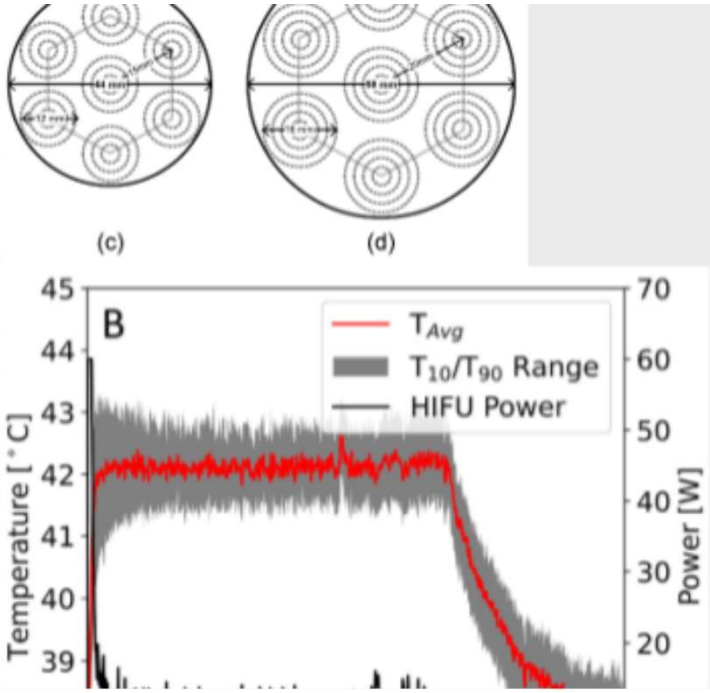


Clinical application of ultrasound for hyperthermia

Roel Deckers

UMC Utrecht

Imaging & Oncology Division

Ultrasound vs. Electromagnetic waves

Ultrasound

Advantages
- Small focal spot (~mm)
- Electronic beam steering
- Real-time (feedback) control through image-guidance

Disadvantages
- Presence of bone and air cause difficulties

Electromagnetic waves

Advantages
- Heat large tumor volumes (~cm)
- Clinically applied

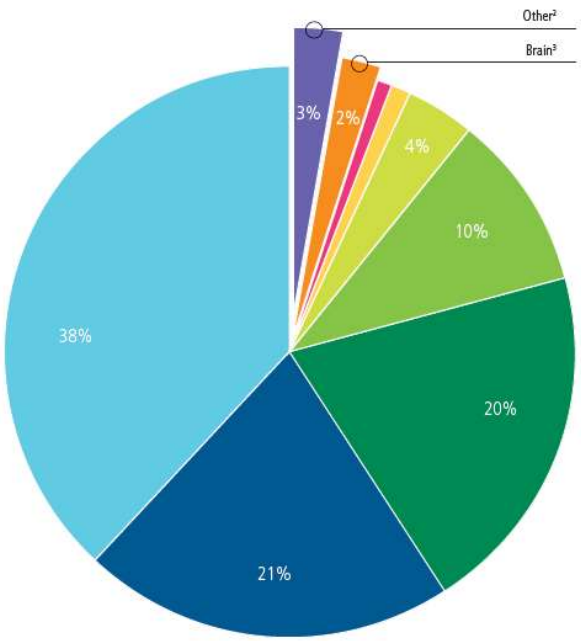
Disadvantages
- Limited capacity for the compensation of inhomogeneous heating rates and local heat sinks
- Temperature control is achieved via a-priori treat planning
- Monitoring based on thermocouples

Patient HIFU treatments by indication

Cumulative

467,162 total treatments[1]

Uterine fibroids	179,250	38%
Liver tumors	98,014	21%
Prostate diseases	92,625	20%
Pancreatic tumors	46,246	10%
Uterine adenomyosis	17,717	4%
Other[2]	13,154	3%
Brain[3]	8,417	2%
Glaucoma	6,179	1%
Cancer, unspecified	5,560	1%

