Clinical applications of MRLinac in radiotherapy

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Image was generated with AI tool for illustrative purposes

OECI2024

Disclosures

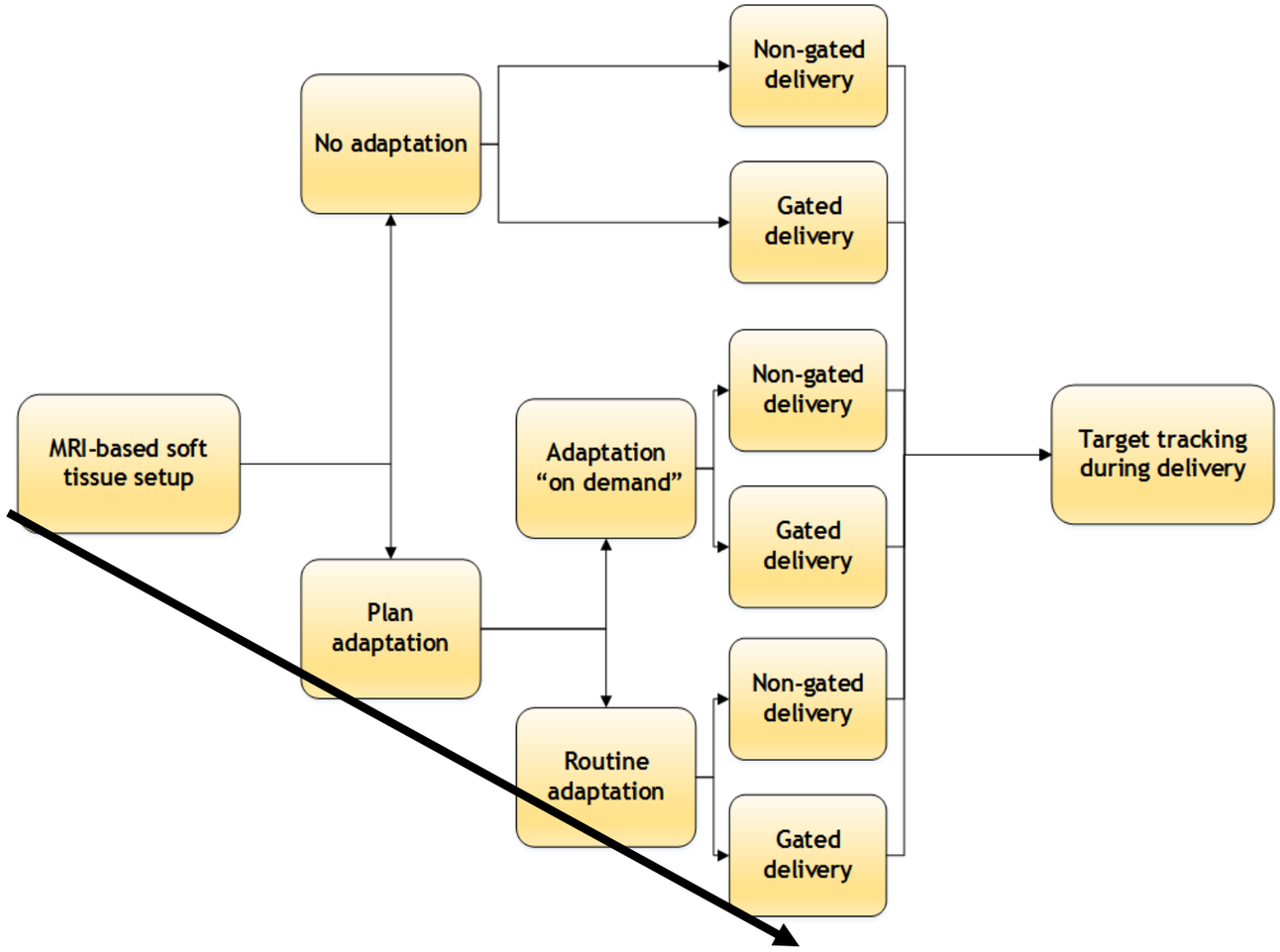
Recieved speaker honorarium and travel fee from ViewRay Inc and Elekta

No other disclosures

Overview

- online adaptive MRI guided radiotherapy
- our routine workflow for adaptive MRIgSABR – in pancreatic cancer
- clinical outcomes of MRIgSABR for adrenal mets
- clinical outcomes of MRIgSABR for prostate cancer
- MRIgSABR for kidney cancer

Online adaptive radiotherapy using the MR-Linac



SMART

Stereotactic

MR-guided

Adaptive

Radiation

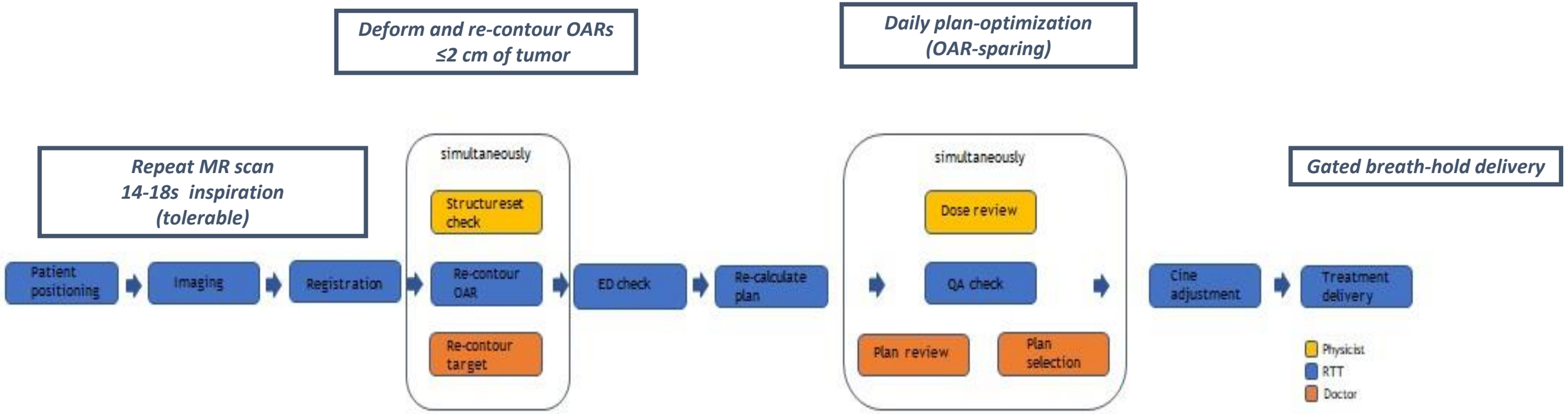
Therapy

Frank Lagerwaard

Focus on demonstrating clinical and dosimetric benefit of daily adaptation

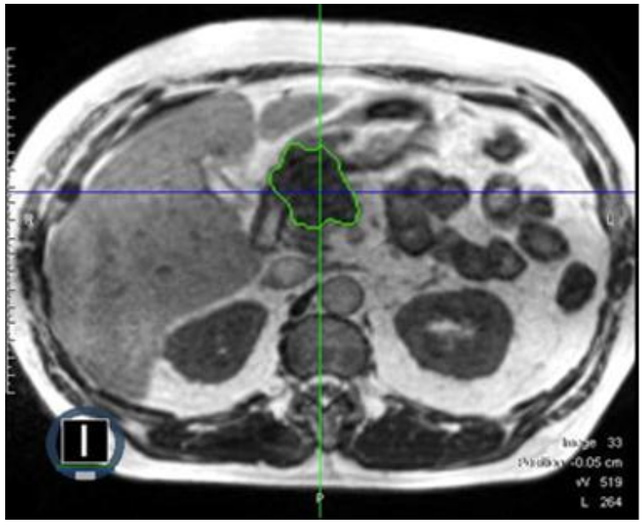
Routine workflow for online adaptive SABR@ AmsterdamUMC

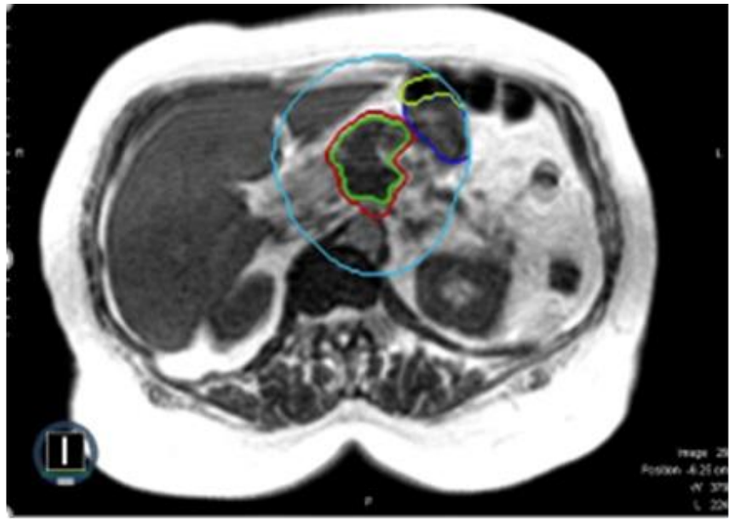
for a variety of clinical indications – with focuss now on pancreatic tumors

