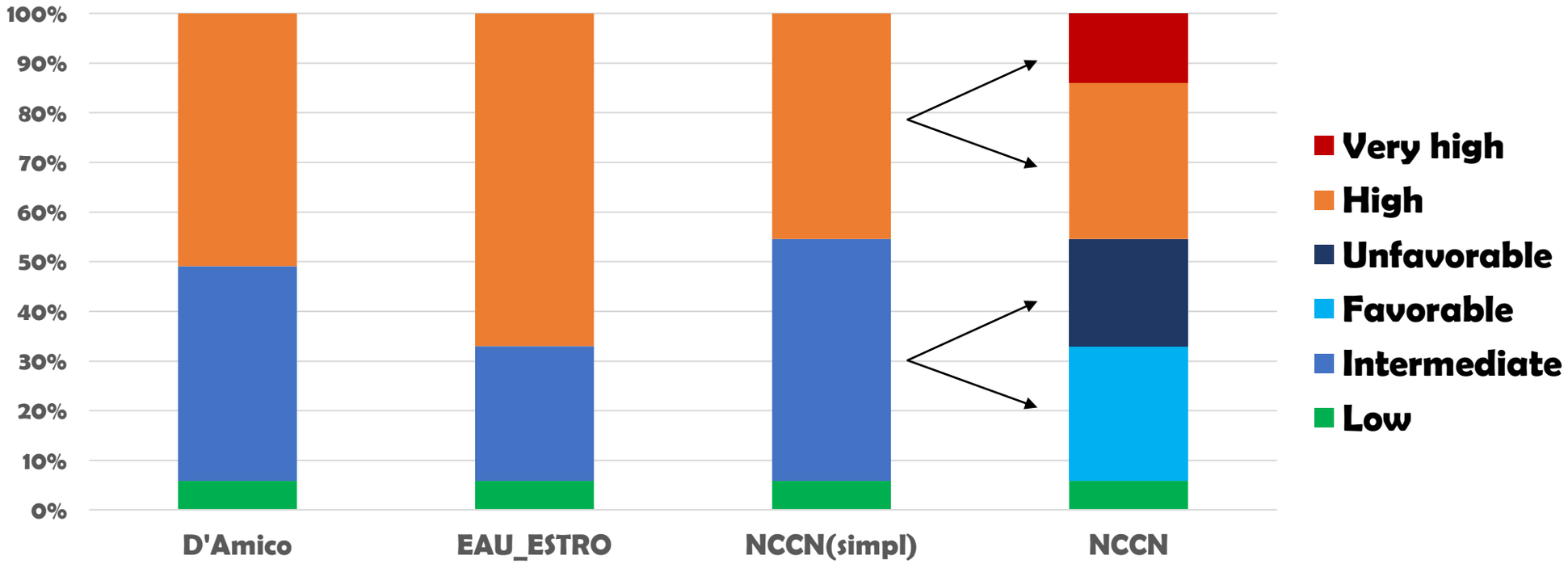
Late toxicity in the context of prior studies

	Late G≥2 GU (1- 2 years)	Late G≥2 GI (1-2 years)
Arcangeli (2011) Hypofx arm	8%	4%
HYPRO study (2015) Hypofx arm	30% ("cumulative")	10% ("cumulative")
CHHiP (2016) Hypofx arm(s)	3%	5%
PROFIT study (2017) Hypofx arm	22.2% ("late")	8.9% ("late")
RTOG-0415 (2017) Hypofx arm	27% ("late")	22.4% ("late")
HYPO-RT-PC (2019) Hypofx arm	8%	4%
Pace-B (2019) SBRT arm	-	-
MRgRT study (2019) SBRT	3%	0%

- Clinician-reported outcomes
- !! Different fractionation schemes (and mobility margins) !!
- !! Varying scoring systems & time points, most values estimated from graphs!!

Risk Classification

EAU_ESTRO	Low risk	Intermediate risk	High risk
	5.9% (N=16)	27.1% (N=74)	67.0% (N=183)



*EAU_ESTRO: two or more risk factors indicates high risk
*NCCN_2019 (simpl): favorable and unfavorable combined
*NCCN_2019: includes favorable/unfavorable/very high rsk groups

Oncological outcomes (N=284)

Overall survival
@3 years: 93.2%

Biochemical recurrence-free survival (bNED)
@3 years: 83.5%

Local control
@3 years: 89.4%

Low & intermediate risk: 98.3%
High risk: 82.6%

Conclusions

- MRgRT has proven clinical feasibility in 500+ patients
- Clear technical RT benefits have translated to:

  - Low patient-reported early and late urinary toxicity
  - Very low patient-reported early and late rectal toxicity

- Initial oncological outcomes are better than expected:

  - >95% local control rates @3yrs for int/low risk patients (room further further hypofractionation, e.g. 2 fractions?)

  > 80% local control rates @3yrs for high risk patients (higher than in literature, but room for dose-escalation?)

Thanks for your attention