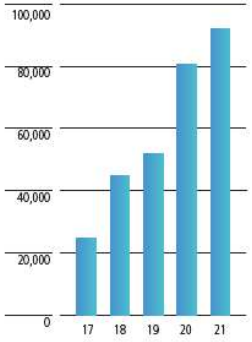


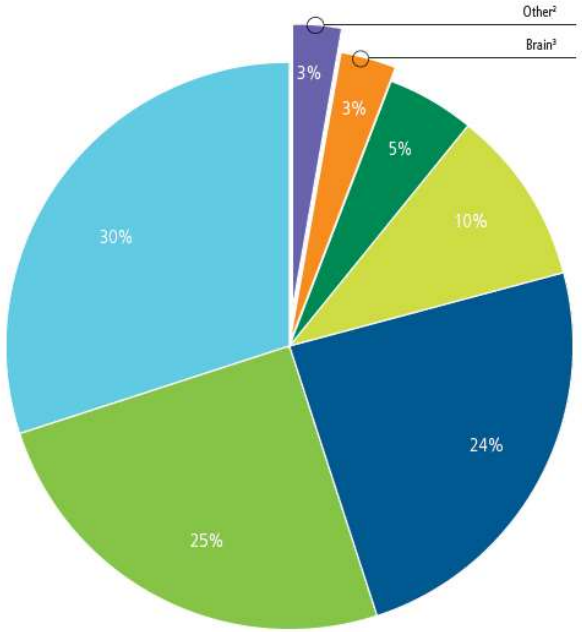
2021

92,365 total treatments[1]

Uterine fibroids	27,613	30%
Pancreatic tumors	23,523	25%
Liver tumors	22,325	24%
Uterine adenomyosis	9,147	10%
Prostate diseases	4,334	5%
Brain[3]	2,906	3%
Other[2]	2,502	3%
– Glaucoma	15	—
– Cancer, unspecified	—	—

Annual Patient Treatments





None of these applications is hyperthermia-related!

Source: https://www.fusfoundation.org/

Evolution of FUS for HT: 1st generation

Unfocused single element + single thermocouple

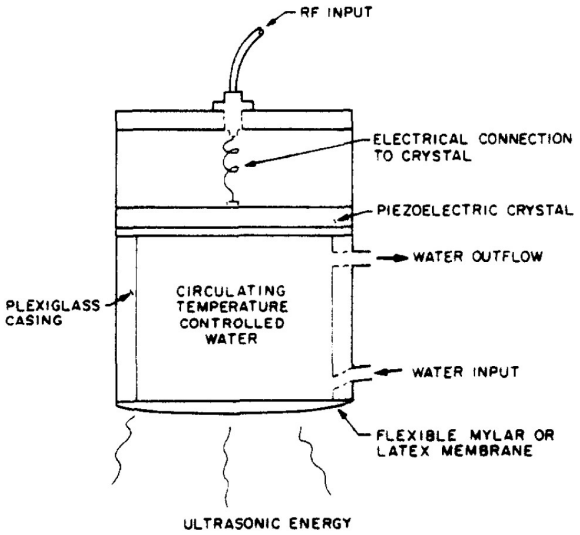


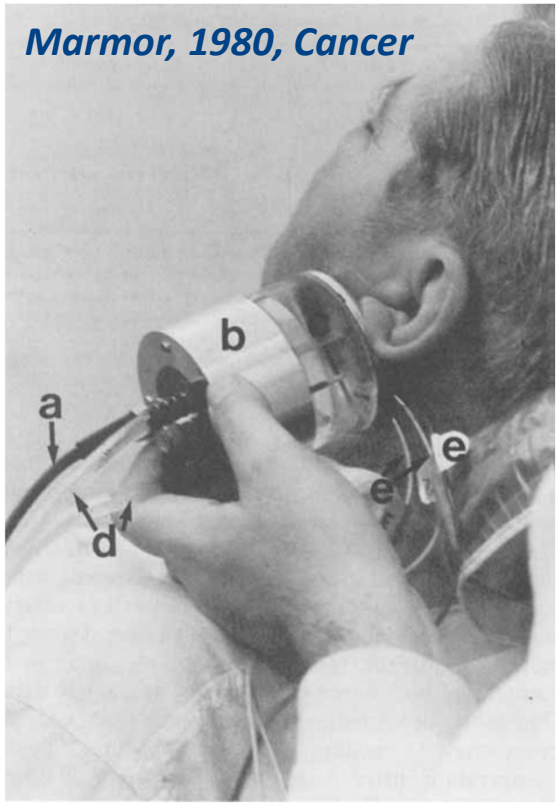
Fig. 1. Clinical ultrasound transducer and housing. Temperature of the circulating water was adjusted to control skin temperature by thermal diffusion. 2 cm and 4 cm field sizes were used.

