UMC Utrecht

IMAGINE
Beeldgestuurde Oncologische Behandelingen

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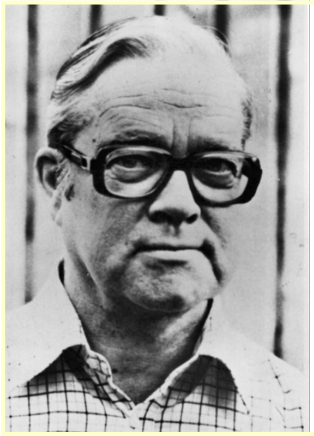
Vice dean Life Sciences
Professor of Functional Medical Imaging
Utrecht University

University Medical Center Utrecht

From the golden era of surgery

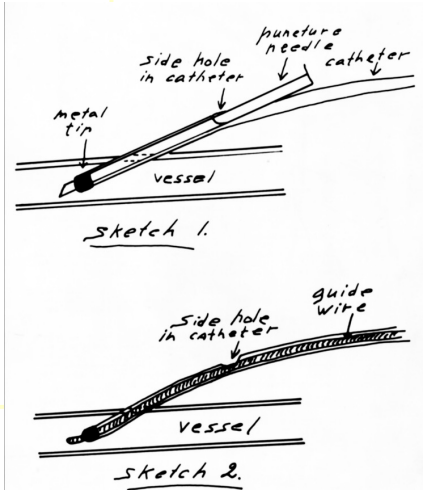
Billroth, AKH Wenen, 1889

To minimally invasive treatment of vascular diseases

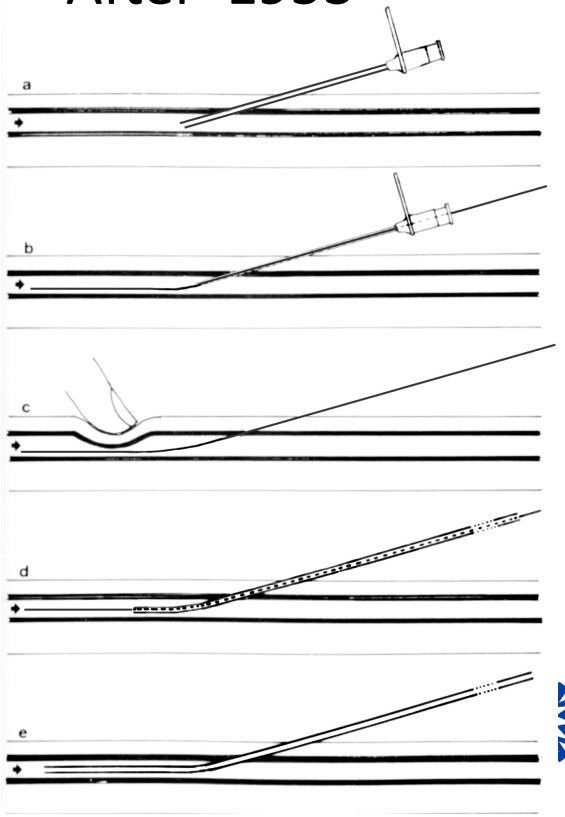


Sven Ivar Seldinger

Before 1953



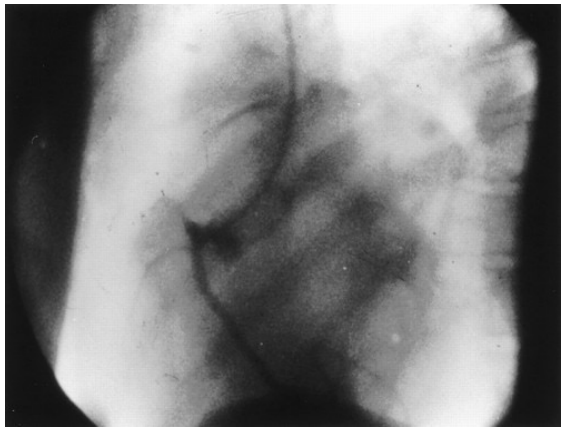
After 1953

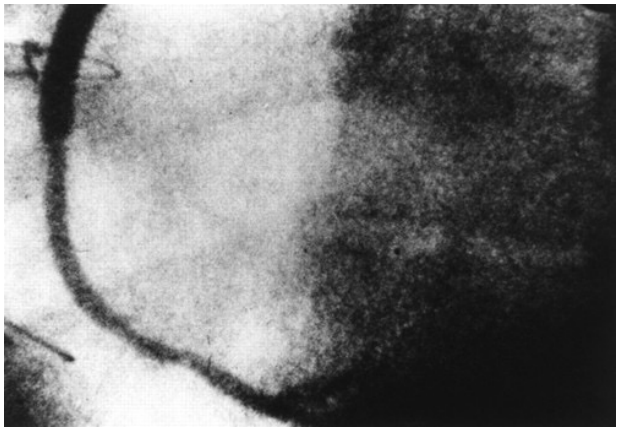


Coronary Angiography – from diagnosis

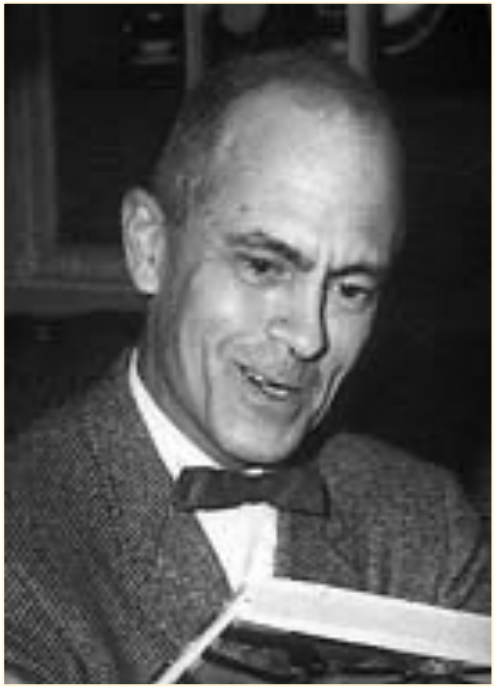
Mason Sones

1958

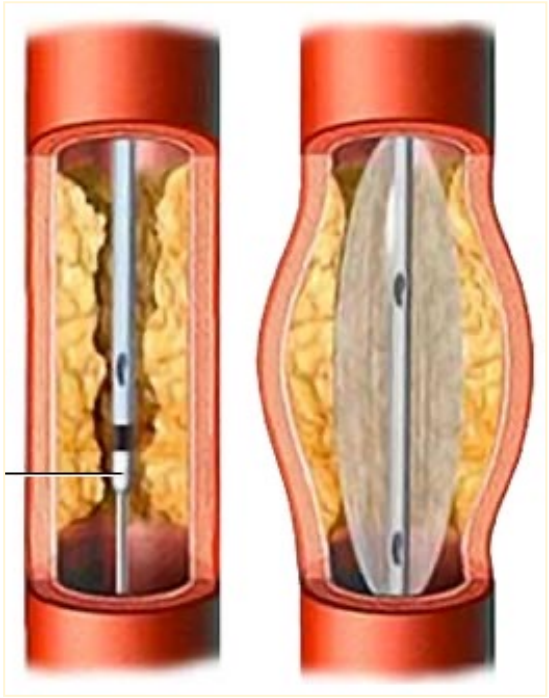


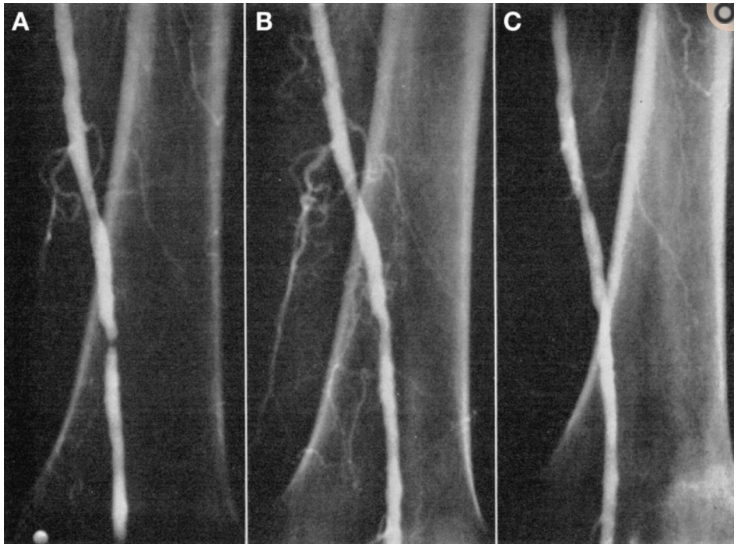


To treatment

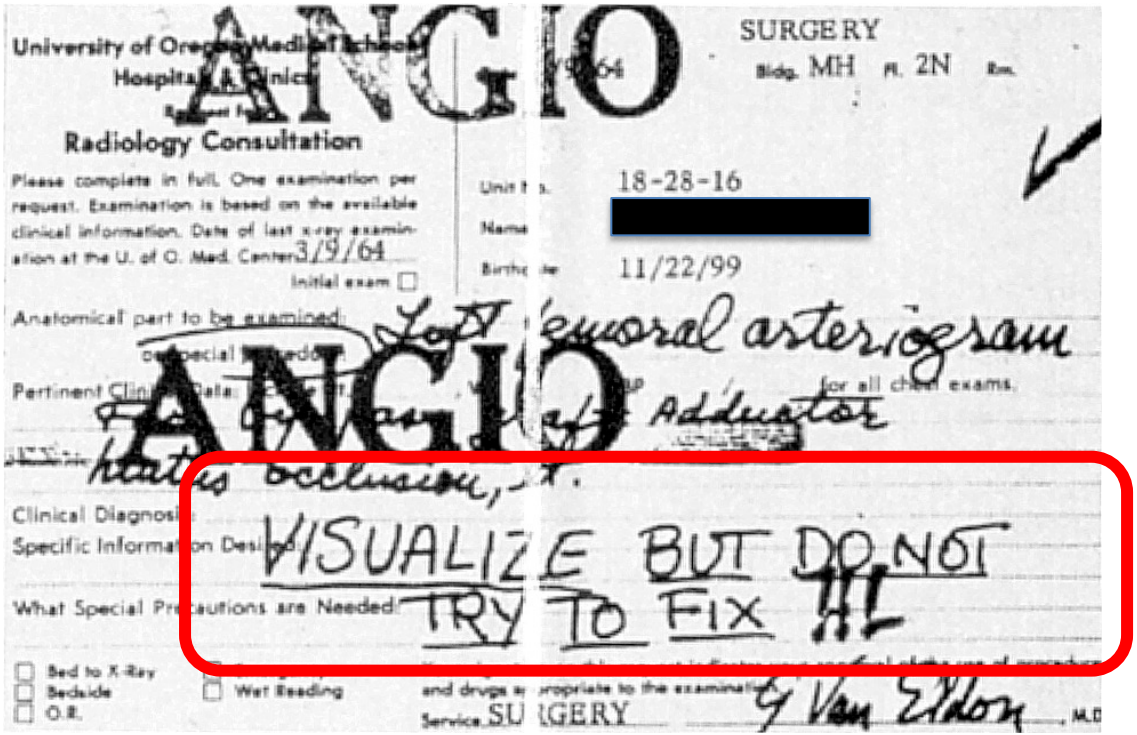