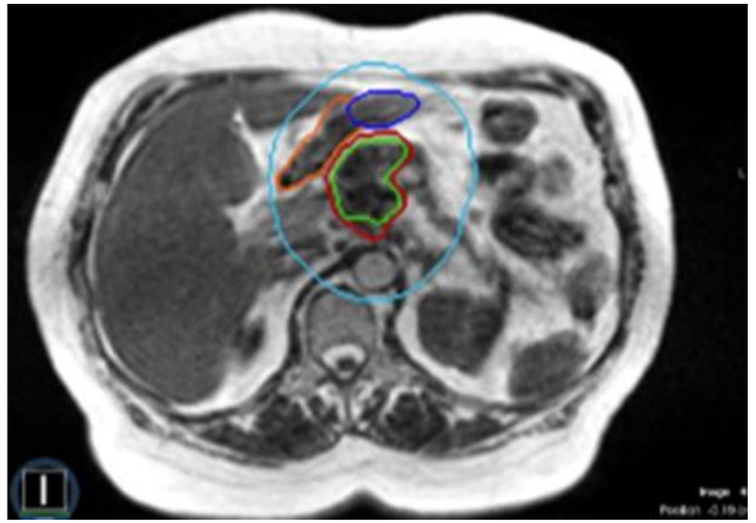


Part of the workflow runs parallel

Use of adaptive MRIgSABR for pancreatic cancer



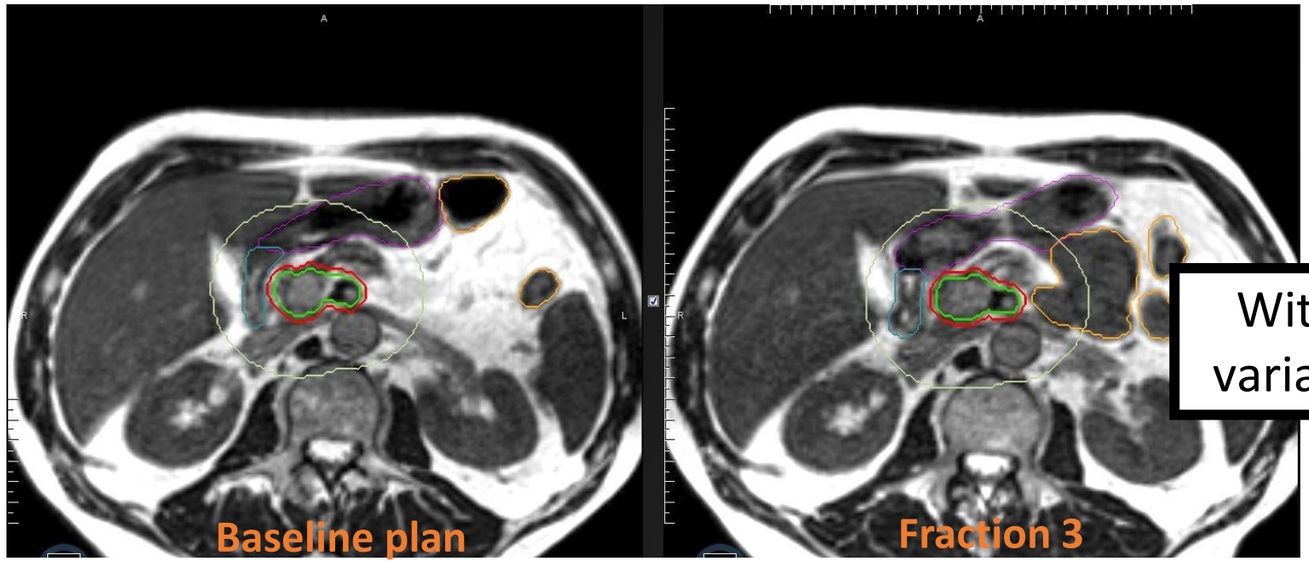




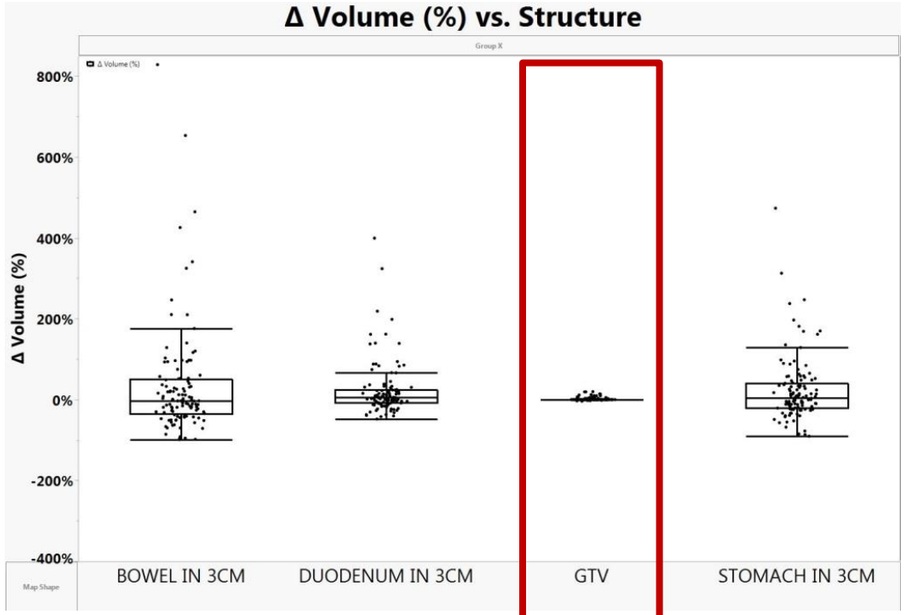
Close proximity of organs at risk (OAR) poses a challenge to SABR delivery

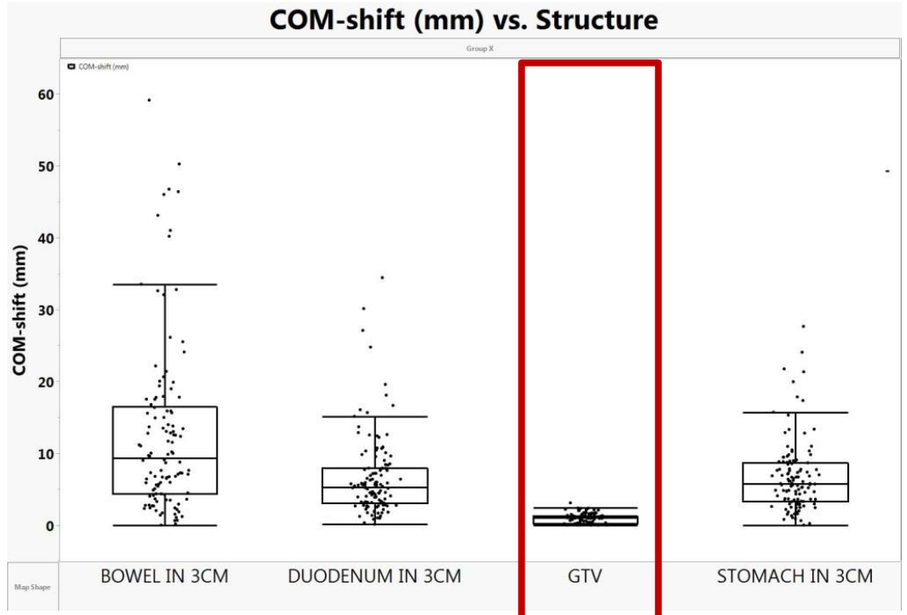
- pancreatic tumours ideally suited for online MRIguided-adaptive SABR

Why daily plan adaptation?



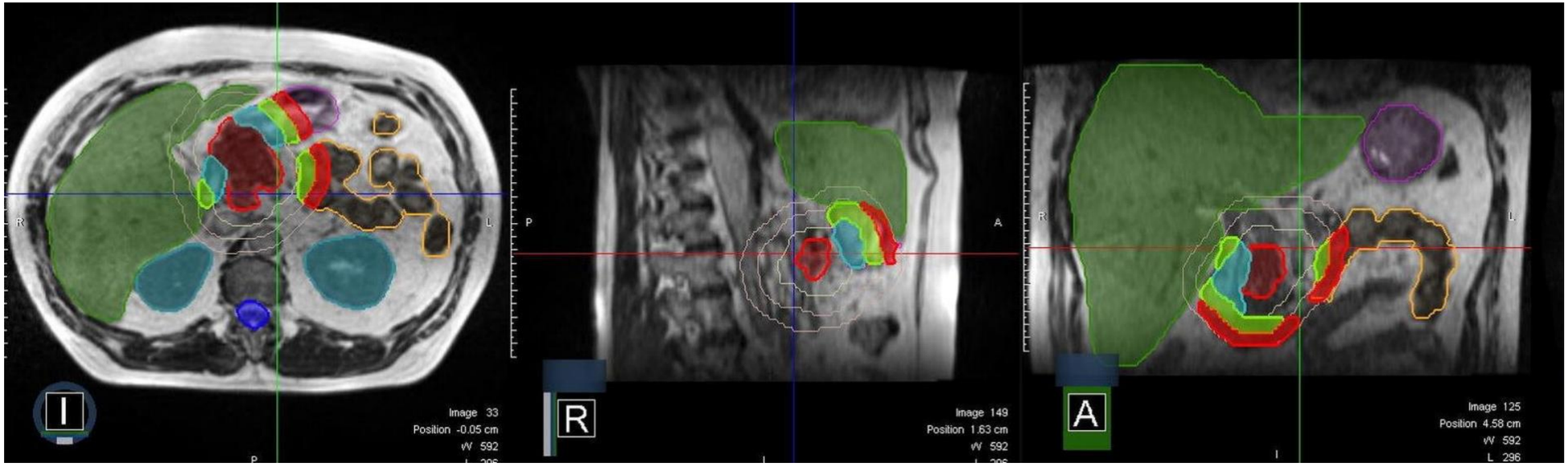
With daily setup on the GTV, there is a large interfraction variation on both the **volume** and **position** of adjacent OAR





Concept of daily adaptation

- for **SABR**, the **high dose region** around the PTV is most important for **toxicity**
- a planning procedure was developed using rings up to 2 cm around the PTV
- **only parts of organs** within these **rings** need to be adjusted to the anatomy
- optimal organ sparing prevails over target coverage
- adaptive process needs to be fast and feasible – patient is in treatment position



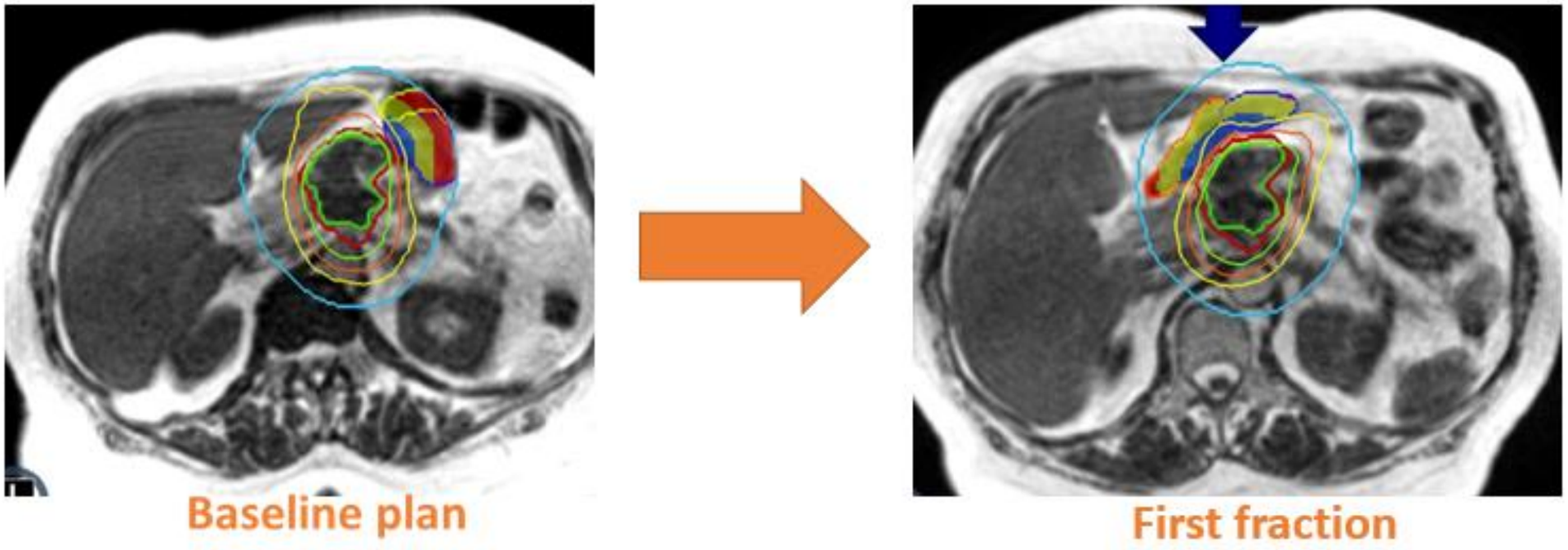
Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer

O. Bohoudi et al./Radiotherapy and Oncology 125 (2017) 439–444

Daily re-optimization

Needs to be **fast** (patient on couch) and **accurate** (relevant high-dose)

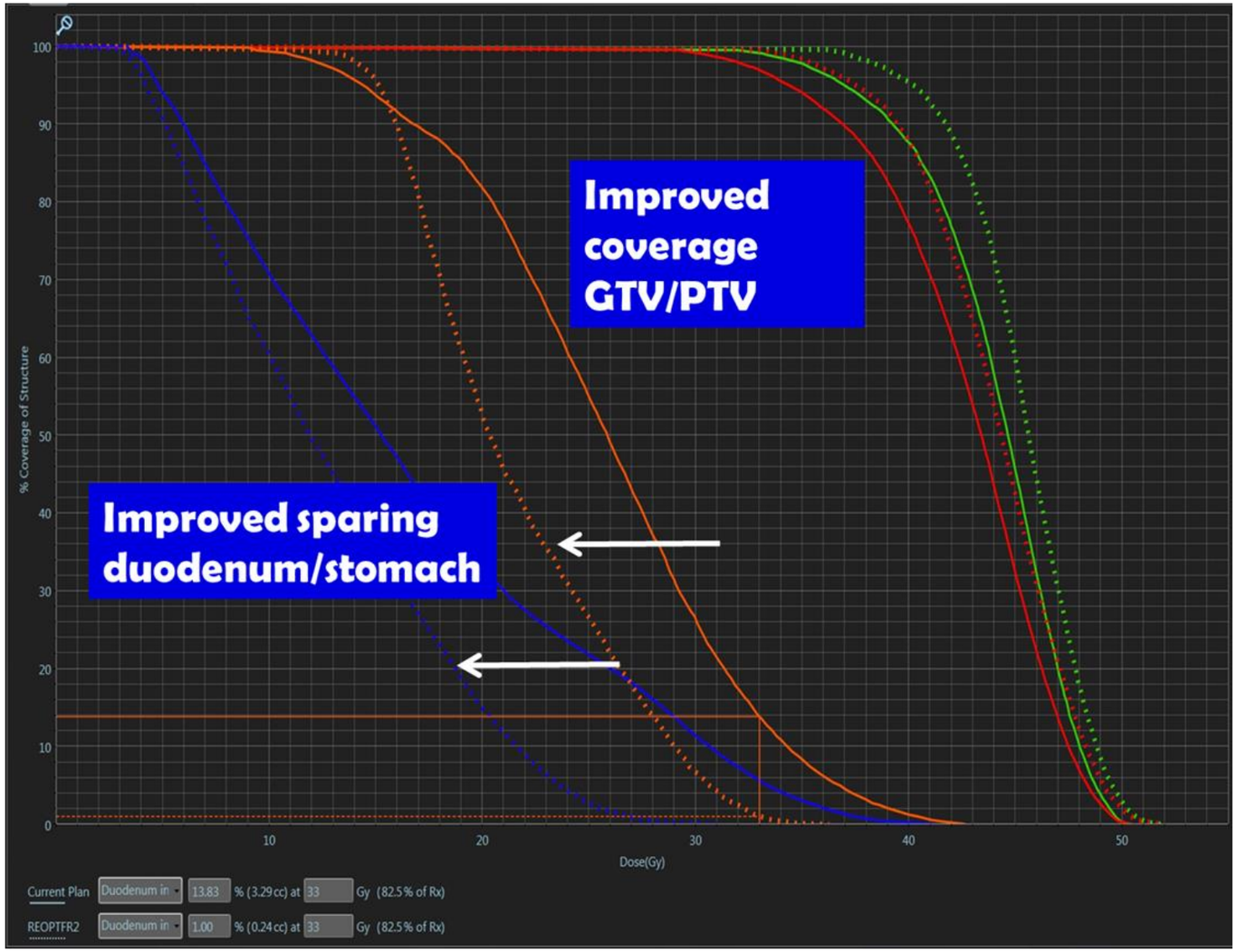
1. Propagation, deformation, manual adjustment of GTV and partial OARs
2. Position/volume of partitioned OARs (and PTV) guide plan re-optimization
3. Generating steepest dose gradients where needed for “anatomy of the day”
4. Re-optimized IMRT plan allows fast QA (same beam number/directions)