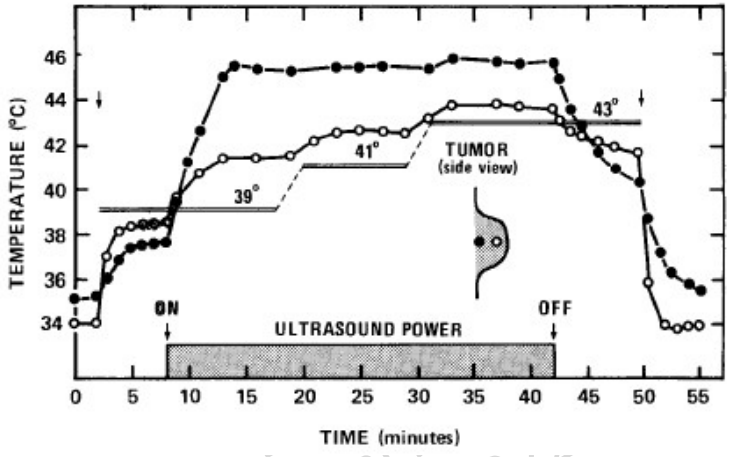
Marmor & Hahn 1978 IJROBP

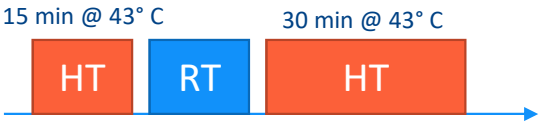
✓ Simple to construct and operate

✗ Lack of spatial and temporal control of the heating

Combined RT and HT in superficial human tumors







- 2 US transducers were used:
  - 2.05 MHz → 4 cm US field
  - 3.0 MHz → 2 cm US field
- Multiple thermocouples to monitor temperature
- 15 patients with multiple superficial metastatic tumors
- Each patient's own tumor was used as a control
- 7 of 15 patients had an improved response in the tumor that received hyperthermia with irradiation

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US-induced HT for the treatment of human superficial tumors

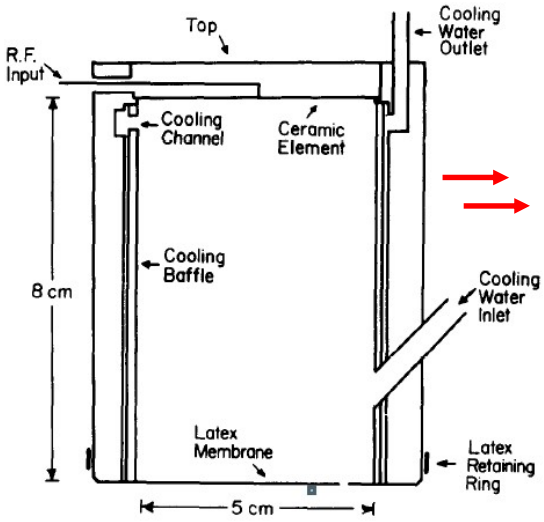

Table 2. Tumor responses to local ultrasound hyperthermia

Diagnosis	Evaluable patients	Partial responses	Complete responses
Melanoma	10	3	2
Sarcoma	7	4	1
Squamous cell carcinoma			
Head and neck	3	2	1
Lung	2	0	0
Adenocarcinoma			
Lung	2	0	0
Breast	3	2	1
Renal	1	0	0
Total	28	11	5
Percent responses		39	18

- 3 US transducers were used:
  - f = 1-3 MHz
  - Diameter = 2.5, 3.75 and 5 cm
- Multiple thermocouples to monitor temperature (in 14 pts)
- 28 patients with recurrent or metastatic disease
- Temperatures ranging from 43° to 50° C

Corry, 1982, IJROBP

Table 3. Responses by treatment temperature

Temperature range	No. evaluable patients	(Responses) No. PR	No. CR	% (CR + PR)	Response duration (days) Median	Range
43–44°C	15	6	2	53	29	14–60
45–47°C	7	3	0	42	46	21–60
48–50°C	6	3	2	83	250	200–340+