Charles Dotter 1963

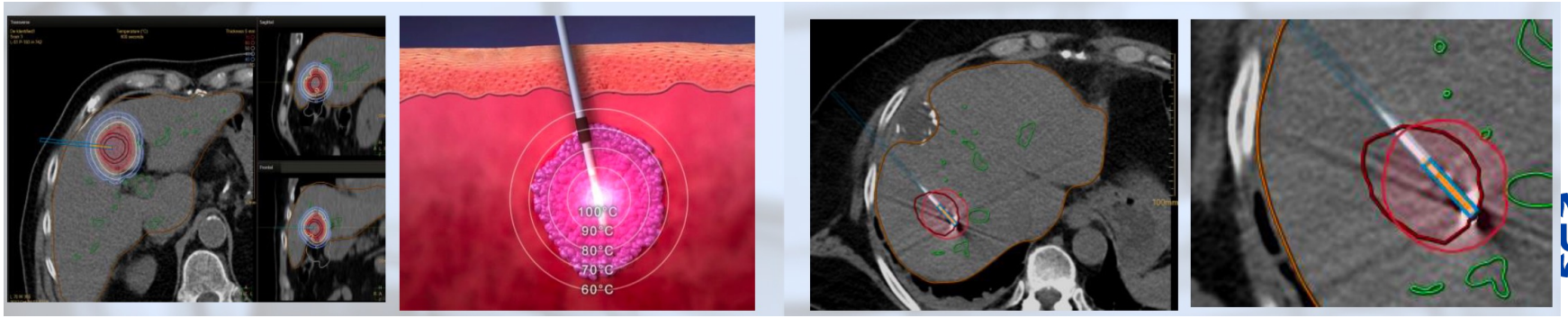




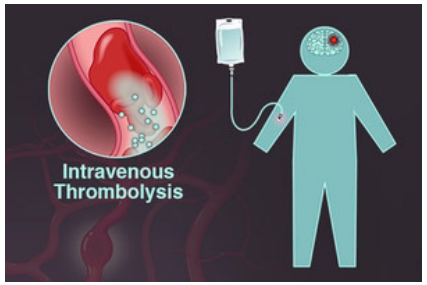
Turf battles and innovation in medicine



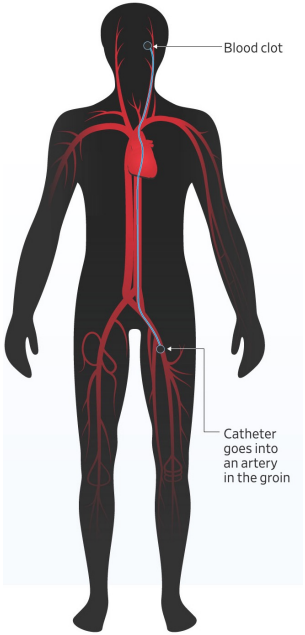
“Angio Suite”

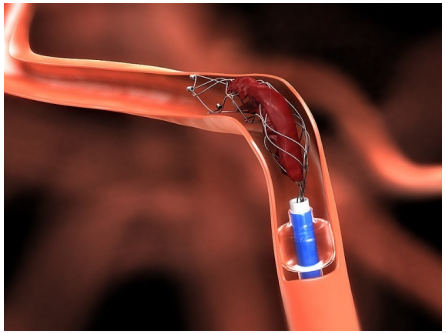


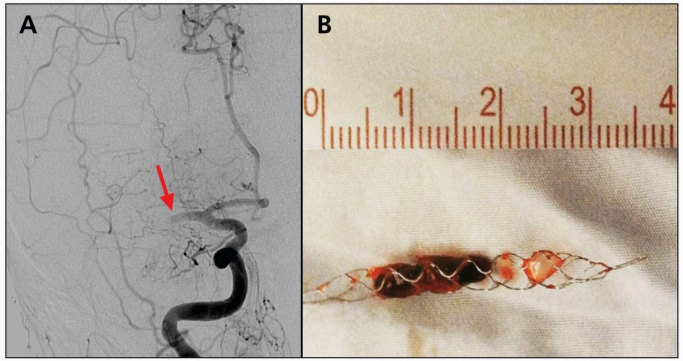
IAT: Intra Arterial Thrombectomy



Intravenenous trombolysis (1995)

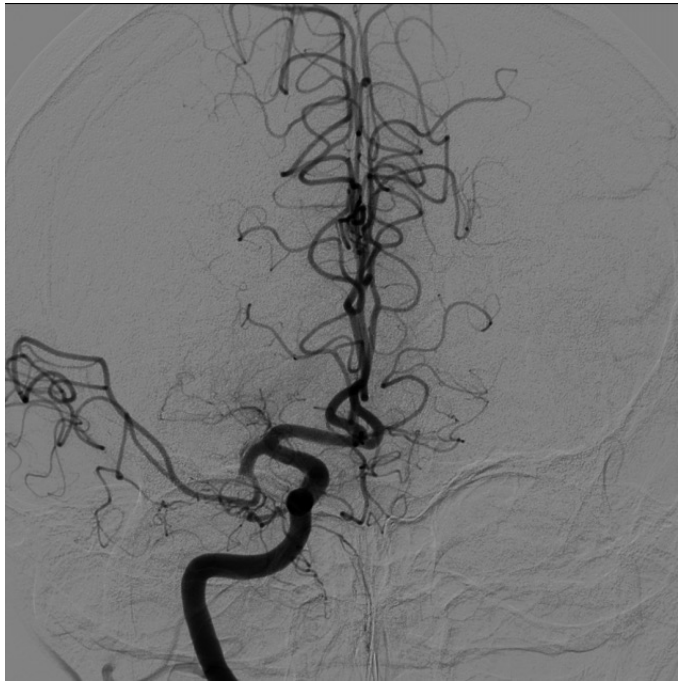




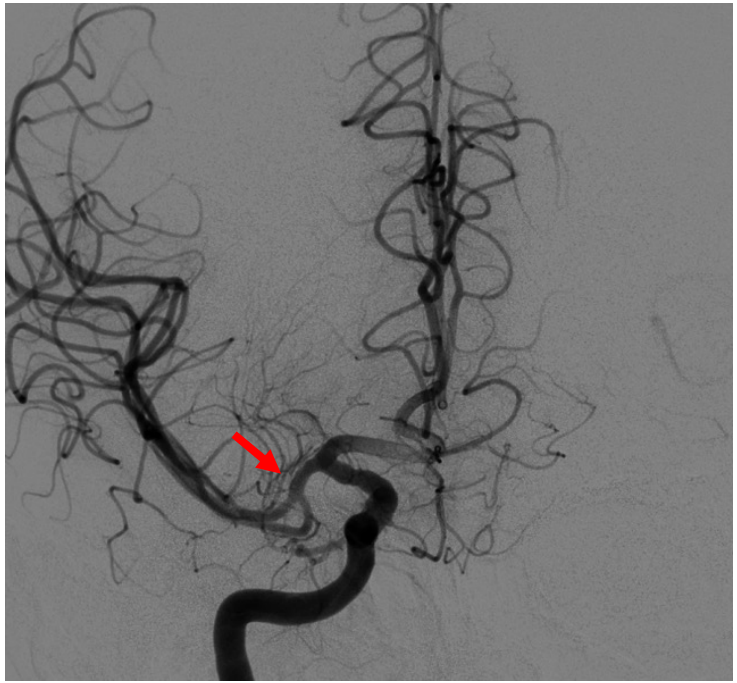


Endovascular trombectomy (2015)

Endovascular trombectomy

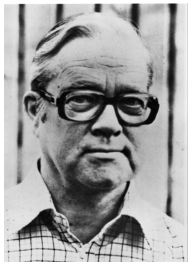


Before



After

IAT: Intra Arterial Thrombectomy

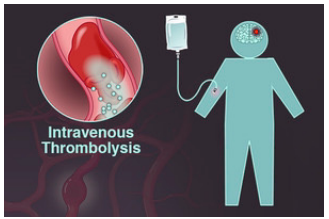


Seldinger

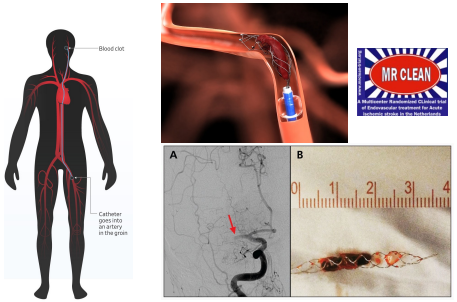
Sones

Dotter

1953 1958 1963

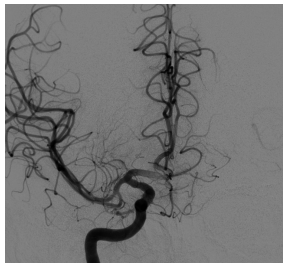


Intravenous thrombolys (1995)



Endovascular thrombectomy (2015)