Bohoudi et al, Radiother Oncol 2017

Clear (individual) benefit; example pancreatic SMART

daily plan adaptation



Results for a group of pts also show dosimetric benefit of daily plan adaptation:

Bohoudi et al, Radiother Oncol. 2019 Mar;132:16-22

Identify LAPC pts who benefit from daily plan adaptation

Radiotherapy and Oncology 132 (2019) 16–22

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Identification of patients with locally advanced pancreatic cancer benefitting from plan adaptation in MR-guided radiation therapy

Omar Bohoudi [a], Anna M.E. Bruynzeel [a,*], Martijn R. Meijerink [b], Suresh Senan [a], Ben J. Slotman [a], Miguel A. Palacios [a], Frank J. Lagerwaard [a]

Adaptive planning assessed for:

- 180 fractions
- comparing non-adapted plans with re-optimized plans
- using GTV coverage and high-dose OAR constraints

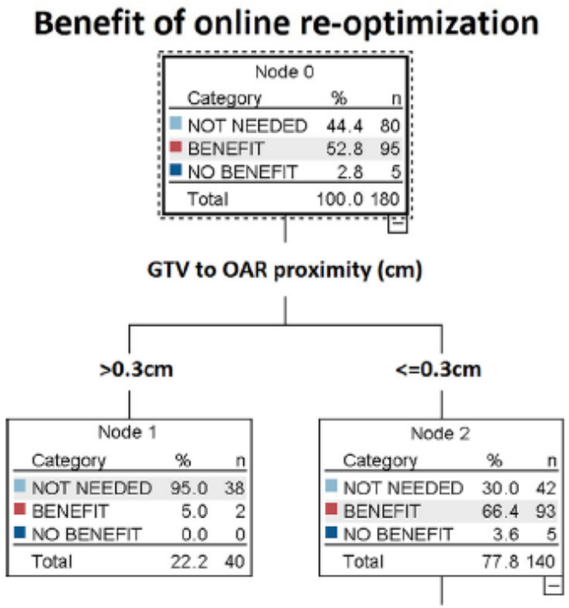
➢ Identify subgroups that are likely to benefit or not from routine plan adaptation

Conclusion:

•benefit in approx. half of Fx,

•improving target coverage and OAR sparing

Plan adaptation relevant: cases where GTV to OAR distance ≤ 3 mm



Dosimetric benefit of adaptive MRIgRT translating in clinical benefit

CLINICAL INVESTIGATION

A Multi-Institutional Phase 2 Trial of Ablative 5-Fraction Stereotactic Magnetic Resonance-Guided On-Table Adaptive Radiation Therapy for Borderline Resectable and Locally Advanced Pancreatic Cancer

Int J Radiation Oncol Biol Phys, Vol. 117, No. 4, pp. 799–808, 2023

- Jan 2019-2022 136 ptn included with pancreatic cancer
- 5Fx 10 Gy
- adaptive SABR for 93.1% of all delivered fractions

Primary endpoint was met:
reduction from a historic comparison of 15.8% to 8% in grade 3 toxicity rates @90 days

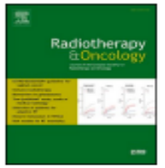
Dosimetric benefit of adaptive MRIg SABR → to clinical benefit for patients

Radiotherapy and Oncology 191 (2024) 110064

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original Article

Stereotactic MR-guided on-table adaptive radiation therapy (SMART) for borderline resectable and locally advanced pancreatic cancer: A multi-center, open-label phase 2 study

M. Chuong et al

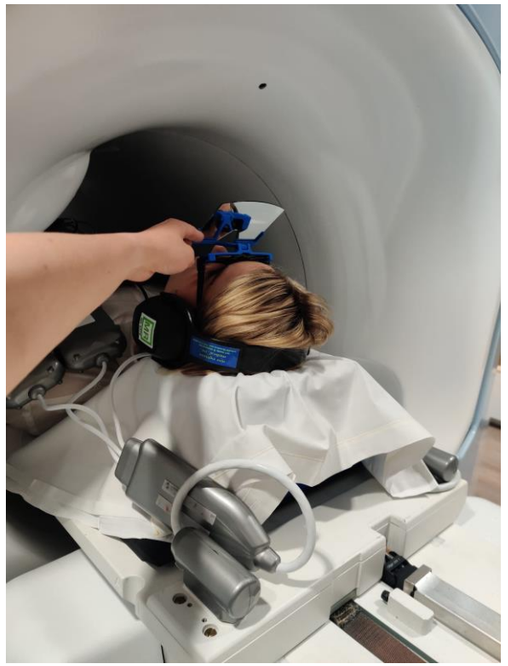
- Jan 2019-2022 136 ptn
- 5Fx 10 Gy
- adaptive MRIgSABR for 93.1% of all delivered fractions

✓ median follow-up from SMART 14.2 mo

✓ median OS - 14.2 mo
✓ 2-year OS - 40.5%
✓ 2-year LC – 78.2%

✓ late grade ≥ 3 toxicity 5.3%

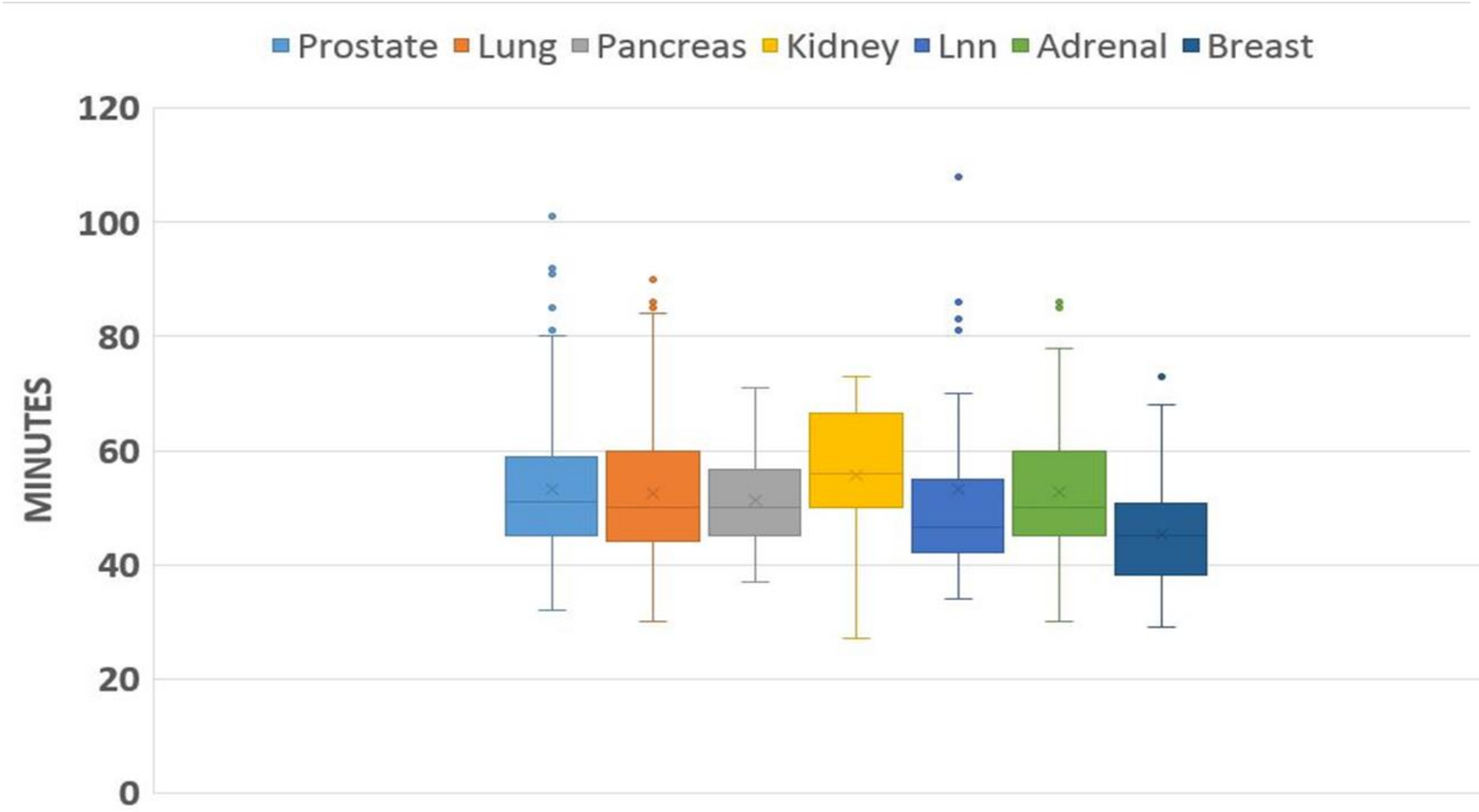
Patient-controlled breath-hold gated delivery

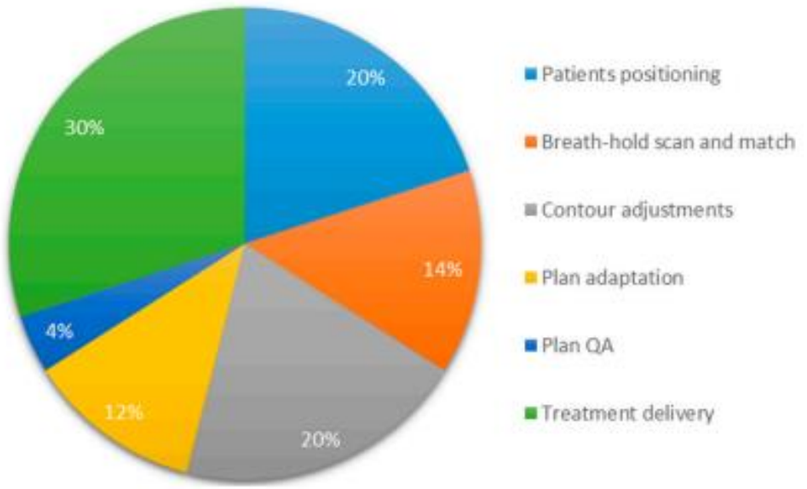


Real-time cine MR imaging on the feedback monitor

- **motion monitoring** is conducted using **real time cine MRI imaging**
- use of patient-controlled breath-hold delivery
- a step and shoot IMRT technique delivered in 5 fractions
- **beam on only** when the **target is inside** the gating boundary (PTV)

Total SMART time duration per fraction





average duration of different components of SMART with gated breath-hold delivery

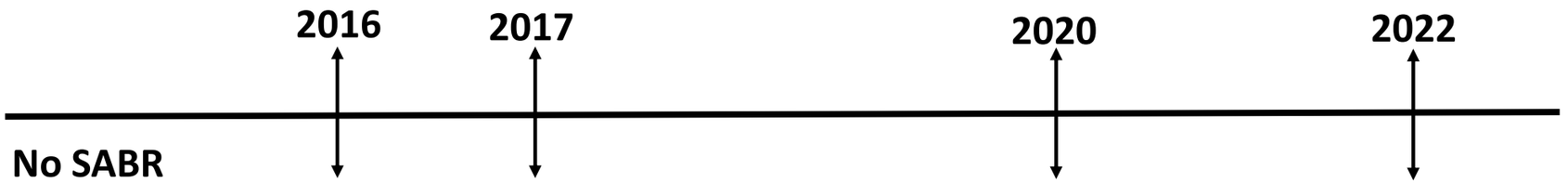
1/3 of total time adaptive part of the treatment