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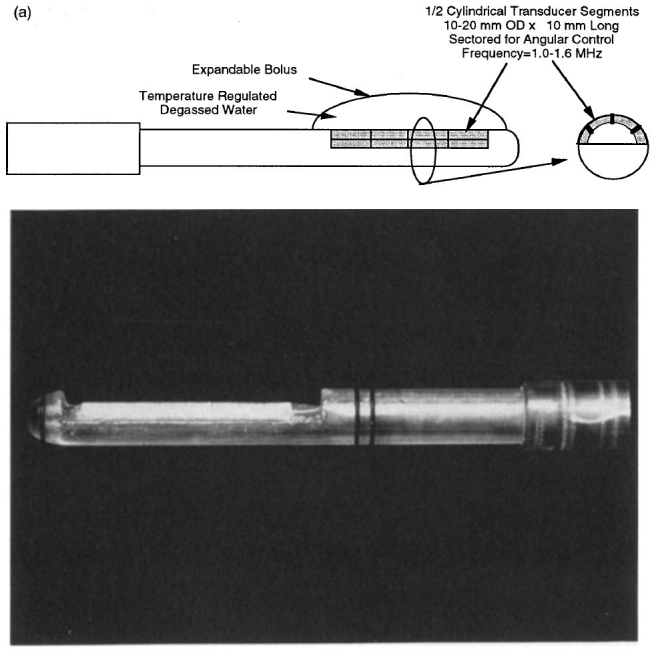
Transrectal ultrasound hyperthermia (TRUSH)

Intracavitary ultrasound devices for transrectal application of prostate hyperthermia



Publication	Clinical studies
Diederich, 1990, Med Phys	Design & development of multielement intracavitary US applicator
Fosmire, 1993, IJROBP	Phase I feasibility & safety study in 14 patients
Algan, 2000, Cancer	Phase I/II study; HT + RT; 26 patients
Hurwitz, 2002, IJROBP	Phase II study; HT + RT; 30 patients
Hurwitz, 2005, IJH	Phase II study, HT +RT, 37 patients
Hurwitz, 2011, Cancer	Long-term results of Hurwitz, 2005

- Safe, feasible, favorable toxicity profile
- Therapeutic temperatures achieved
- Disease free survival at 2 y was significantly improved (84% vs 64%)

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State-of-the-art FUS prostate systems

There are four focused ultrasound manufacturers that are approved in the US for the ablation (destruction) of prostate tissue:

Sonablate Corp.

TULSA-PRO, Profound Medical

Exablate® Prostate system, Insightec

Focal one, EDAP-TMS

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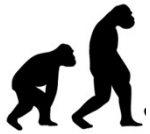
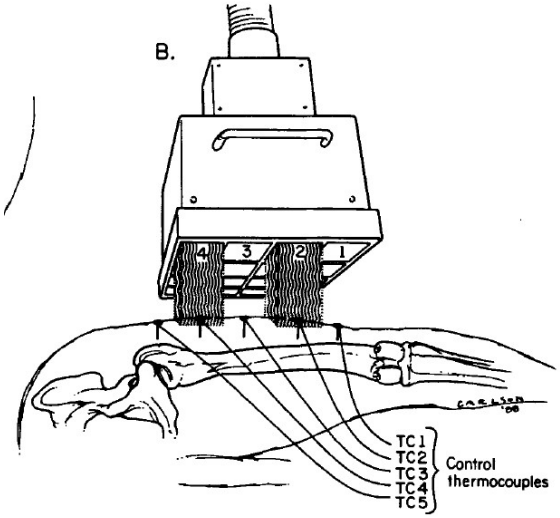
No hyperthermia studies performed with these systems!