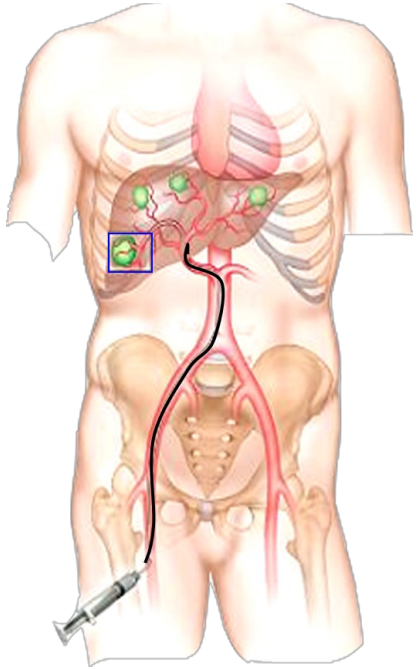
Before



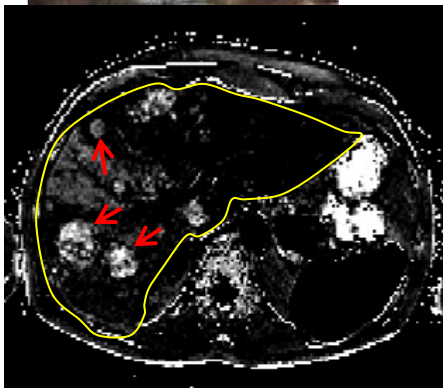
After

2015

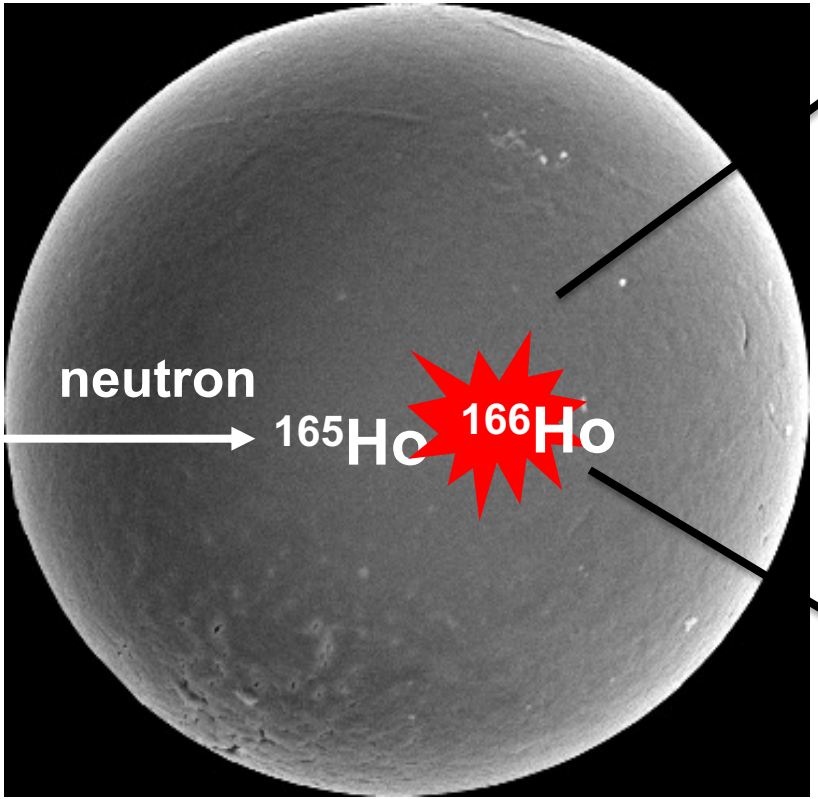
From vascular to cancer treatments: Radio embolization



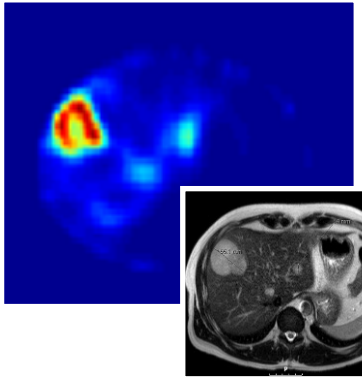
Holmium poly(L-lactic acid) microspheres



Paramagnetic MS: Accumulation in and around tumor

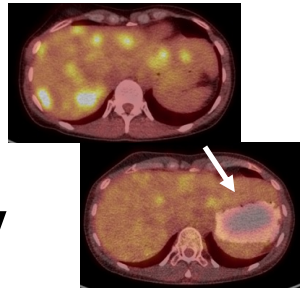


γ 81 keV

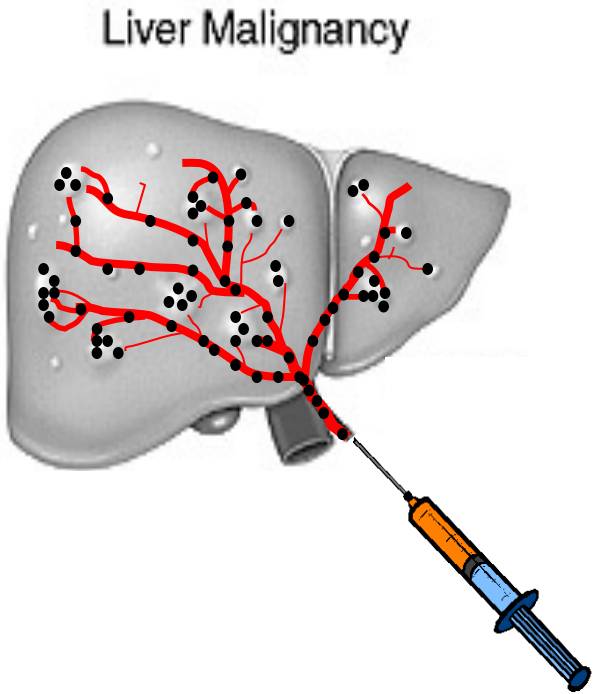


β

1.84 MeV



Holmium poly(L-lactic acid) microspheres



Holmium-166

T ½ = 1.1 days

1.84 MeV β-max

8 mm tissue range

γ-imaging

Liver:

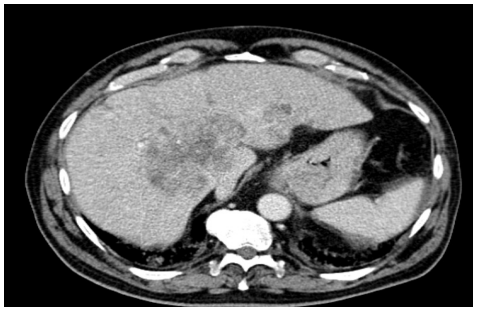
- **70% portal vein**
- **30% hepatic artery**

Tumor:

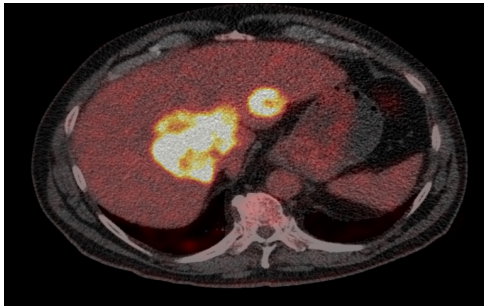
- **99% hepatic artery**

Holmium-166 Radioembolization

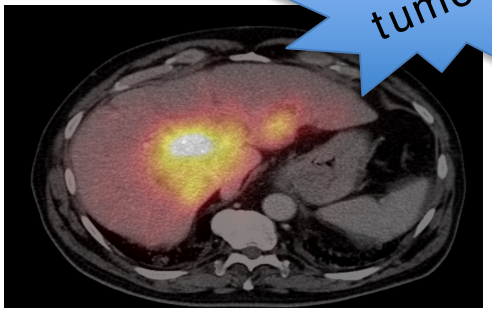
Clinical case: salvage mCRC patient



Baseline CT

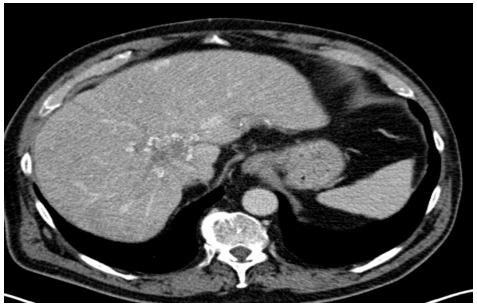


Baseline PET/CT

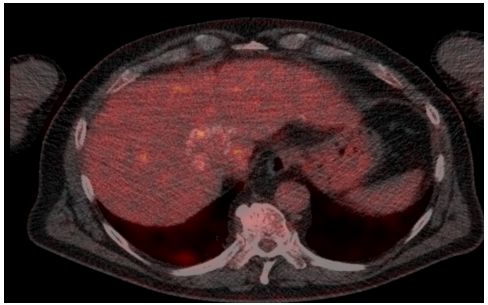


Post-treatment SPECT/CT

>200 Gy tumor dose



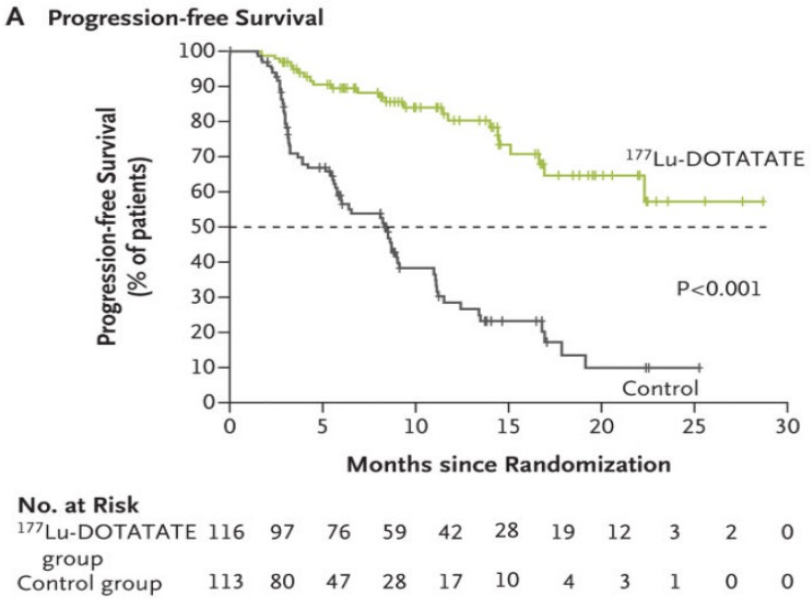
3-months CT



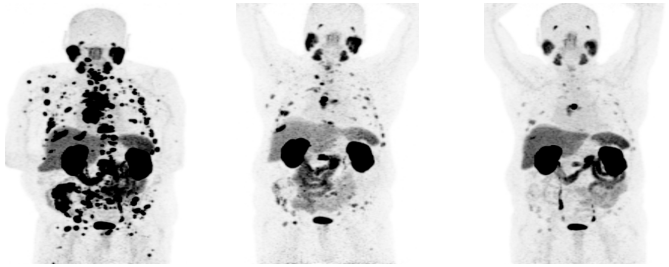
3-months PET/CT

6-months CT

Theranostics



Kwekkeboom et al. J.Clin.Onc. 2008
Strosberg et al. New Engl J Med 2017

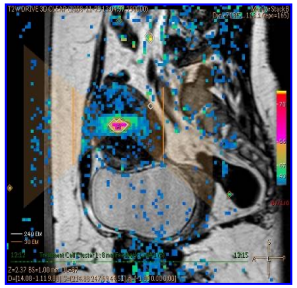


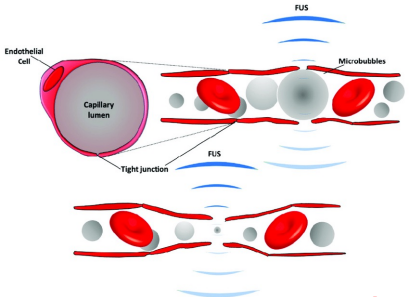
Baseline | 2 cycles PSA↓ 80% | 4 cycles PSA↓ 95%