- on average 54 min, largely independent from indication
- **NOW – time per fraction between 25-40 min**

Impact of (multidisciplinary) cooperation

map the role of (adaptive) SABR in pancreatic cancer pts

Cooperation with ‘key specialists’ generating evidence, eg. for pancreatic cancer



2017: CROSSFIRE MRgRT vs IRE in LAPC

2020: CROSSFIRE MRgRT vs IRE in LAPC; PANCOSAR BSC vs MRgRT; ARCADE MRgRT rec; FIBROPANC MRgRT preop

2022: PANCOSAR BSC vs MRgRT; ARCADE MRgRT rec; FIBROPANC MRgRT preop; PREOPANC5 MRgRT + chemo+ IT; LAPSTAR Chemo vs Chemo + MRgRT LAPC

Locally Advanced Pancreatic Cancer After Systemic Therapy: MR-guided Ablative Radiotherapy

A Randomized Controlled Trial & Nationwide Quality Assurance Project

LAPSTAR

KWF KANKER BESTRIJDING

Randomized controlled trial

All Dutch ptn with LAPC:

- not eligible for tumor resection after initial chemotherapy (at least 2 mo)
- isolated tumor progression
- unfit for surgery

Randomization

Stratification: chemotherapy regimen
disease status (high/low risk)

Intervention arm 5Fx10 Gy MRIgRT followed by continuation SoC

6-12 cycles chemotherapy + BSC

78 patients in each arm

Aim: to investigate the **efficacy of ablative MRIgRT** on **health-related quality of life** (HRQoL) **deterioration-free survival** in pts with LAPC **in addition to SoC**

Amsterdam UMC

OECI2024

MRIgSABR for adrenal mets

Image was generated with AI tool for illustrative purposes

Clinical outcomes and toxicities of adaptive MRIgRT of adrenal metastases

A retrospective multi-institutional pooled analysis

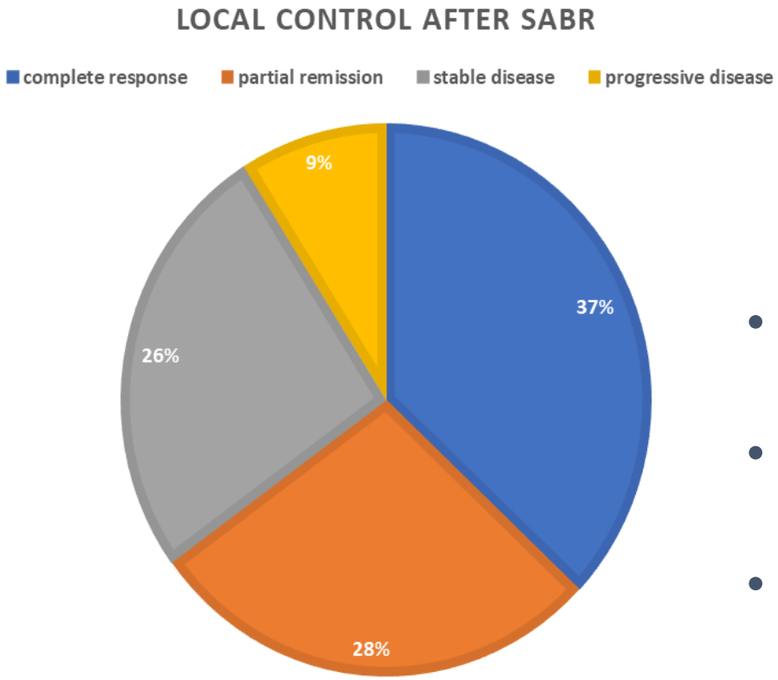
- ❑ 11 USA and European institutions
- ❑ **255 patients (269 adrenal tumors) treated between 2016-2022**
- ❑ Solitary (26%), oligometastatic (2-5 - 58%) or polymetastatic (16%)
- ❑ Systemic therapy used by approx. 60%

- ❑ **med BED_{10} 100 Gy** (range 37.5-132)
- ❑ med GTV 22 cc med PTV 37 cc
- ❑ **almost 90% of fractions used adapted plans**

Ozyar et al, Clinical and Translational Radiation Oncology 46 (2024)

Clinical outcomes and toxicities of adaptive MRIgRT of adrenal metastases

A multi-institutional pooled analysis

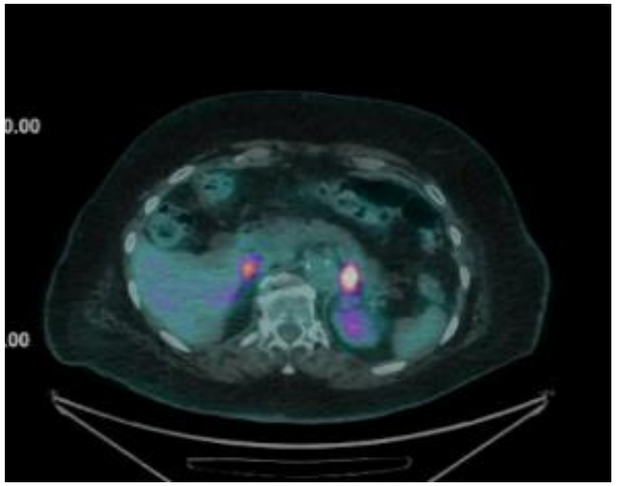


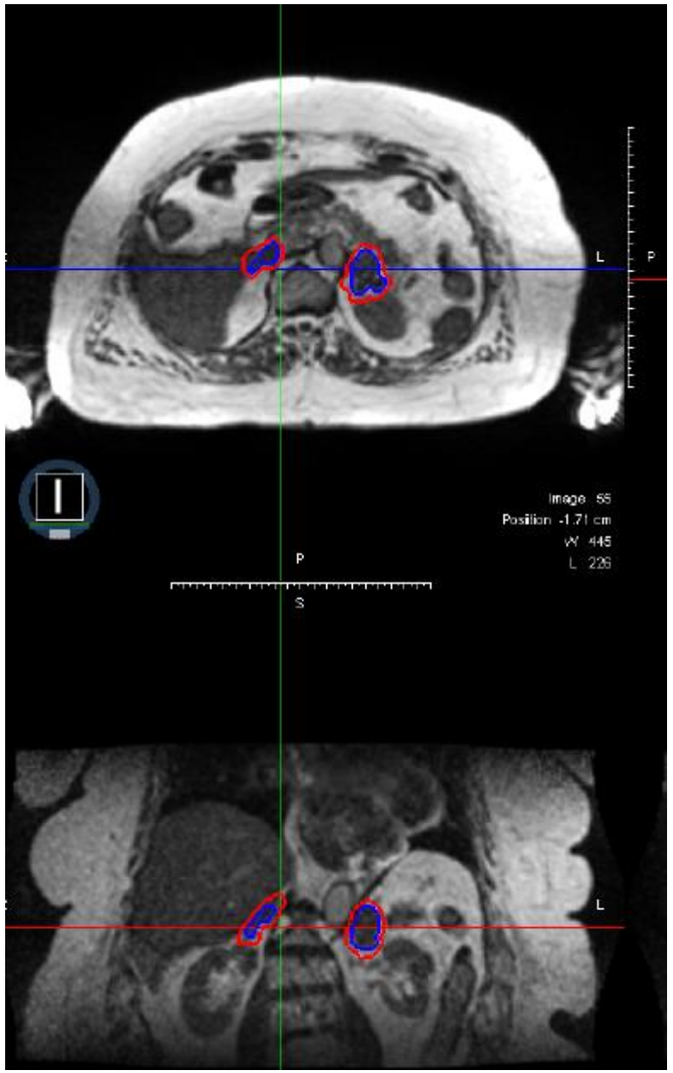
- ✓ Median follow-up: **17.7** months (IQR 5.5-21.7)
- ✓ Median Overall Survival (OS): **30.4** months
- ✓ **1**- and **2**- year OS of **75%** and **57%**

- **no LR** with a **BED_{10} >100 Gy,** with a **single FX** or a **dose >10 Gy**
- sign **higher OS** in ptn achieving a **CR** and **with ECOG scores of 0-1** on MVA
- 0.8% ≥ grade 3 chronic toxicity

Adaptive MRIgRT represents new standard of care for adrenal tumors

Case with bilateral adrenal mets



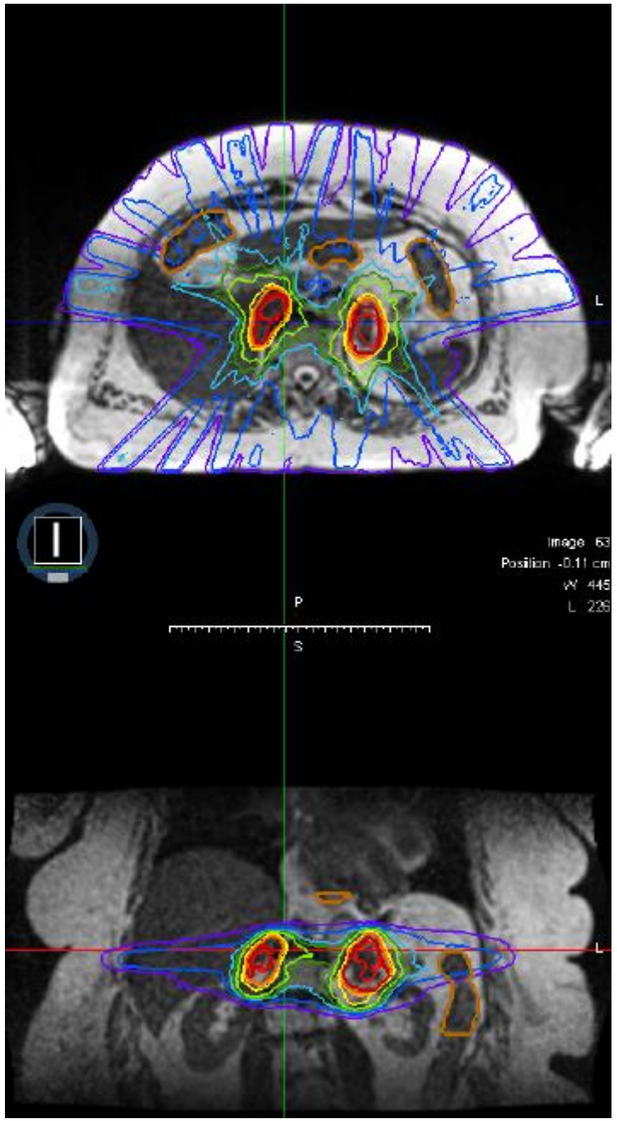


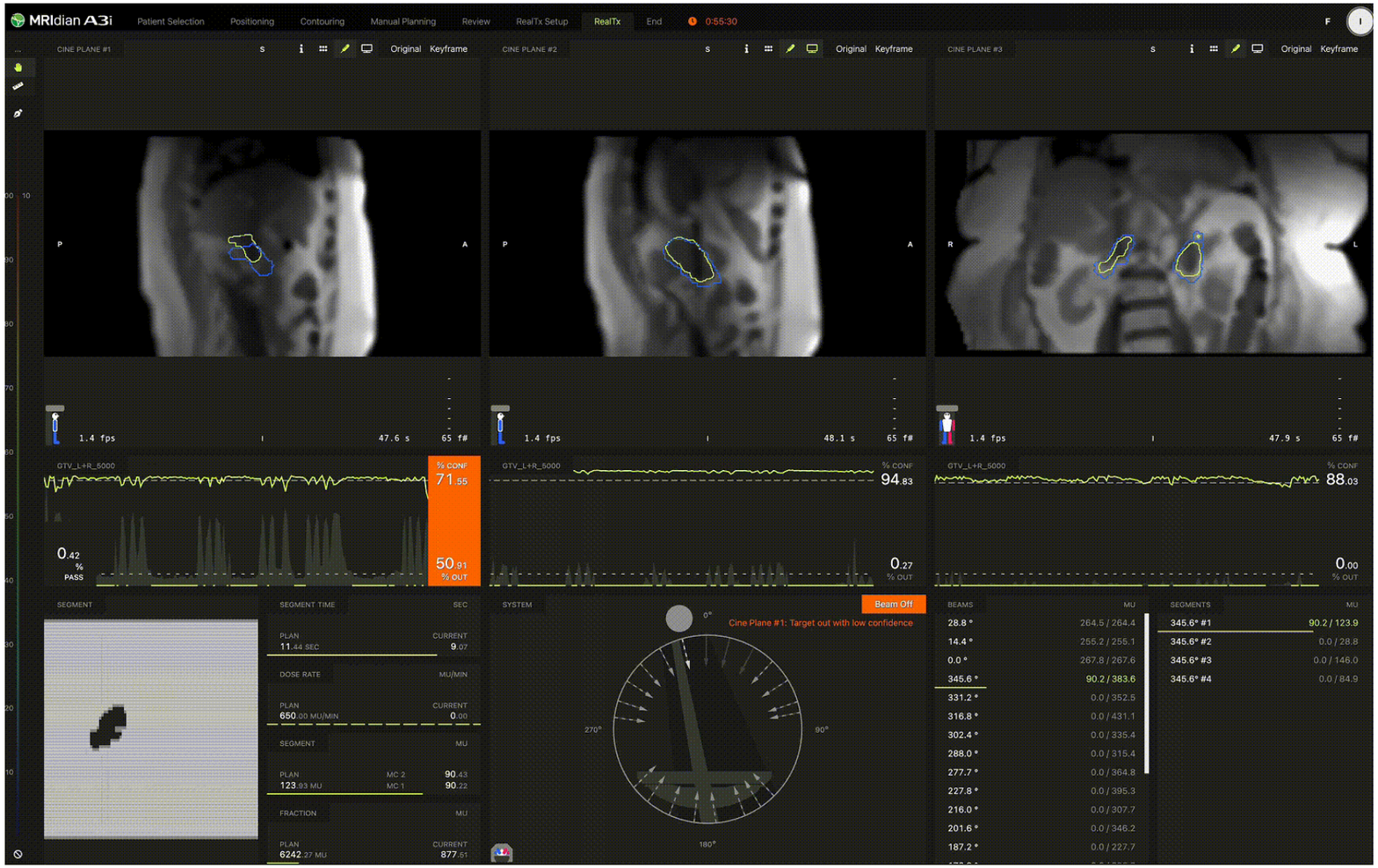
74 year old lady
cT4N3M1c NSCLC since 3-22