Technically feasible: Salgaonkar, 2014, Med Phys

Evolution of FUS for HT: 2nd generation

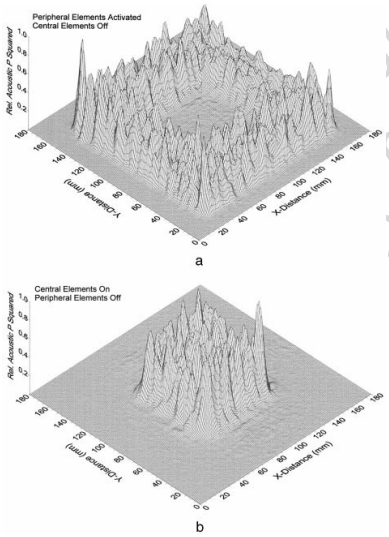


Separately controllable stationary transducer arrays + multiple thermometers

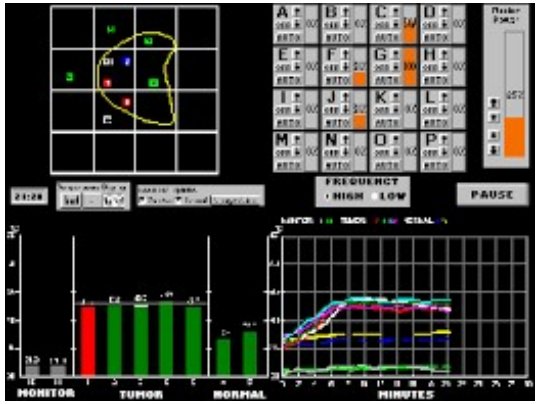


Ogilvie et al. 1990 IJH

Sonotherm 1000



Diederich et al. 1999 UMB



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Clinical studies using Sonotherm 1000 system

Publication	Target site	Therapy	# patients	Outcome
Bornstein, IJROBP, 1993	Locally or regionally recurrent or advanced adenocarcinoma of the breast	Chemo + HT + RT	29 in total (13 US; 16 MW)	Overall complete response rate was 53%.
Myerson, IJH 1999	H&N (21), chest wall or breast (15), trunk (7), extremety (4)	RT + HT	44 patients with 47 lesions (28 US; 19 MW)	Complete and partial response rate were 51% and 17%
Xia, Int J Clin Oncol, 2001	H&N (15), breast (9), lung (8), esophagus (6), colorectal (6), STS (5), extremety (3), other (2)	RT + HT	54 patients	Complete and overall response rates were 32.6% and 78.8%,
Varma, IJH, 2012	Locally advanced breast cancer	RT + HT	57 patients	four (7%) with locoregional recurrence and 16 with distant failure

- Feasible and well tolerated
- No change in late toxicity
- Good response rates

→ Very mixed population
→ Phase I/II studies → no control group

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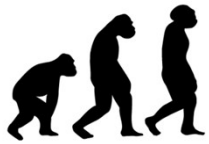
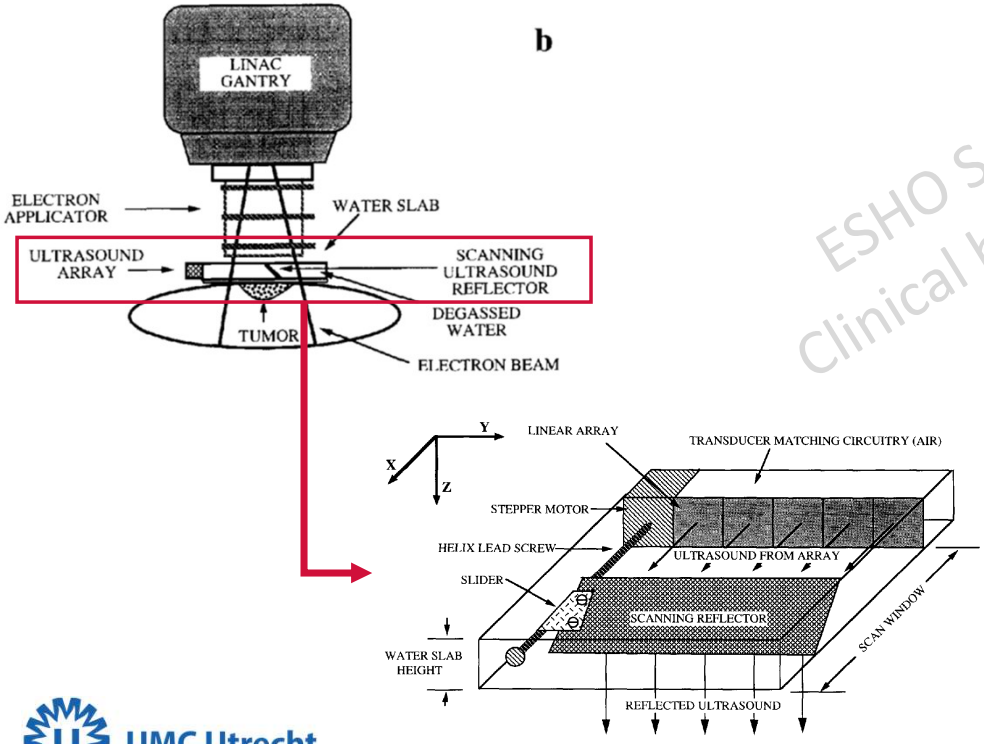
Evolution of FUS for HT: 3rd generation