Prostate cancer:
lutetium-177-PSMA-617 treatment

2008 2017 20XX

MR Guided Ultrasound





Fibroids

Tumors

Tremor

BBB disruption (dementia, brain tumors)

Immune Sensitization

High Intensity Focused Ultrasound (HIFU) Triggers Immune Sensitization of Refractory Murine Neuroblastoma to Checkpoint Inhibitor Therapy Cli.Cancer Research 2020

2000

20XX

Historical situation at department of Radiotherapy at the UMC Utrecht

Research:

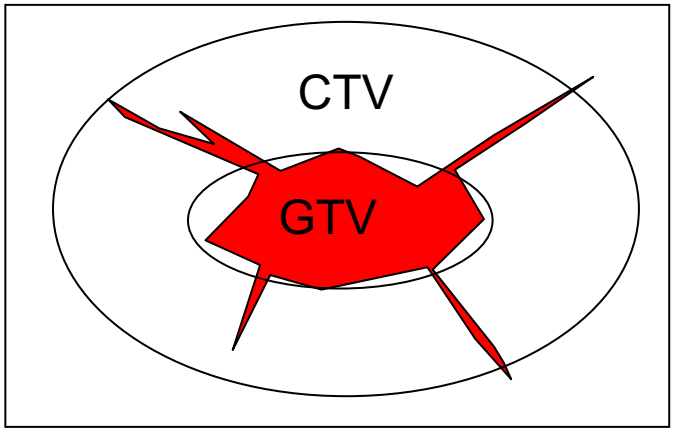
Hyperthermia to treat tumors

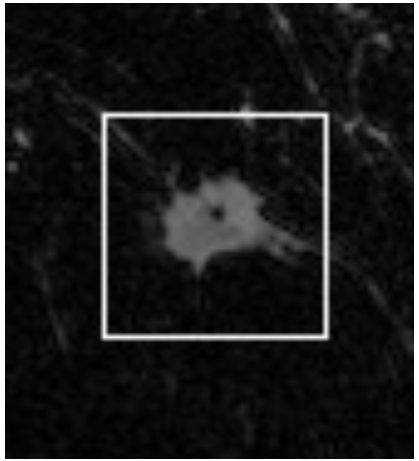
Clinic:

Conventional Radiotherapy

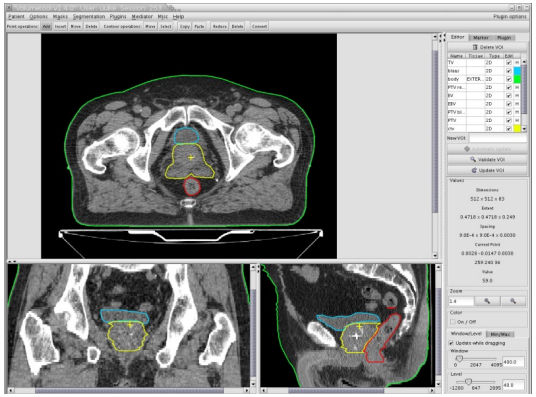
Traditional Oncology Treatment

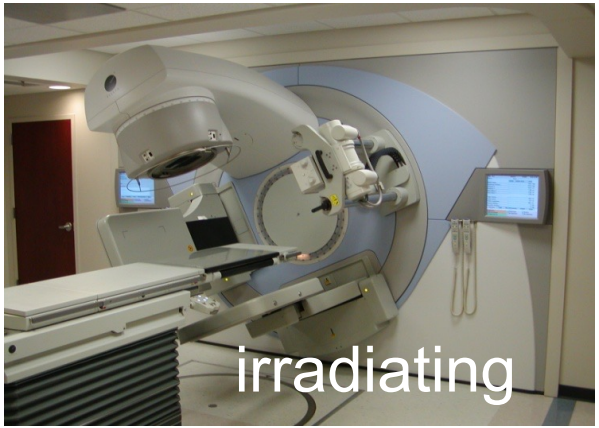
	distant	CTV	GTV
Chemo	+	+	-
RT	-	++	+/-
Surgery	--	-/+	+