Oligoprogressive disease of bilateral adrenal mets during capmatinib

She was referred for SABR of both adrenal mets

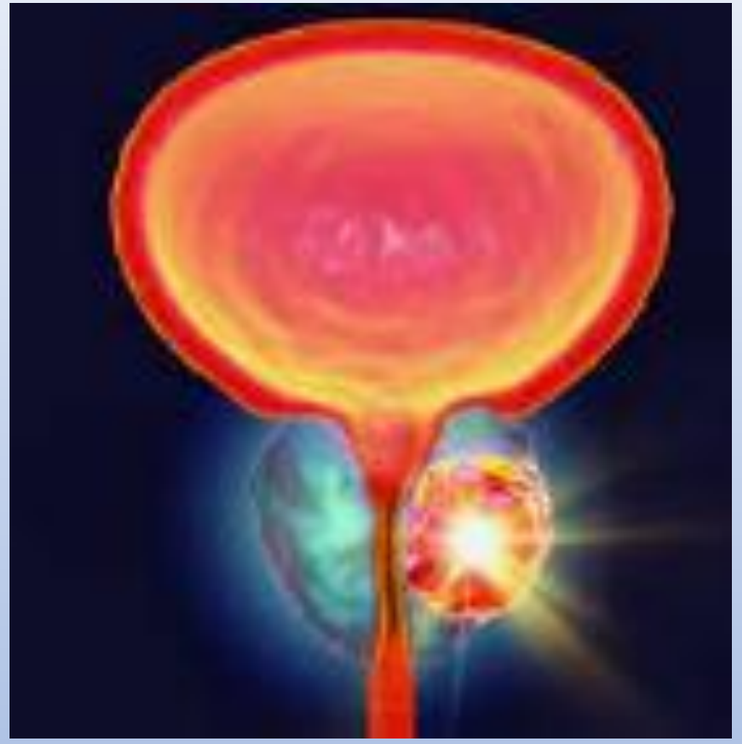
Case with bilateral adrenal mets





lesions separately during real time cine MR imaging on a sagittal plane coronal plane used during tracking to see both lesions

MRIgSABR in prostate tumors



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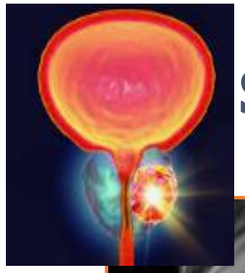
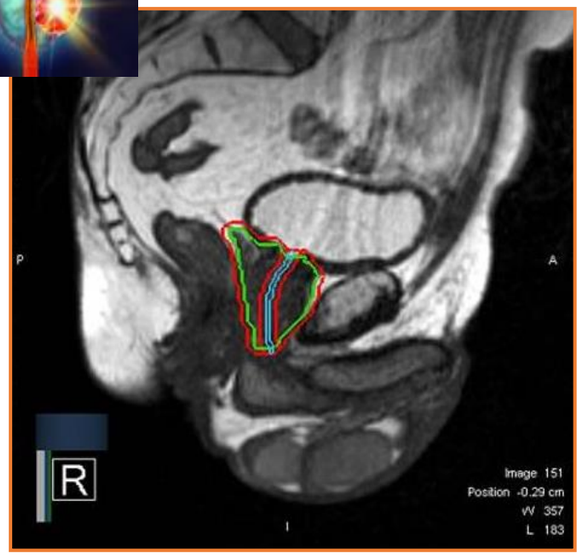
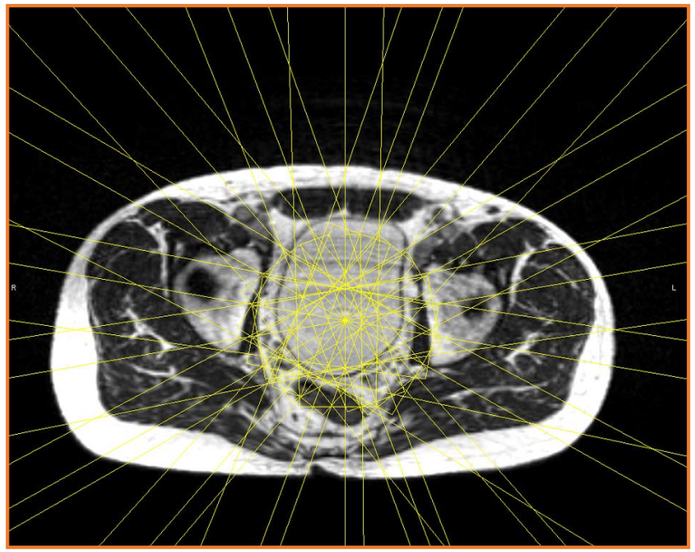


SMART study for localized prostate cancer; a phase II study





- Prospective single arm phase II study
- 101 pts cT1c – cT3b localized prostate ca
- IPSS ≤ 19; prostate volume ≤ 90 cc
- 5 Fx 7.25 Gy
- 3 Fx per week

Advantages MRIgRT:

- ✓ superior soft tissue contrast
- ✓ no need for fiducials
- ✓ daily plan adaptation
- ✓ continuous MR imaging during gated delivery
- ✓ use of 3 mm margins

→ resulting in improved sparing of OARs

Aim: to investigate the clinical benefits of this novel approach on toxicity and quality of life

Bruynzeel, et al. IJROBP, 2019

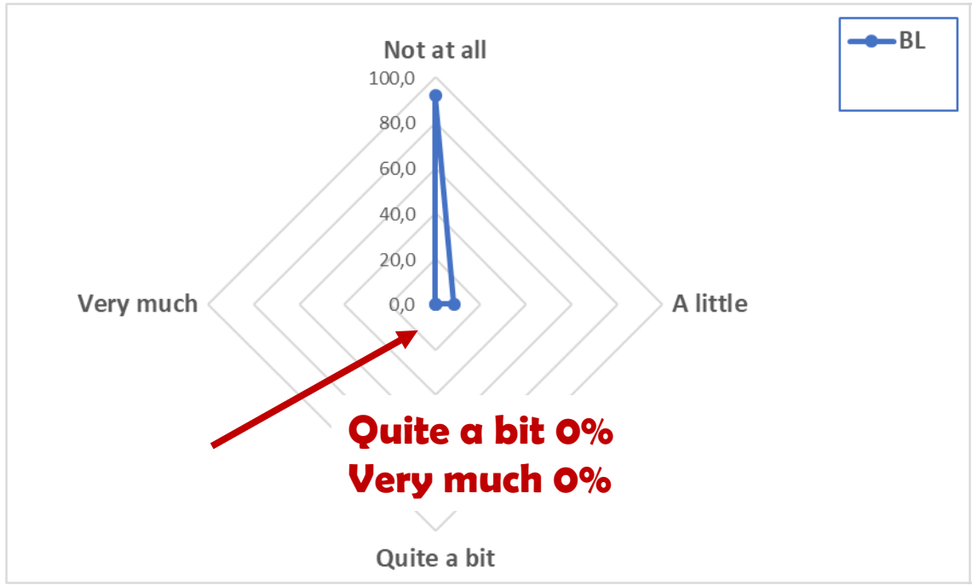
Side effects reported by the clinician

	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%

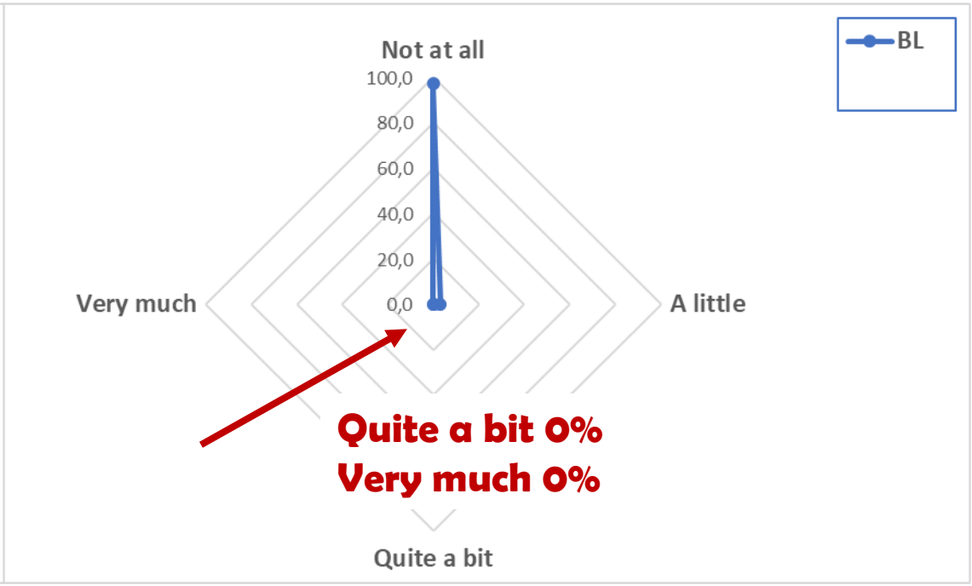
Bruynzeel et al, IJROBP, 2019. Tetar et al, Eur Urol Oncol, 2020

Side effects reported by patient

Is there a relevant limitation on daily activities due to urinary symptoms?



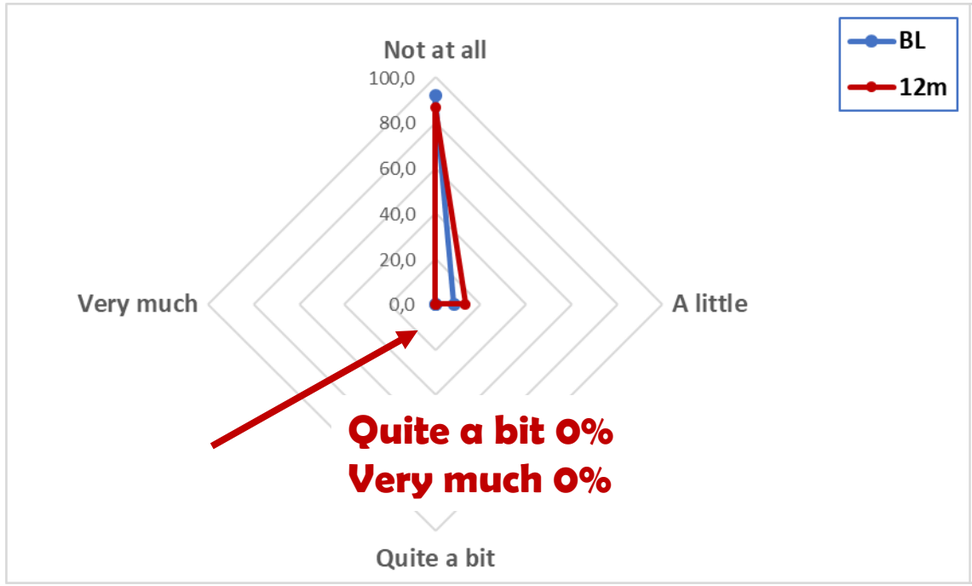
Is there a relevant limitation on daily activities due to bowel symptoms?