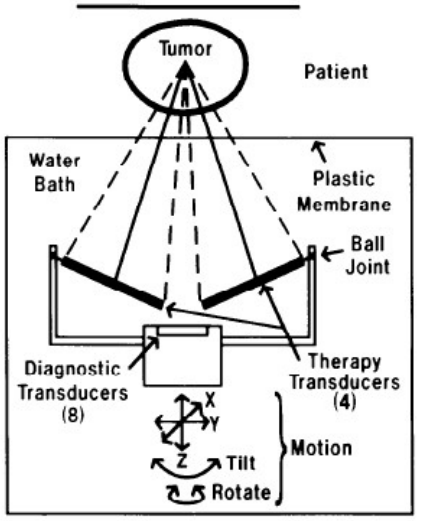
3rd generation: mechanical scanning of the ultrasound beams

The SURLAS system

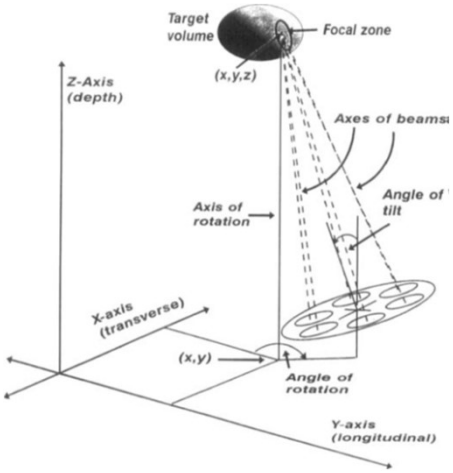


Moros et al. 1995 IJROBP

SFUS



Shimm et al. 1988 IJROBP



Hand et al., 1992, IJH

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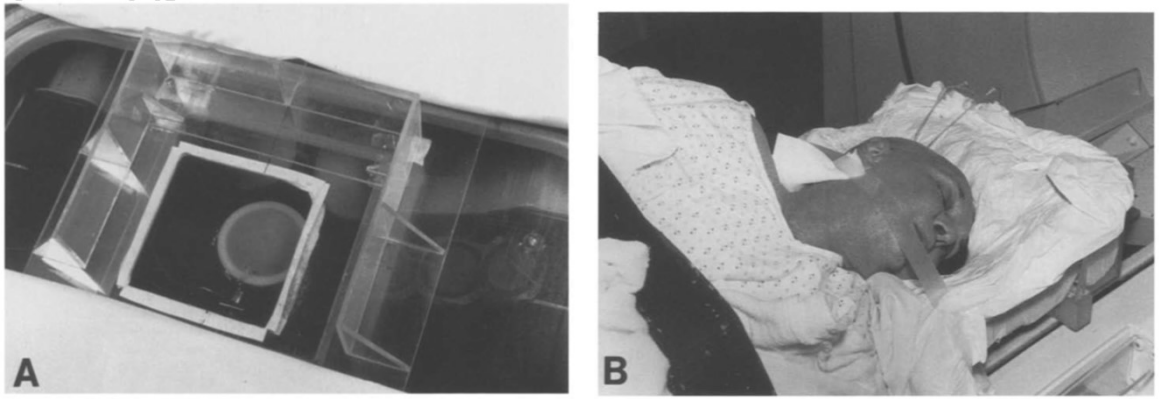
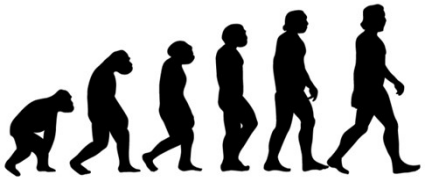
Clinical studies using SFUS

	Target site	Therapy	# patients
Harari, IJROBP, 1991	Pelvis (22), chest wall or breast (14), H&N (8), groin (8), axilla (7), extremity (5), abd wall (3), thorax (3), deep abd (1)	RT + HT	87 tumors in 71 patients
Guthkelch, J Neuro-Oncol, 1991	Brain tumors	HT + RT	15 patients