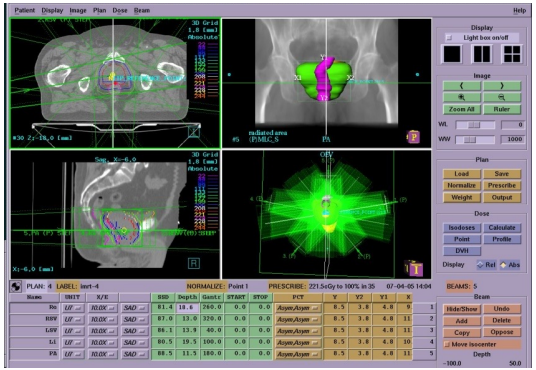




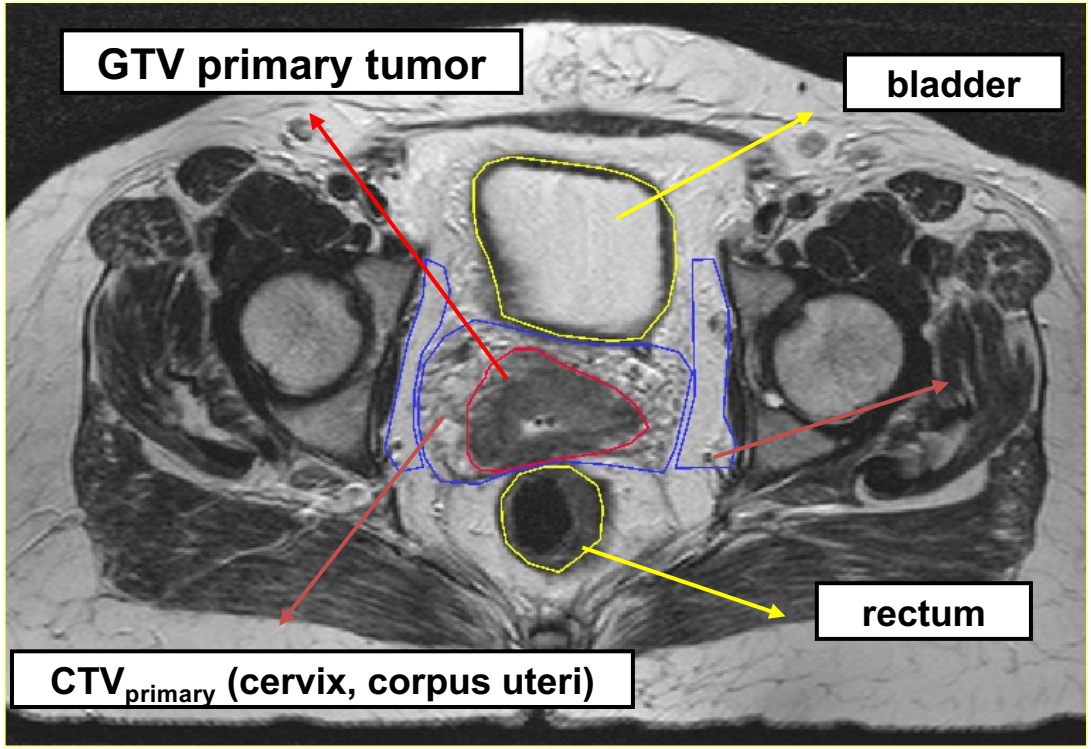
The radiotherapy workflow



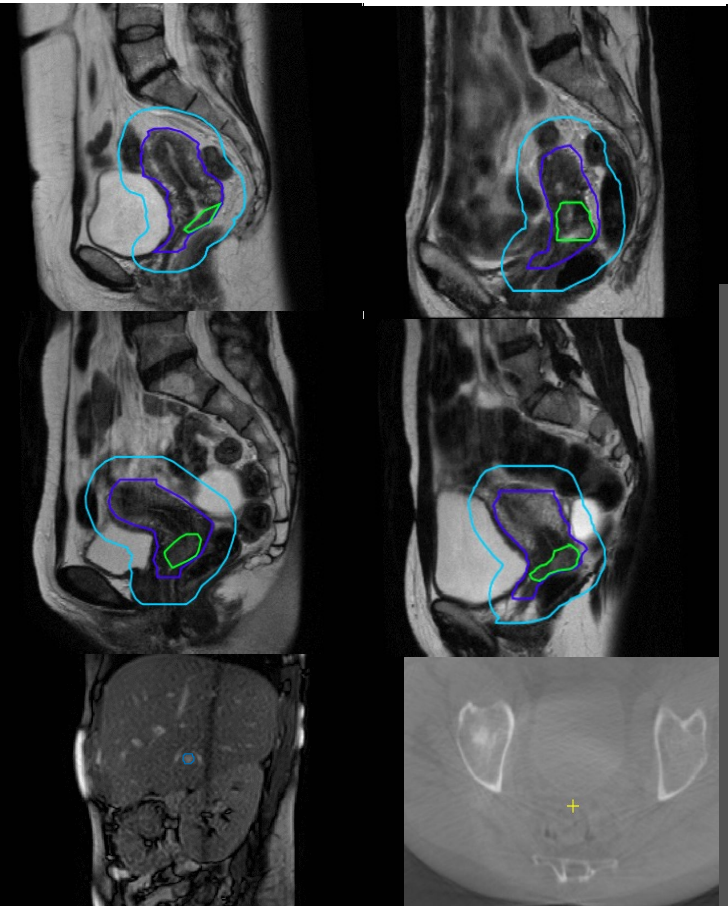


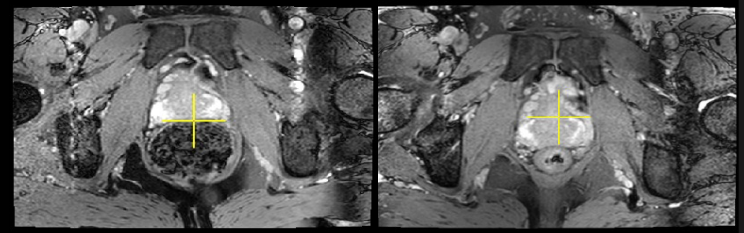


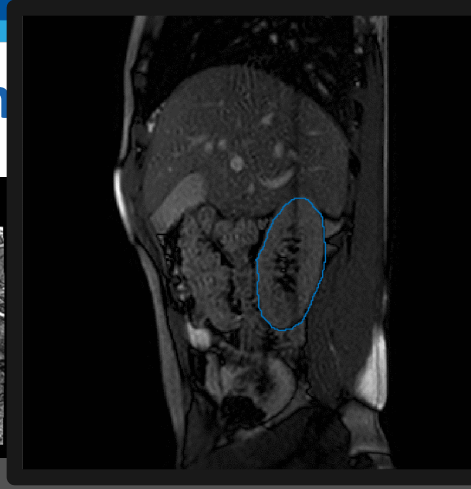
1. MRI: superior soft tissue contract



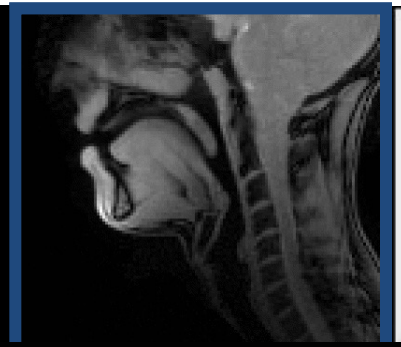
2. Uncertainty in visualization and day to day position

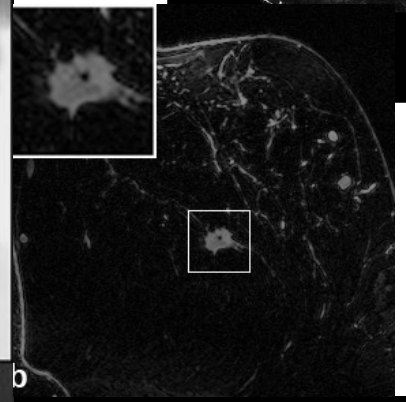


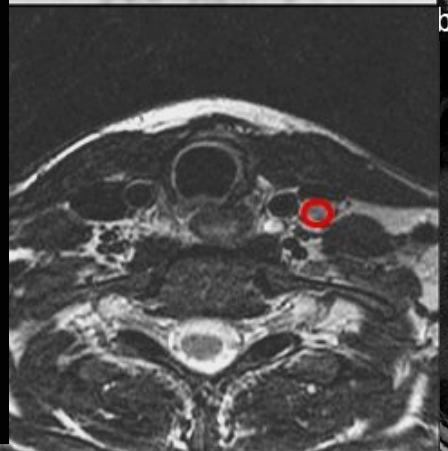


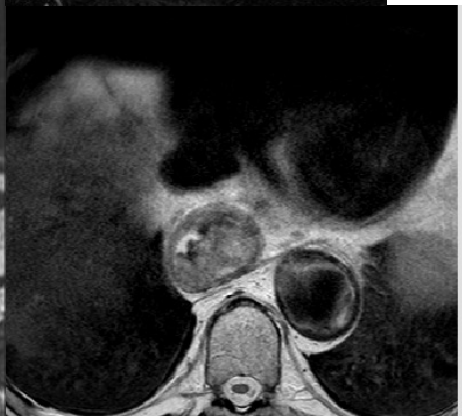


3. MRI guided Radiotherapy, see what you treat









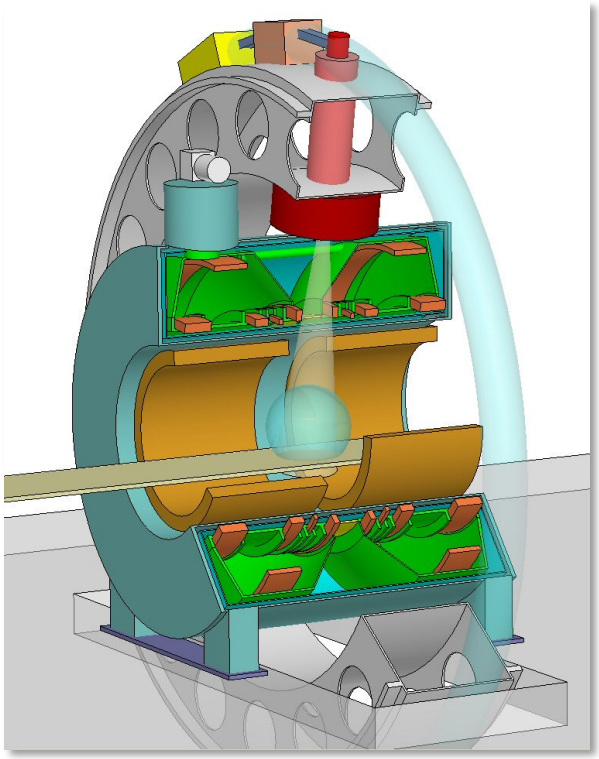
1998 Discussion on optimal Radiotherapy

- Knowing the exact location of the tumour:
  - (Bulky) primary tumour
  - Tumour infiltrations
  - Involved lymph nodes, metastases
- Knowing the tumour characteristics, radiation sensitivity
- Knowing the organs at risk for radiation damage
- **Being able to paint the radiation dose accordingly**
- Being able to see the treatment response, response assessment

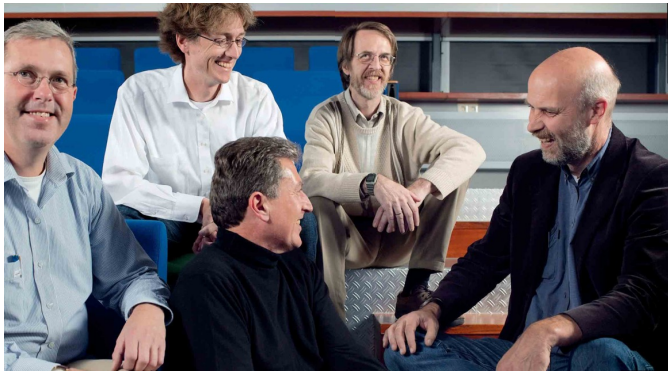
Brahme and Agren, 1987
Webb and Nahum, 1993
Lagendijk and Hofman, 1999
Thames et al., 1992
Goitein et al., 1996
Ling et al. 2000

UMCU solution: Integrating a Philips MRI scanner with a Elekta radiotherapy accelerator