Tetar et al, Eur Urol Oncol, 2020

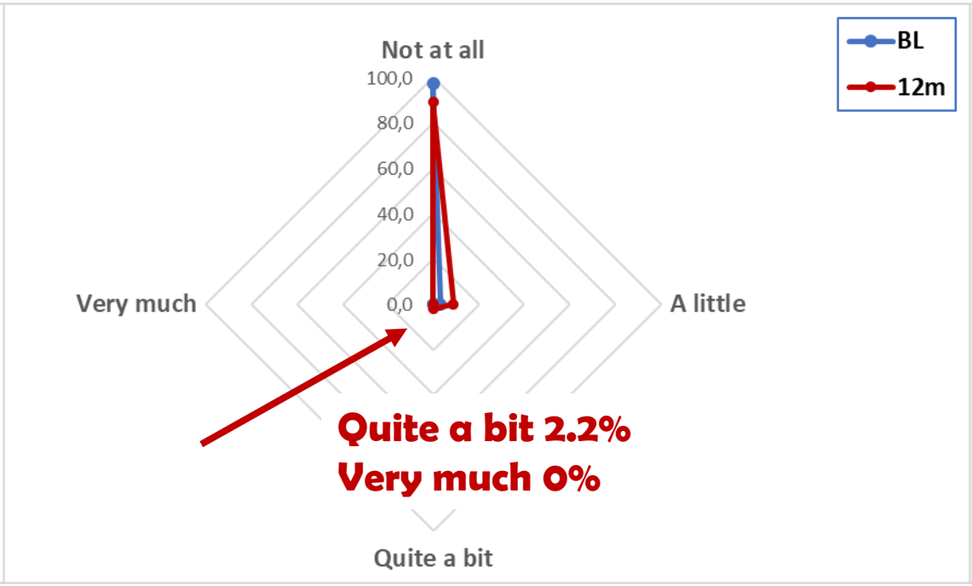
Side effects reported by patient

Is there a relevant limitation on daily activities due to urinary symptoms?



P=0.17
Paired T-test based on N=88

Is there a relevant limitation on daily activities due to bowel symptoms?



P=0.07
Paired T-test based on N=89

Acute toxicity comparison of magnetic resonance-guided adaptive versus fiducial or computed tomography-guided non-adaptive prostate stereotactic body radiotherapy: A systematic review and meta-analysis

Leeman et al, Cancer, 2023

Aim of review and meta-analysis:

to compare acute GU and GI toxicity rates between MRIg-A-SABR and CT-SABR

Inclusion criteria eligible trials:

- ✓ prospective trial evaluating prostate SABR
- ✓ ≥10 pts
- ✓ 4-5 Fx TD of 35-40Gy
- ✓ acute toxicity rates
- ✓ studies published during or after 2018

Two groups: MRIg-A-SABR treatment on a MR-Linac with daily online plan adaptation

CT-SABR treatment with cone-beam CT and/or fiducial-based IGRT

Acute G2+ GU or GI toxicity MRIg-A-SABR vs CT-SABR

- 29 prospective studies – 9 MRIg-A-SABR; 20 CT-SABR
- 2547 pts (329 vs 2218)
- more high-risk pts in MRIg-A-SABR (49 vs 15%)
- more use of ADT in MRIg-A-SABR (69 vs 22%)

•MRIg-A-SABR daily online adaptive planning
•no sign difference in PTV margins used
•no difference in (low) use of rectal spacers

- acute G2+ GU 16 vs 28%
- acute G2+ GI 4 vs 9%

➢ MRIg-A SABR is associated with sign reduced risk of acute G2+ GU or GI toxicity

➢ **reduced risk of physician assessed acute GU and GU toxicity** –
further investigation is needed to pinpoint the specific underlying causes

The MIRAGE study – phase III study – MRIg vs CTg SABR

Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer

Aim: to demonstrate that **aggressive PTV margin reduction** with **MRI-guided SABR** reduces acute toxicity following SABR for localized prostate cancer

INTERVENTIONS Patients were randomized 1:1 to SBRT with CT guidance (control arm) or MRI guidance. Planning margins of 4 mm (CT arm) and 2 mm (MRI arm) were used to deliver 40 Gy in 5 fractions. No daily plan adaptation

MAIN OUTCOMES AND MEASURES The primary end point was the incidence of acute (≤90 days after SBRT) grade 2 or greater GU toxic effects (using Common Terminology Criteria for Adverse Events, version 4.03 [CTCAE v4.03]). Secondary outcomes included CTCAE v4.03–based gastrointestinal toxic effects and International Prostate Symptom Score (IPSS)–based and Expanded Prostate Cancer Index Composite-26 (EPIC-26)–based outcomes.

Primary end point: incidence of acute grade 2+ GU toxicity

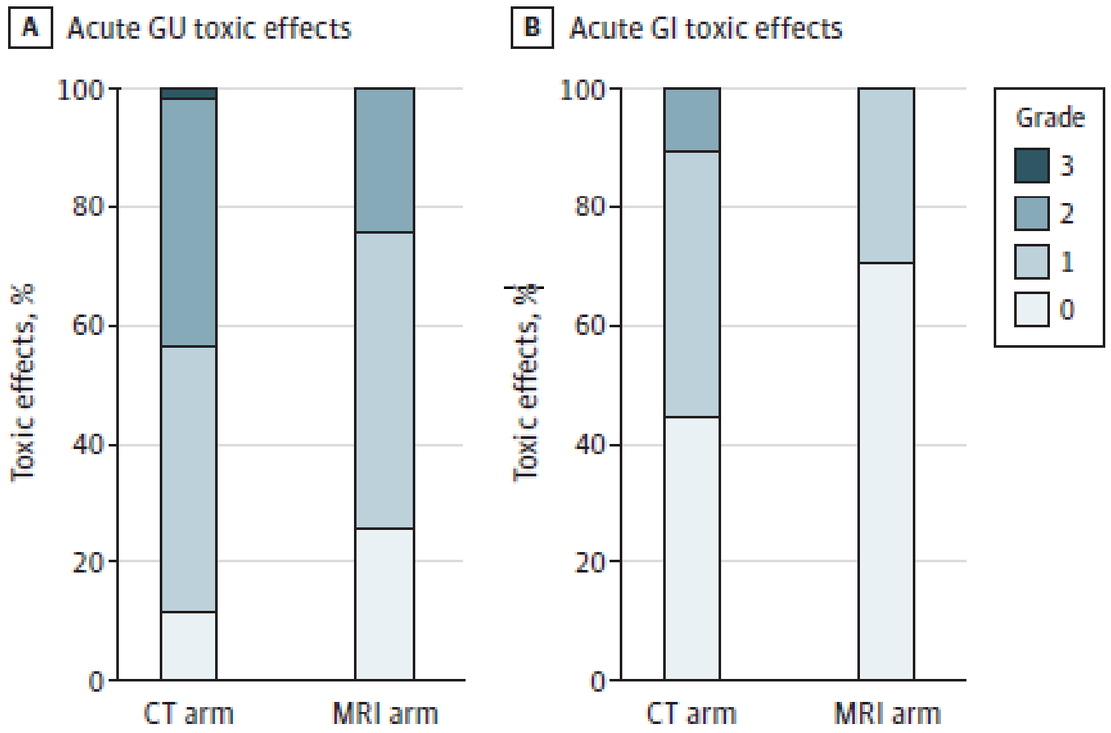
- study was initially designed to detect a 14% reduction in acute toxicity, from 29% to 15%, based on data from prior studies

Kishan et al, JAMA Oncol 2023

The MIRAGE study – phase III study – MRg vs CTg SABR

After 100 pts: a prespecified interim analysis

- incidence of acute G2+ GU sign reduced in men receiving MRIgSABR (22 vs 47%)
- revised power calculation was performed
- conditional power of 89% could be maintained with only 154 pts
- trial closed to accrual early



90-day end point:

G2+ GU 24.4% MRIgSABR vs 43.4% CT

G2+ GI 0 vs 10.5%

The MIRAGE study – phase III study – MRg vs CTg SABR

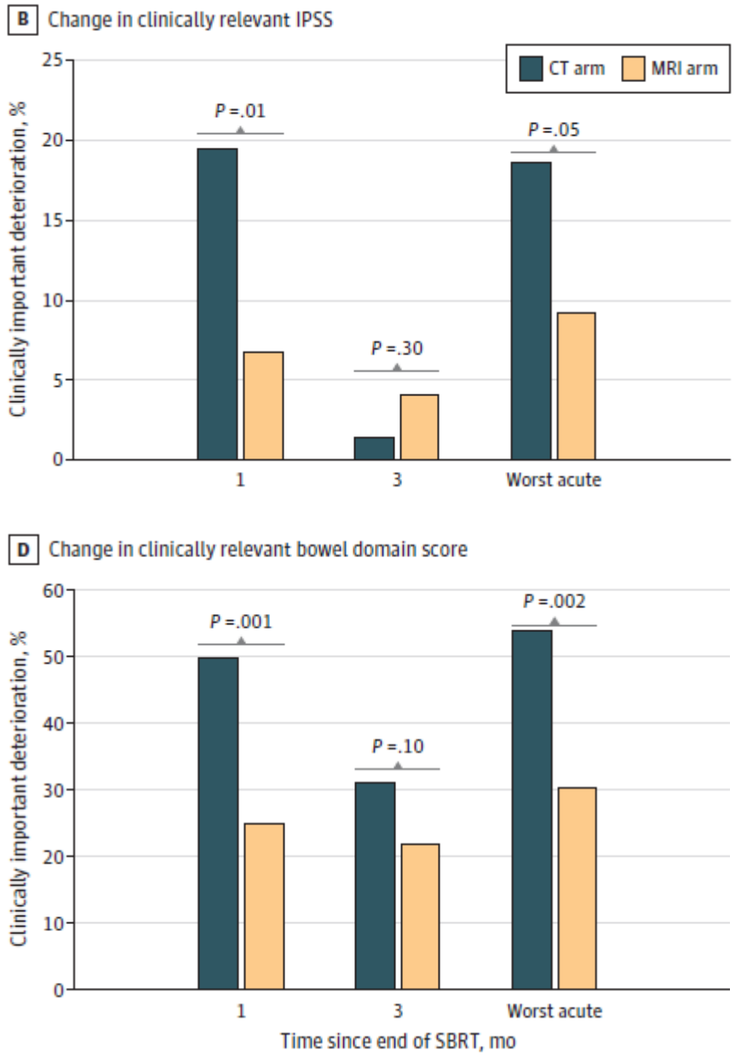
Patient-reported outcomes:

MRIgSABR @1 mo sign lower:

- large increase in IPSS
- clin sign decrease in EPIC-26 urinary incontinence
- clin sign decrease in EPIC-26 bowel scores

but not @3 months

PTV margin reduction afforded by MRI guidance resulted in the observed reduced acute toxicity risks



HERMES trial –interim toxicity results

- single –center noncomparative randomized phase II trial
- intermediate to high risk prostate cancer
- pts allocated to : 5-Fx (36.25 Gy) or 2-Fx (24 Gy) with a focal GTV boost (27 Gy) using MRIg-A-SABR

Primary endpoint: cum incidence of acute G2+ tox from start to 12 weeks posttreatment

Interim analysis was performed after 10 patients treated in both groups

R. Westley, et al, IJROBP, 2024

HERMES trial –interim toxicity analysis

Table 3 Maximum grade of CTCAE GU toxicity experienced per patient between end of radiation therapy and 3 months post-radiation therapy

	5-fraction SBRT				2-fraction SBRT			
Genitourinary CTCAE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
No.	0	9	1	0	1	7	2	0
%	0%	90%	10%	0%	10%	70%	20%	0%

- this interim analysis has shown acceptable toxicity rates
- recruitment will continue to completion