MR linac system: combination 1.5T MRI and 7MV accelerator



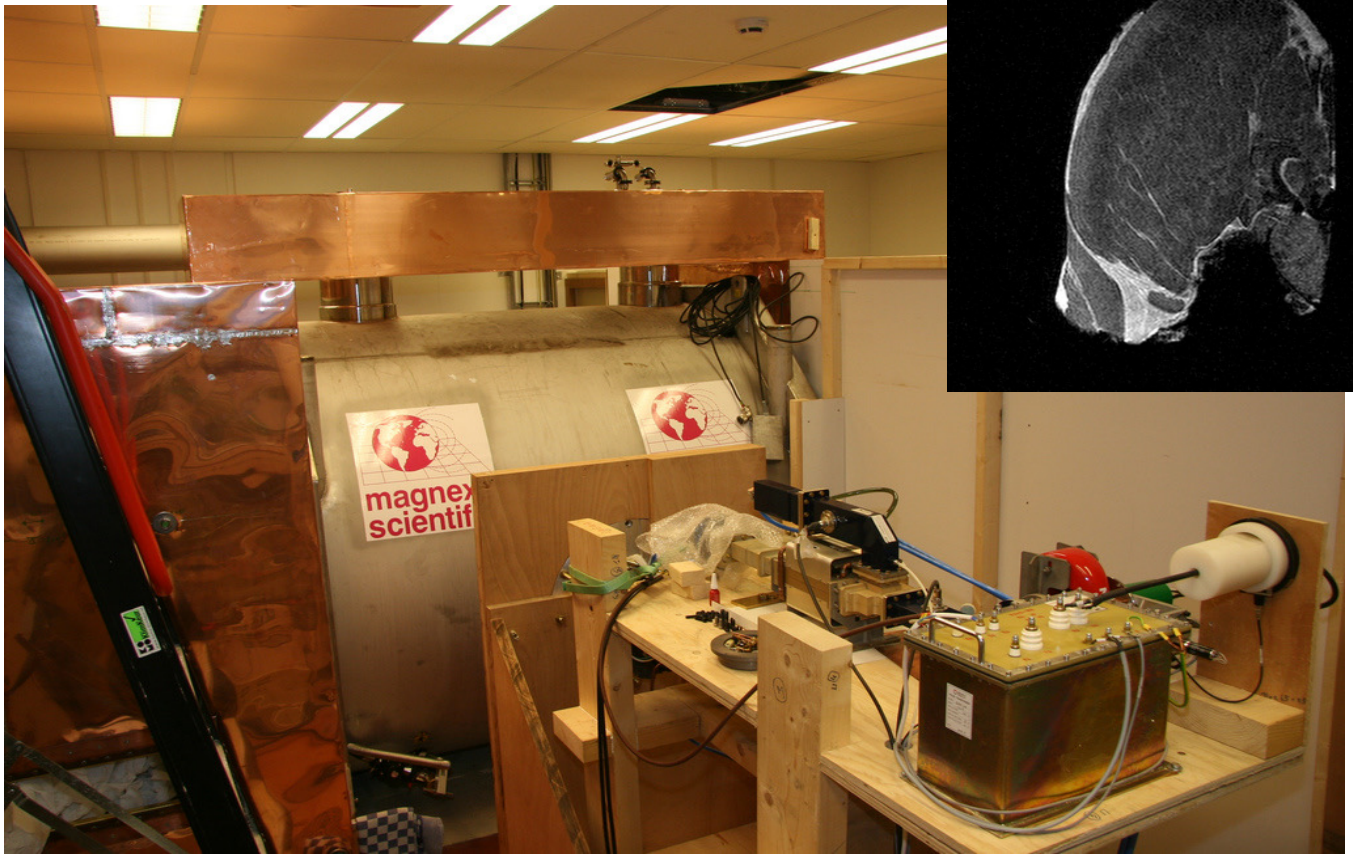
Design

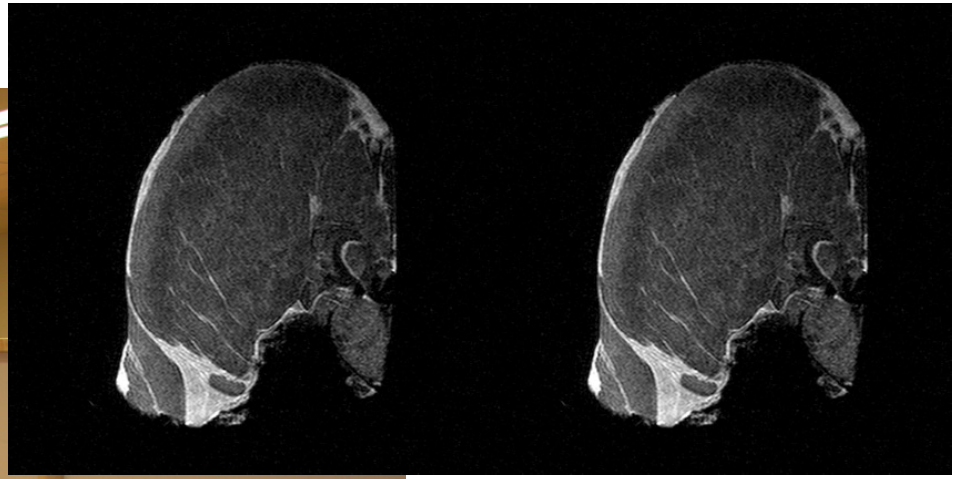


Design team MR-linac: UMCU, Elekta, Philips

Active shielding, decoupling MRI and linac

2009 MRL ‘proof of principle’





Beam-on – Beam-off

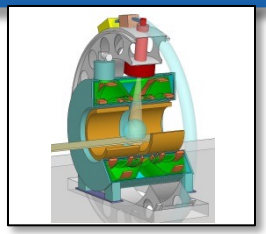
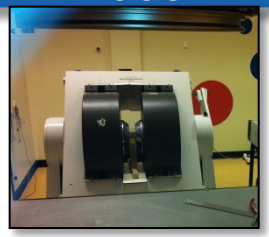
STW
connecting innovators

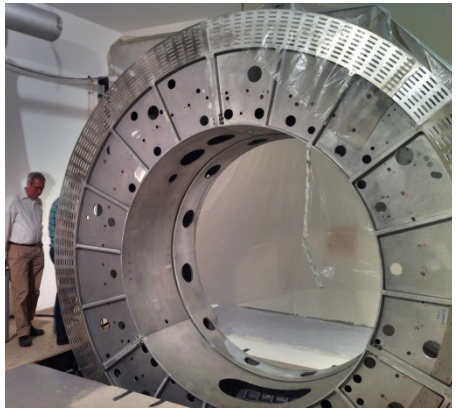
PHILIPS

Elekta

UMC Utrecht

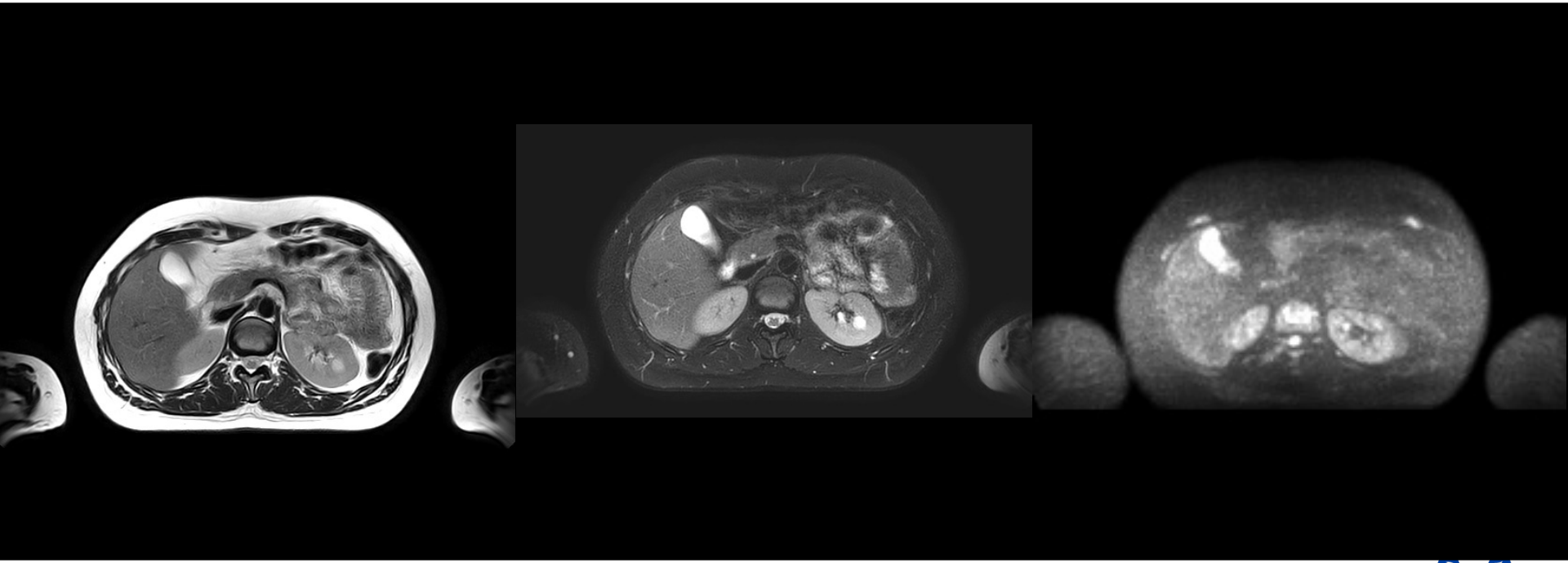
MR Linac development timeline

1999	2004	2005	2009	2012	2014	2018
MRI guided radiotherapy: a MRI based linear accelerator Lagendijk JJW and Bakker CJG 2000 Proc. ESTRO Istanbul 19th Annual Meeting Rad Onc vol 56, suppl. 1, pp S1–S255						
invention	design	Initial exp.	1st prototype	2nd prototype	3rd prototype	Clinical



Jan Lagendijk, Breur Award ESTRO 2022

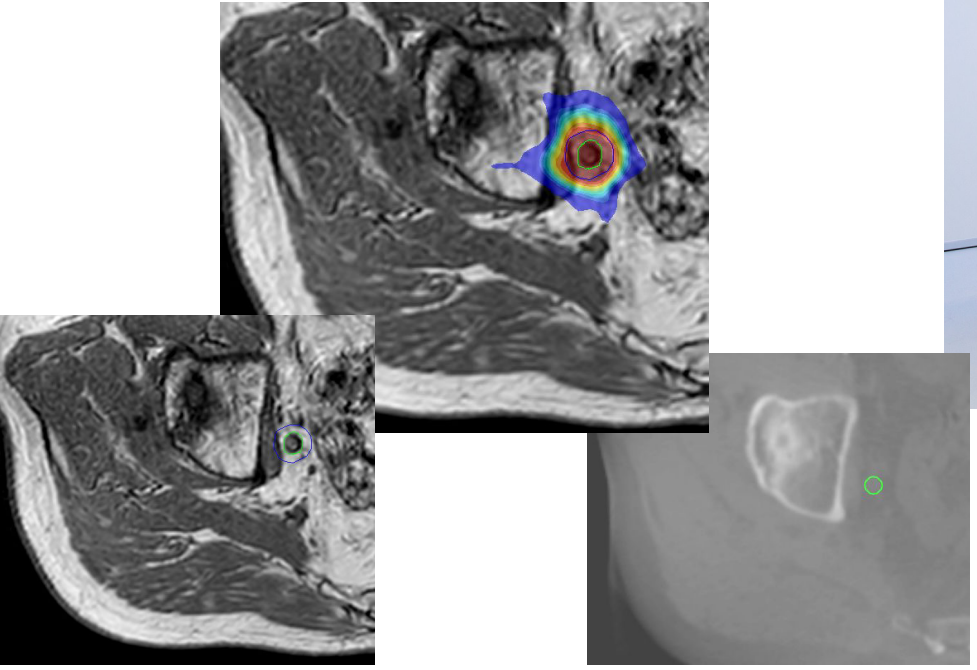
Volunteer imaging on MRL: Motion robust abdomen T2 TSE MultiVane, SPAIR and DWI



Courtesy Mariëlle Philippens, Eveline Alberts

CE certification and start clinical studies

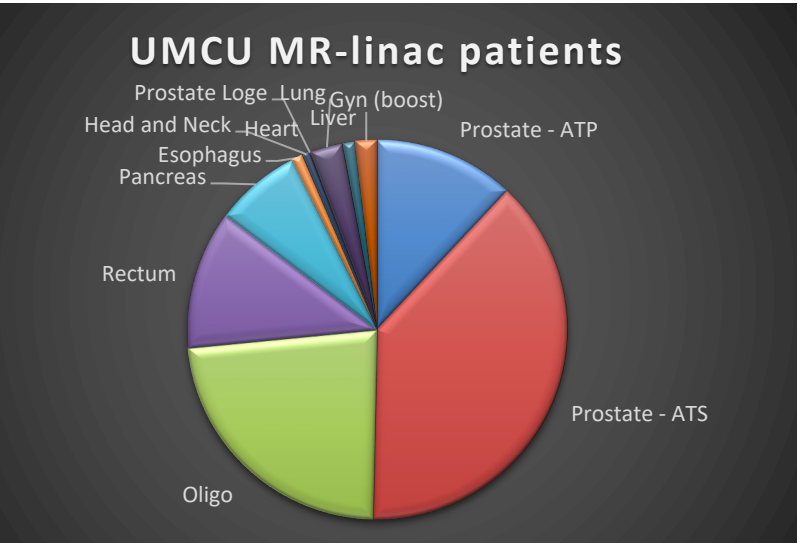
First regular patient treated August 13, 2018 (five fractions lymph node metastasis prostate cancer, SBRT 5x7Gy)

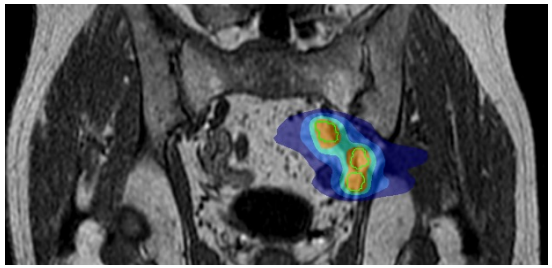


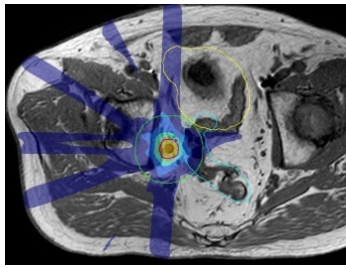
Werensteijn-Honingh et al. 2019

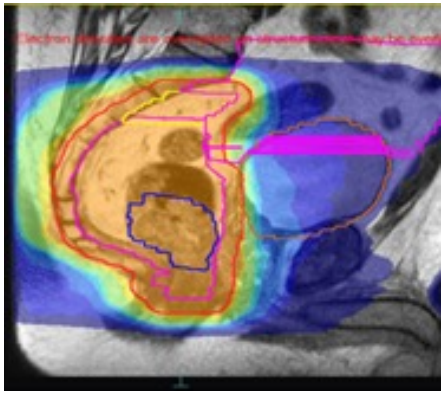
Status Unity UMC Utrecht

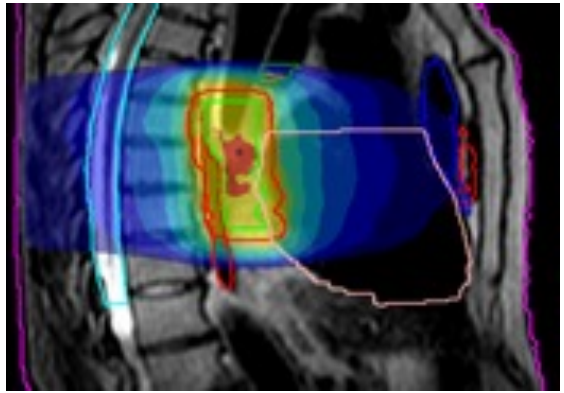
- So far >1500 patients treated
- Three system in the clinic
- Focus on hypo-fractionated treatments (prostate, oligo and rectum)
  - Oligo lymph nodes, single and multiple, SBRT 5x7/3x10Gy
  - Rectal cancer pre-operative, 5x5Gy
  - Esophageal cancer palliation, 5x4Gy
  - Prostate low/intermediate risk, 5x7.25Gy
- All patient on-line treatment planning











International MR-linac consortium

MRI-linac consortium founding members are:

- UMC Utrecht, The Netherlands
- MD Anderson Cancer Center, U.S.A.
- Institute of Cancer Research / Royal Marsden Hospital, U.K.
- Christie NHS, U.K.
- The Froedtert & Medical College Wisconsin, U.S.A.
- Netherlands Cancer Institute - AvL, The Netherlands
- Sunnybrook Hospital, Canada

Over 60 New members (a.o):

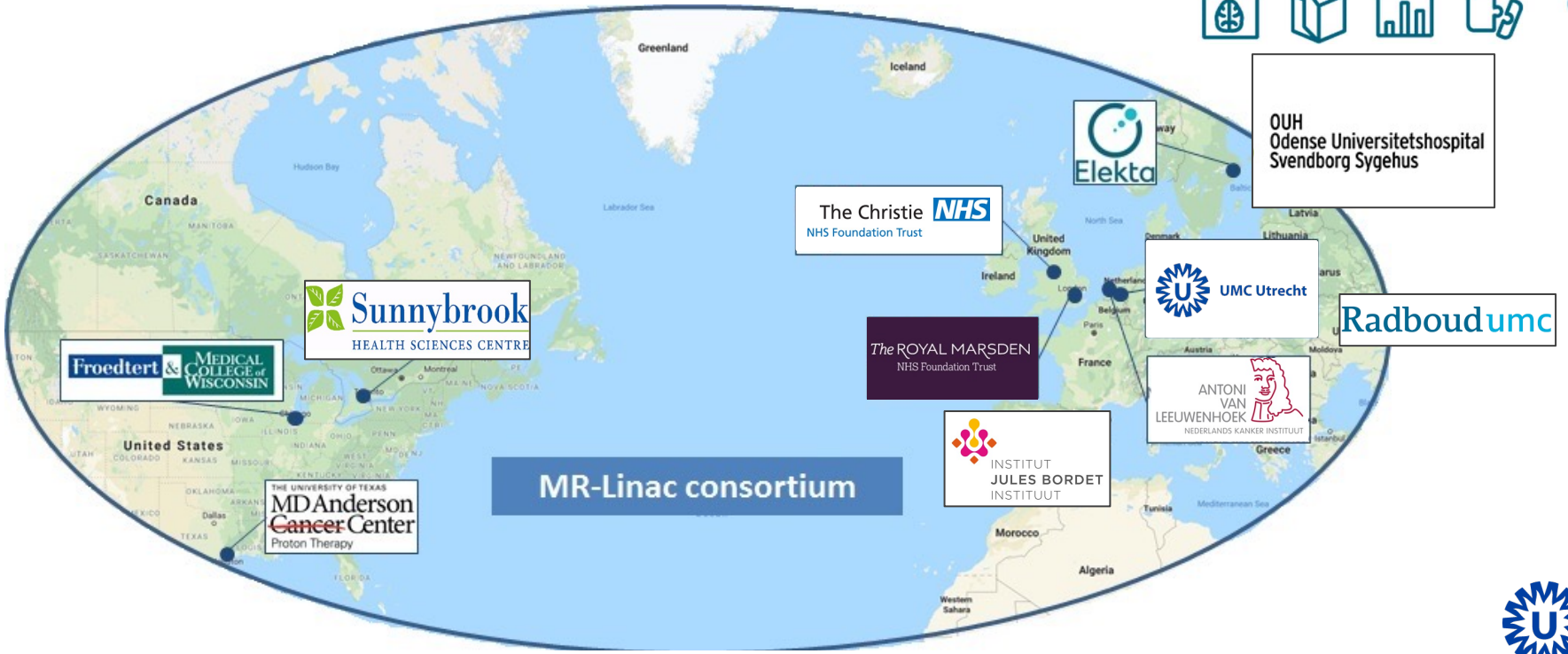
- Chiba University, Japan
- Edogawa Hospital, Japan
- Memorial Sloan Kettering Cancer Center, USA
- Odense University Hospital, Denmark
- Osaka City University, Japan
- Princess Margaret Cancer Center, Canada
- Tubingen University Hospital, Germany
- William Beaumont Hospital, USA
- Uppsala University Hospital, Sweden

Clinical studies:

- Optimization tumour control and avoidance of surgery
  - Hypo-fractionated prostate
  - Rectal cancer boost
  - Primary breast tumours, ablative
  - Primary lung tumours, ablative
  - Oesophageal tumours
  - Pancreas tumours
  - MEN1 tumours, ablative
  - Head and neck tumours
  - Cervix tumours
  - Oligometastases, ablative
  - Liver tumours, ablative
  - Kidney tumours, ablative

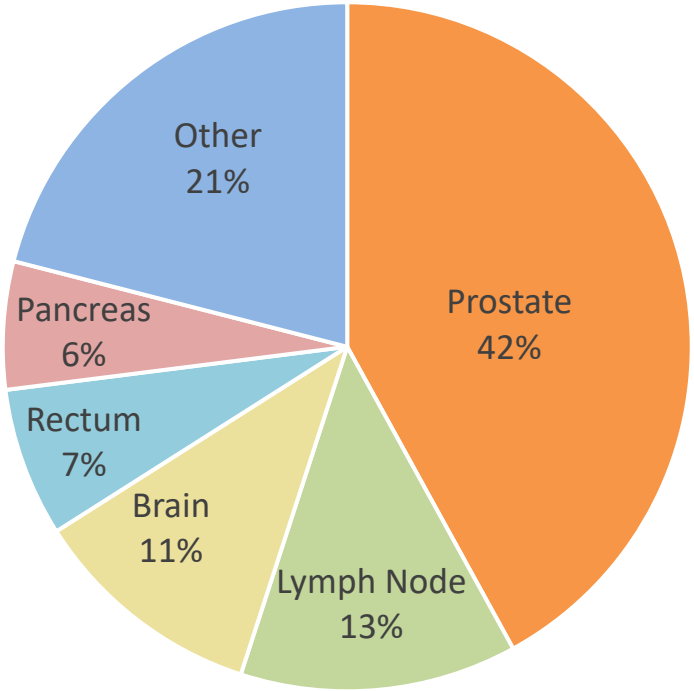
The Momentum Study

Lenny Verkooijen



Safety

1795 patients

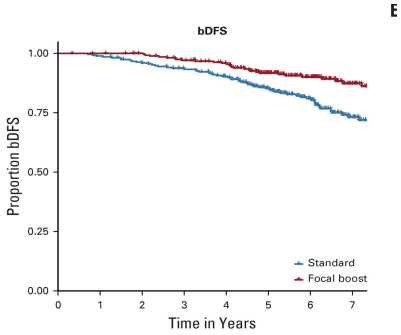


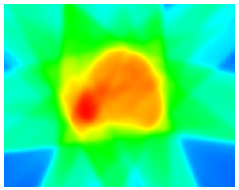
Acute severe toxicity in relation to MRL	N (%)
Grade 3	
Unrelated	85 (5)
Possibly related	9 (0.5)
Related	15 (0.9)
Grade 4	
Unrelated	2
(Possibly) related	0
Grade 5	
Unrelated to MRL	1
(Possibly) related	0