R. Westley, et al, IJROBP, 2024

MRIgSABR in kidney tumors

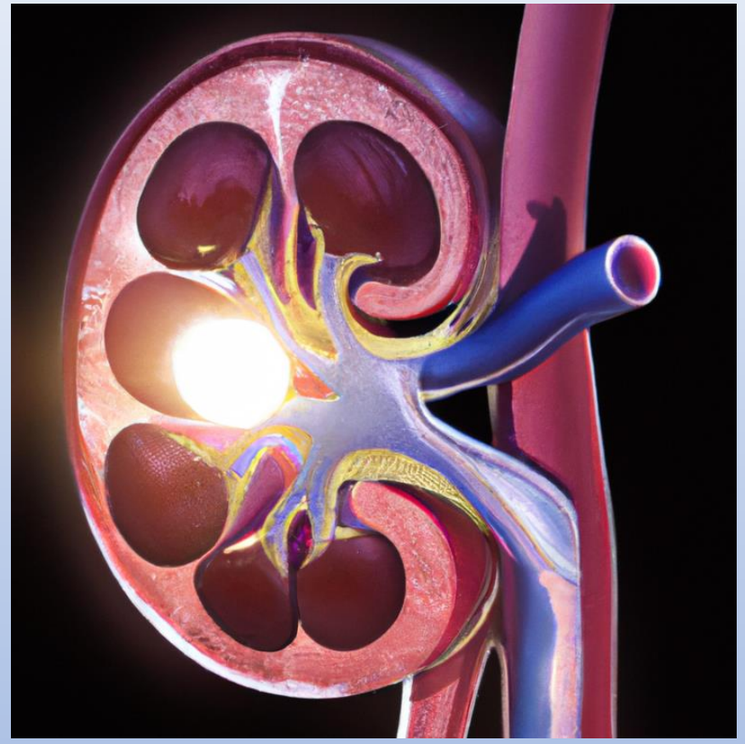
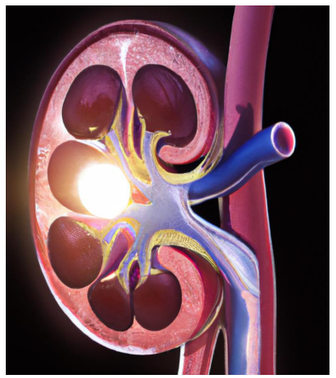


Image was generated with AI tool for illustrative purposes



EAU Guidelines on Renal Cell Carcinoma

European Association of Urology 2023

7.1.4.3.5 Stereotactic ablative radiotherapy

Stereotactic ablative radiotherapy (SABR) has been emerging as a treatment option for medically inoperable patients with localised cT1a and cT1b tumours. Patients usually receive 26 Gy in a single fraction, three fractions of 14 Gy or five fractions of 6 Gy [406, 407]. In a systematic review of non-comparative single-arm studies with a median follow-up range of 5.8–79.2 months, the local control rate was 97.2% and the mean change in eGFR was 7.7 mL/min/1.73 m^2. Grade 3 or 4 toxicities occurred in 1.5% of patients. However, viable tumour cells are often seen in post-SABR biopsies, although their clinical significance remains unclear [407]. Even though early results of SABR are encouraging, more evidence from RCTs is needed [408].

Clinical Trial > Lancet Oncol. 2024 Mar;25(3):308-316. doi: 10.1016/S1470-2045(24)00020-2.

Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): a non-randomised phase 2 trial *Siva et al*

- first multicenter trial of a definitive non-surgical therapy for primary RCC
- **study's primary outcome: 1-year local control of 90% or better - endpoint was met**

- ❖ 70 pts included (2016-2020)
- ❖ median age 77 years
- ❖ 70% man
- ❖ median tumour size 4.6 cm
- ❖ median CCI 7
- ❖ 26Gy or 42 Gy in 3 Fx

Clinical outcomes - median FU 43 months

✓cancer specific survival 100%

✓local control rate 100%

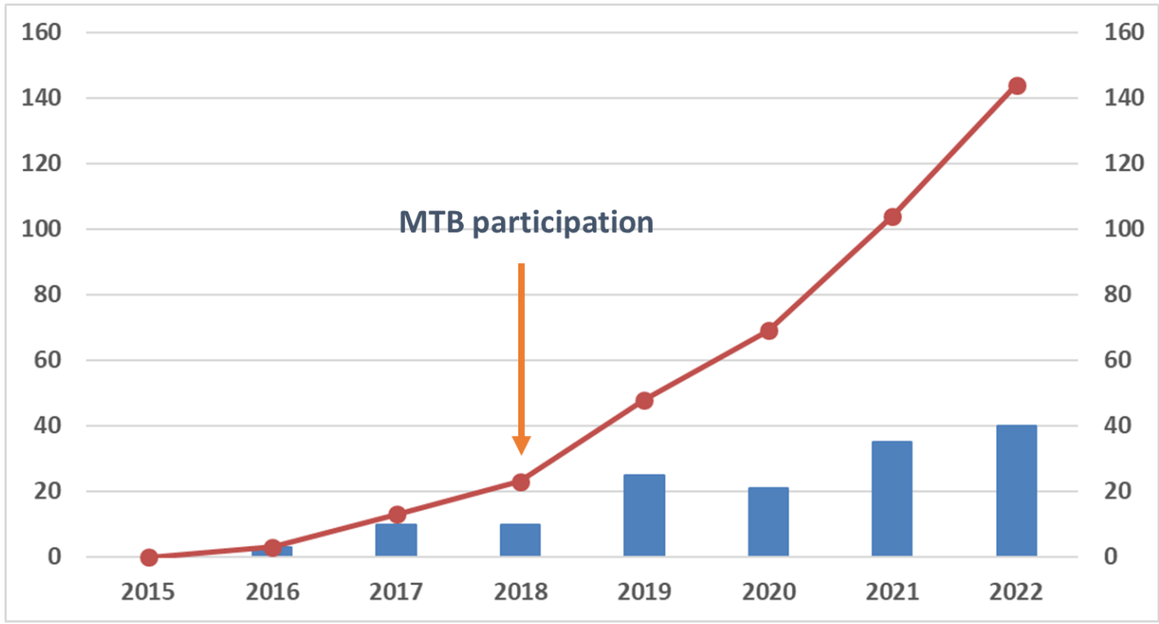
✓kidney function loss – 14.6 ml/min

✓G3 toxicity 10% related to SABR

✓no ≥ grade 4 toxicity

Kidney function loss is comparable to partial nephrectomy, despite larger median tumour size

Evolving role of MRIg SABR for renal malignancies
(including RCC, UCC, recurrences) – *current situation in our region*



number of referrals for MRIgSABR to our RT department

Amsterdam Renal Cancer Network (MTB)
Choice of treatment strategy

Individualized based on:

- ✓ patient and tumor characteristics
- ✓ patient and physician preferences
- ✓ outcome prediction: survival, local control, residual renal function, morbidity

Tailoring treatment for a specific patient

Reasons for SABR referral:

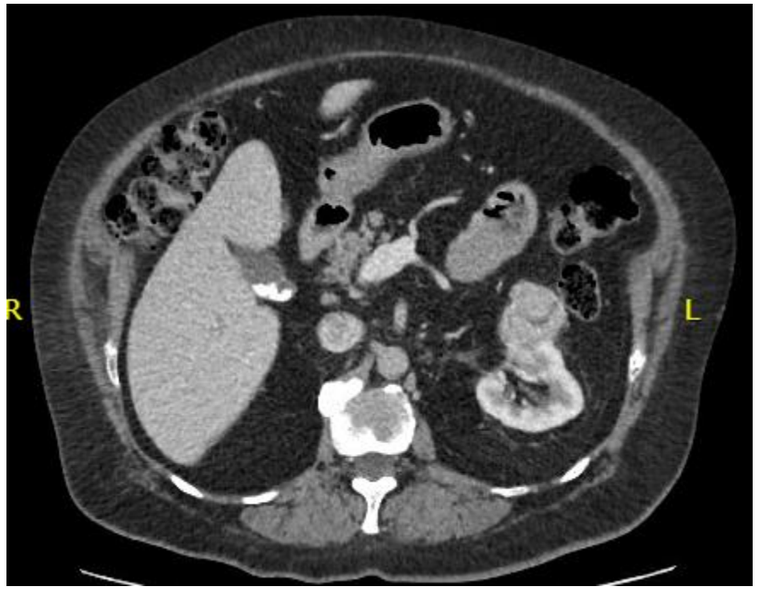
- high surgical risk due to comorbidity
- not suitable for other AT due to tumor size or location
- patient preference

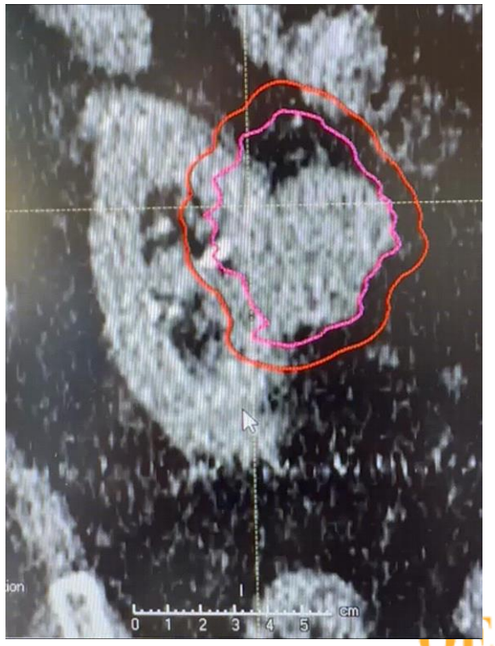
What kind of patients are referred?

73 year old lady
Pathology-proven clear cell RCC, 4.4 cm
Renal function: 41 ml/min

MTB referring hospital – indication for EBRT
4DCT simulation

Due to motion, location and impaired kidney function referred for stereotactic MRIgRT





Importance of management of respiratory motion

Respiratory motion measured with a 4DCT and managed throught the use of an ITV

- ❑ **radiation-induced renal dysfunction is dose-dependent**
- ❑ regional change in eGFR correlates with the volume receiving 50% of dose

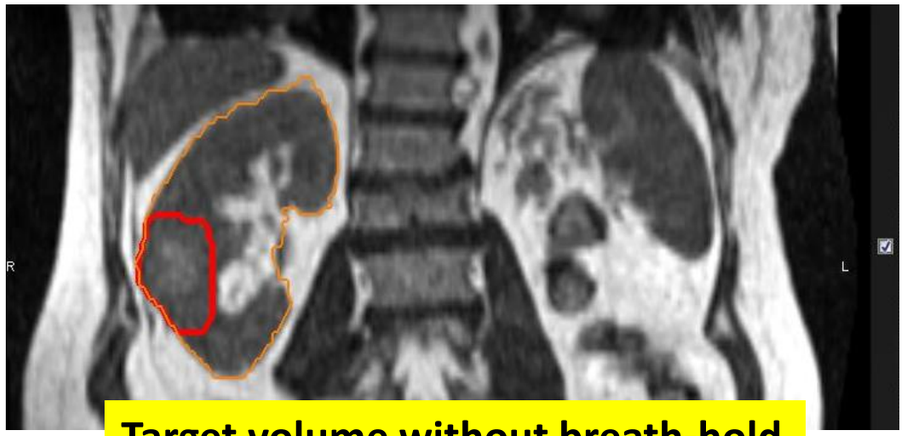
Siva et al, Radiat Oncol, 2016

- ➢ Dose-response relationship observed between dose delivered – subsequent decline
- ➢ sparing functional kidney from high doses may help reduce risk of functional loss

Advanced motion management
respiratory gating, breath-hold, abdominal compression

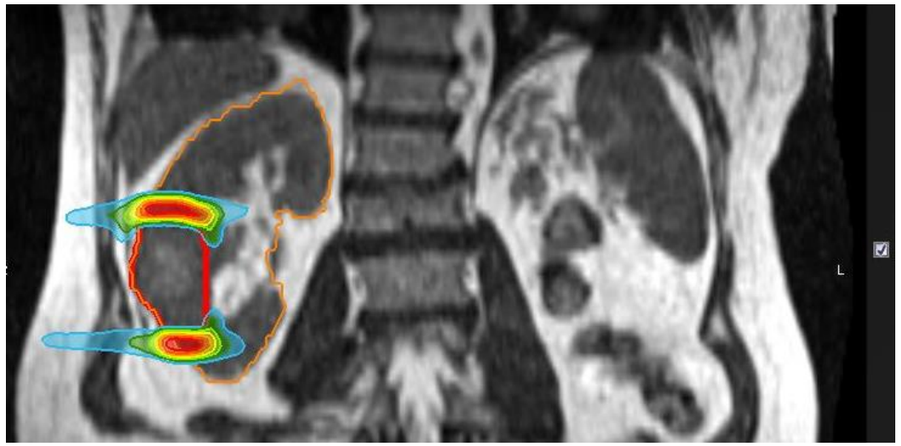
- ➢ leading to smaller treated volumes
- ➢ dose reduction to non-tumour kidney

Nephron sparing effect of gated breath-hold delivery



Target volume without breath-hold

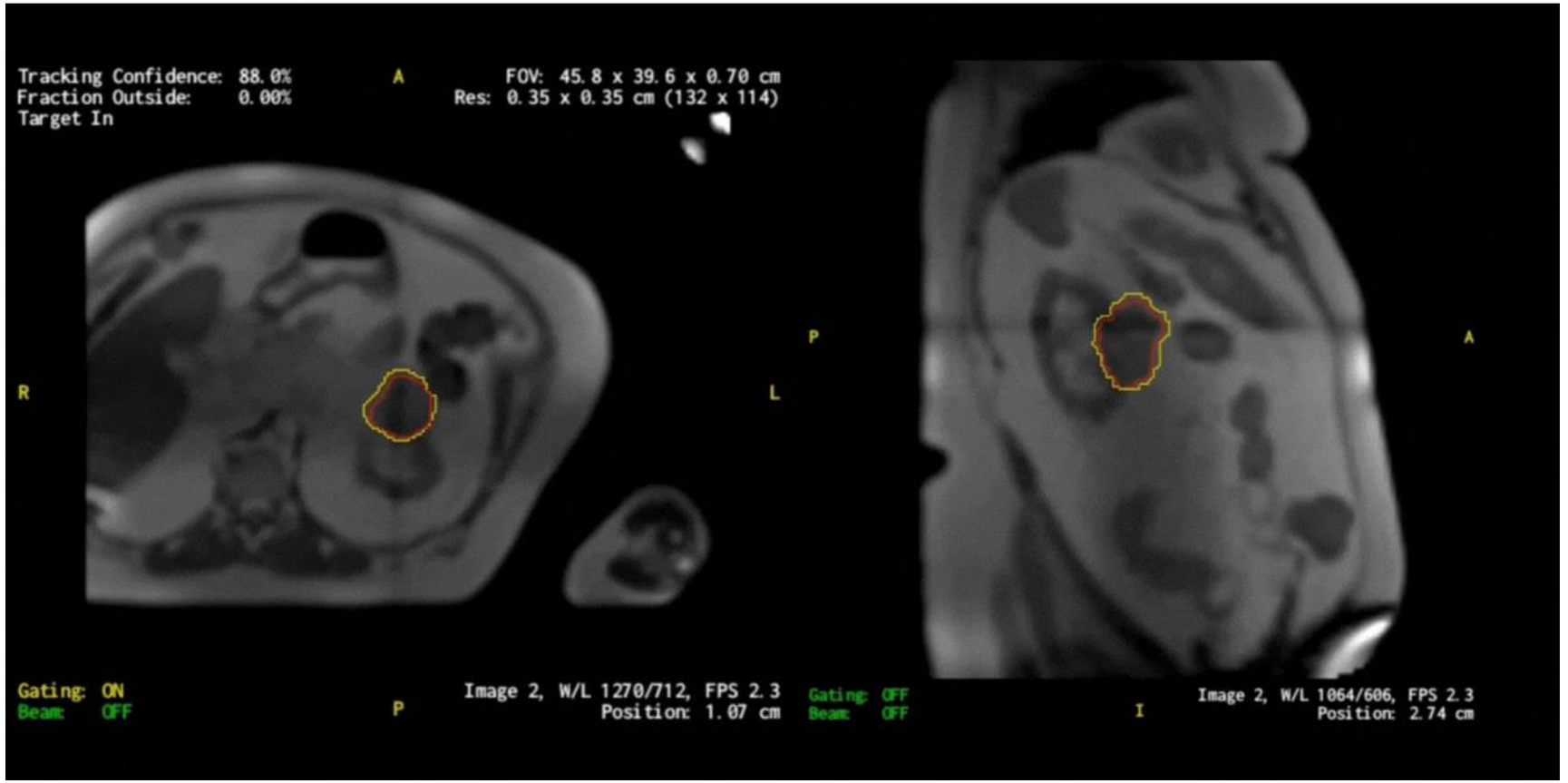
Target volume with breath-hold



Part of normal kidney that would have been irradiated without breath-hold
i.e. Improved sparing of normal kidney (function)

Referred case using gated breath-hold delivery

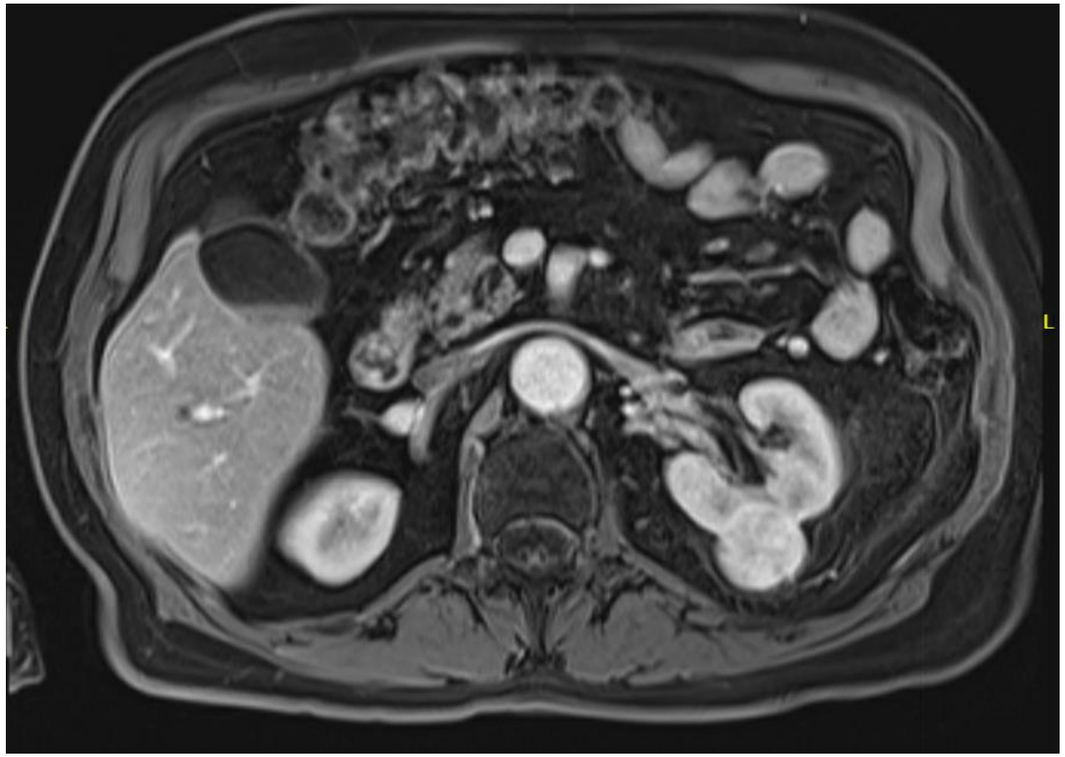
SABR 5Fx 8 Gy
Using gated breath-hold delivery



Motion monitoring conducted using cine MRI imaging in two directions during delivery

The next step in MRIgSABR

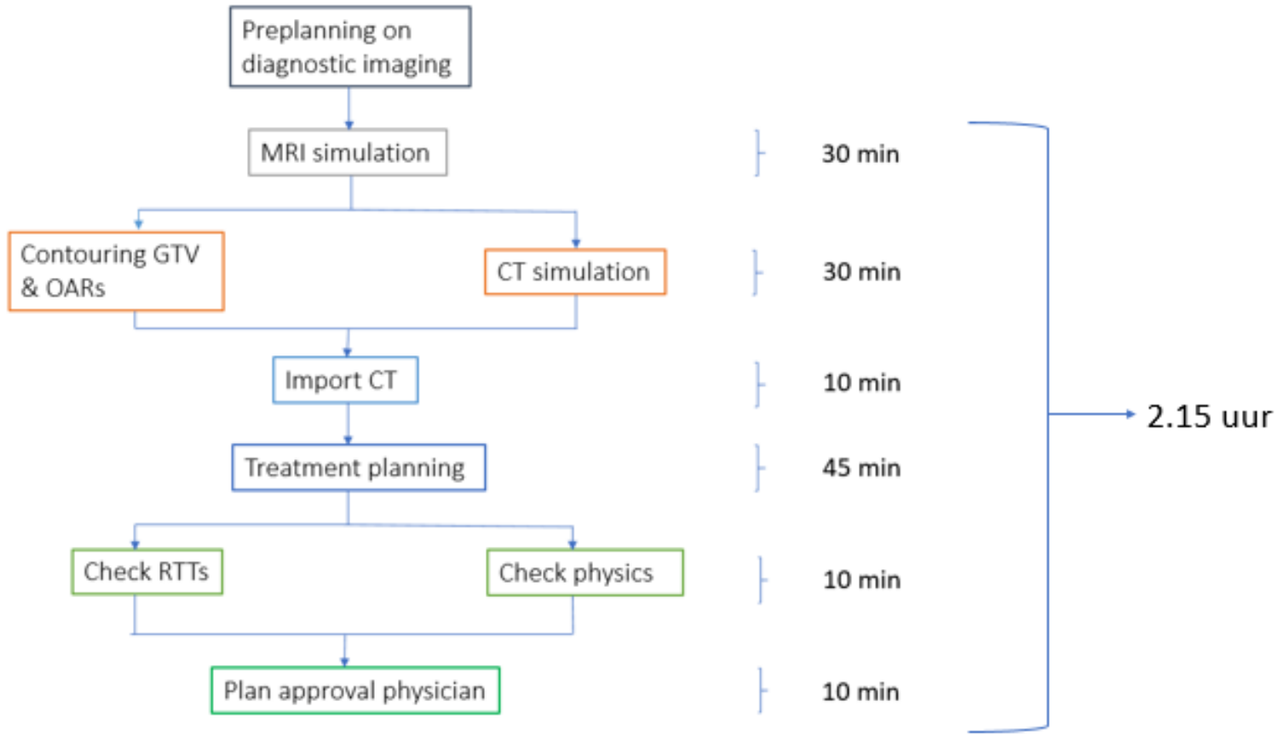
Single-day plan-and-treat



78-year old male patient
ccRCC T1a (3,2 x 2,4 cm) lower pole left kidney

One stop shop treatment kidney cancer

Single-day plan-and-treat



- 1.5 uur
- less time required – contouring
- less time required – treatment planning

flowchart with expected times for each step

One stop shop treatment kidney cancer

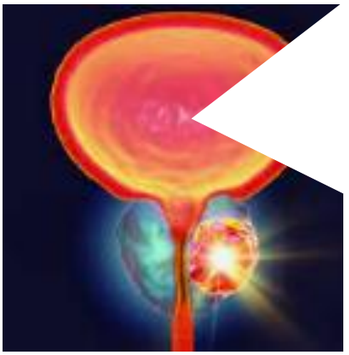
Single-day plan-and-treat

- ✓ motion monitoring is conducted using cine MRI imaging in two directions
- ✓ 54 minutes SMART single fraction of 26 Gy
- ✓ **total duration** – single-day plan-and-treat: 2 hours and 24 minutes

MRIguidedSABR in pancreatic tumors
conclusions

online adaptive MRIgSABR for pancreatic tumors:

- ✓ improves target coverage and decreases high doses in OARs
- ✓ shows a tolerable toxicity profile with a decrease in incidence of acute toxicity
- ✓ shows high local control rate
- ✓ several ongoing phase II and III studies



MRIguidedSABR in prostate tumors
conclusions

online (adaptive) MRIgSABR for prostate tumors:

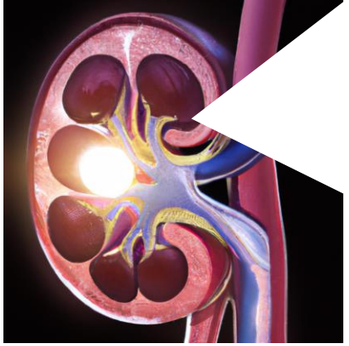
- ✓ is associated with sign reduced risk of acute G2+ GU and GI toxicity
- ✓ longer follow-up needed to evaluate late toxicity and disease controle outcomes
- ✓ studies ongoing – feasibility of ultrafractionated radiotherapy

MRIguidedSABR in adrenal tumors
conclusions

online (adaptive) MRIgSABR for adrenal mets:

✓ obtains high LC rates

✓ well tolerated treatment with low toxicity rates



MRIguidedSABR in kidney tumors
conclusions

online (adaptive) MRIgSABR for kidney tumors:

- ✓ has several advantages that can be used: *superior soft-tissue visualization, non-invasive procedure with real-time gated treatment delivery*
- ✓ can be used as single day plan- and treat for (most) T1a kidney tumors

→ may be a serious competitor for thermal ablations and partial nephrectomy

Thanks to our wonderful team, all our patients and my dearest colleague Frank Lagerwaard *in memoriam*

Thank you for your attention