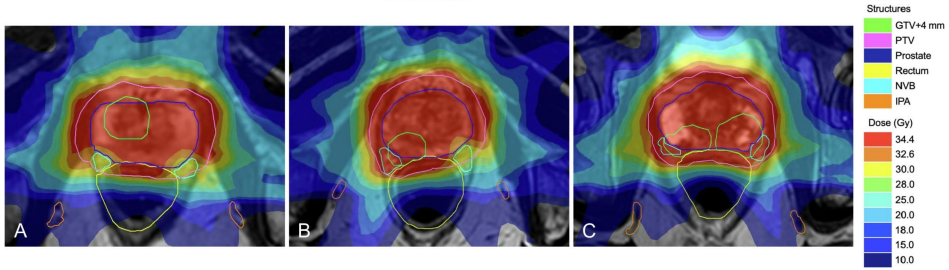
Lenny Verkooijen

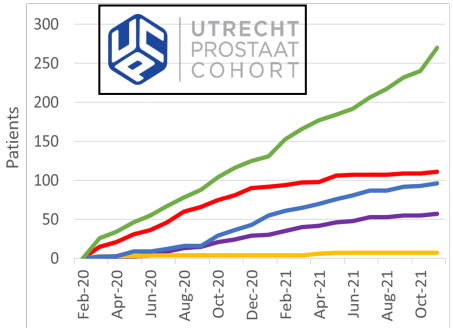
Example: MRgRT Prostate studies

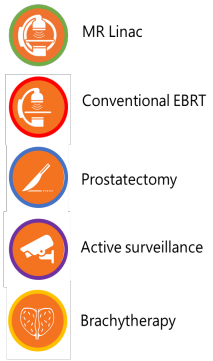
- Dose escalation (Flame) being transferred to the MR-linac (Kerkmeijer et al. J Clin Oncol 2021)
- Erectile function preservation (ERECT trial) (clinicaltrials.gov)
- Intra-fraction re-optimization (margin reduction), ATS followed by multiple ATP's intra-fraction. Hypo in subfractions
- Utrecht Prostate Cohort (UPC) study (clinicaltrials.gov)











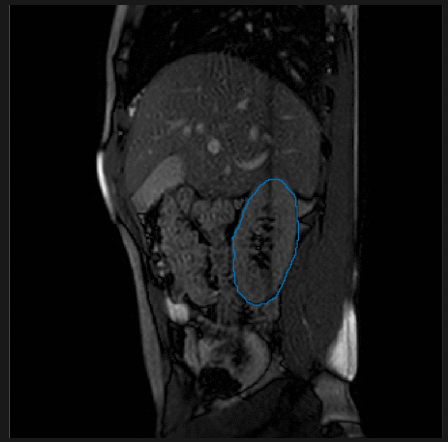
At the UMCU we are developing: Real-time motion tracking & dose accumulation

Patient-ID: 00900 name: F. Ictitious real-time MR-Linac tracking tumor-site: kidney

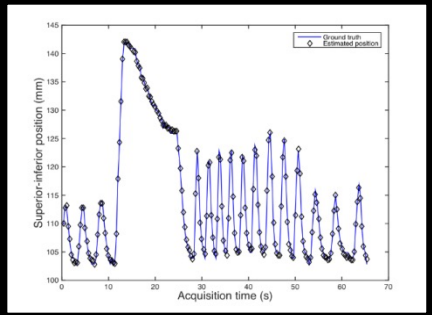
Tracking is ON

Beam is ON

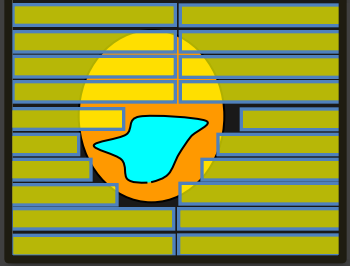
Real-time imaging



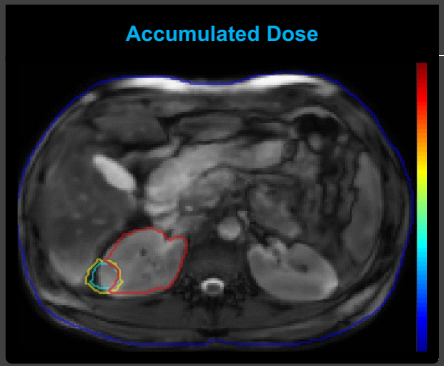
Motion history



Beam's eye view



Accumulated Dose

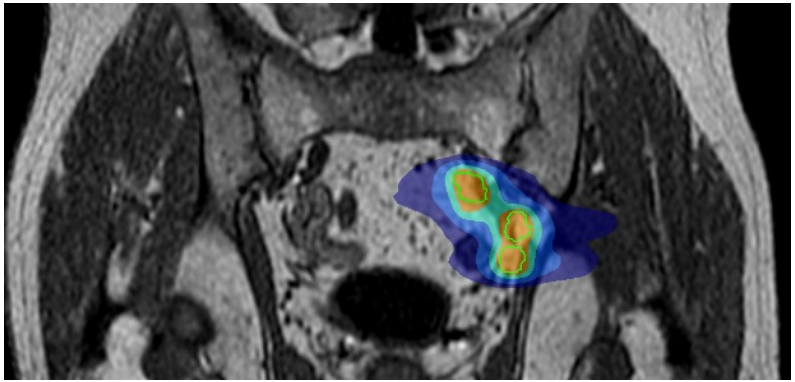


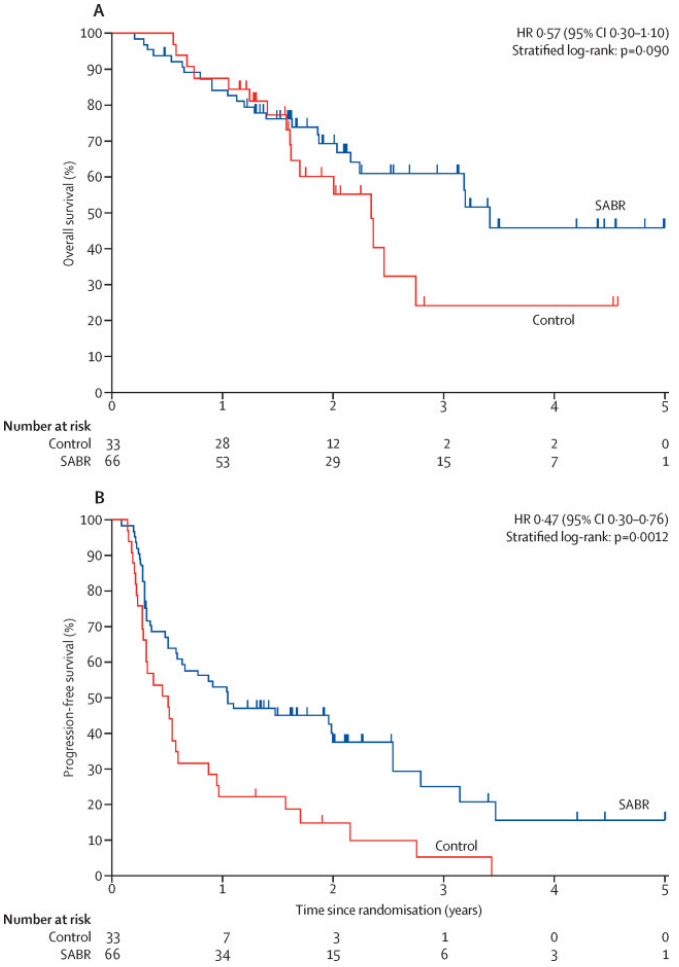
offsets	
FH:	1.0mm
RL:	0.5mm
AP:	0.2mm
resp:	3.2mm

Ao: Huttinga et al. IEEE TMI, 2022
Terpstra et al. PMB 2021
Kontaxis et al. phiRO 2020

MR-Linac for metastatic disease: Potential breakthrough technology

- Oligo-metastases (Palma et al. 2019, Lancet)

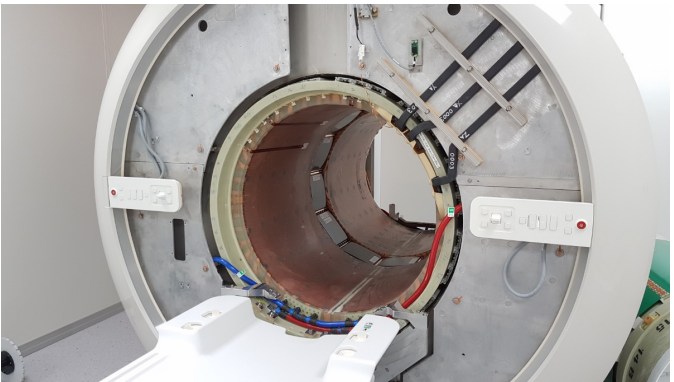


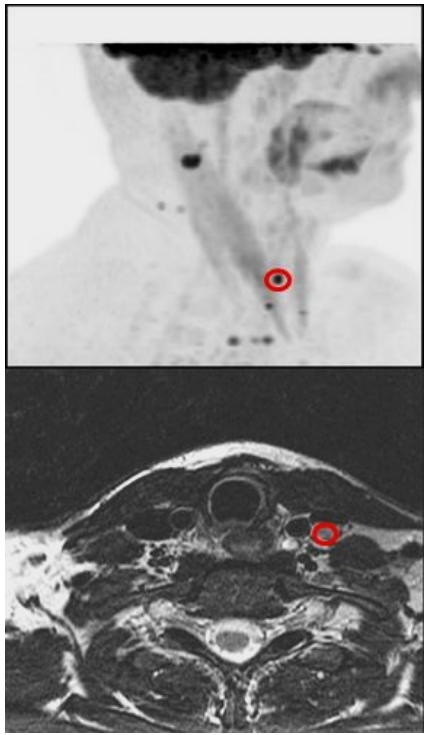


Poly-metastases: Bauman et al., Arrest trial, BMC Cancer 2021

Development MRI/PET → Unity MR-linac pipeline
Wide bore 1.5T MRI/PET RT simulator

- Intrinsic registration between MRI and PET
- Use of MRI based motion registration in the PET reconstruction (search for small tumours)
- Common platform Unity and MRI/PET
- Alternative for the RefleXion system





GE MRI/PET, courtesy Zackrisson, Nyholm, et al. Umeå

Impact MR-linac

Impact on patients:

- Less normal tissue involvement, less toxicity
- Better/higher tumour dose and thus better tumour control
- ‘See what you treat’ results in treatment optimization
- Dose accumulation, response assessment and functional

- ‘**Surgery without a knife**’, less surgery

Acknowledgements UMC Utrecht MR-linac project

Over 70 PhD students

All UMC Utrecht RT staff members

Special thanks to the Utrecht team

Jan Lagendijk

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Chrit Moonen

Marnix Lam

Dennis Klomp

Willem Mali

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