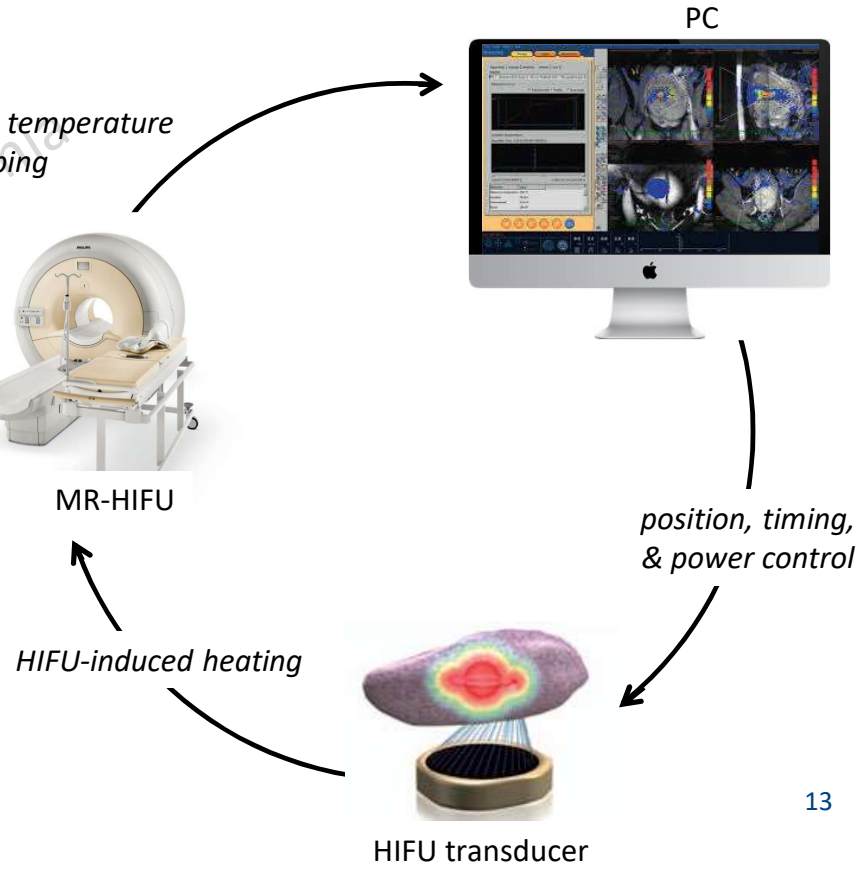
Evolution of FUS for HT: 4th generation



Focused ultrasound transducers that integrate mechanical scanning and electronic beam steering combined with MR imaging (**MR-guided HIFU**)

Profound Sonalleve

Insightec Exablate body



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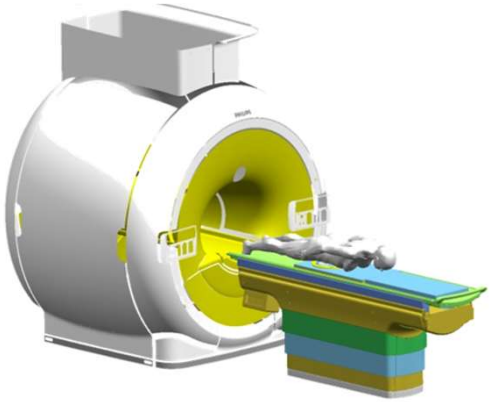
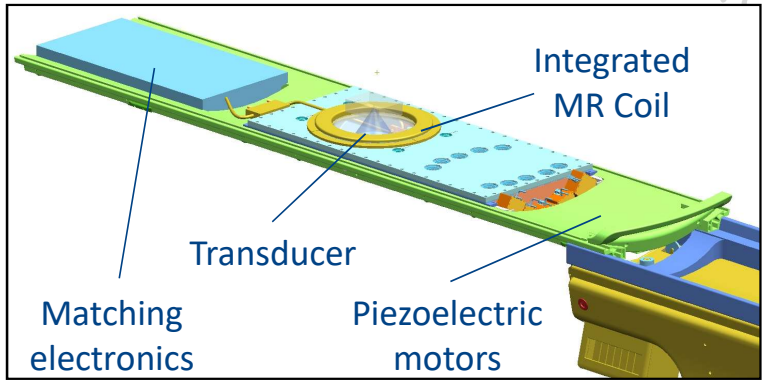
MR-guided HIFU induced hyperthermia

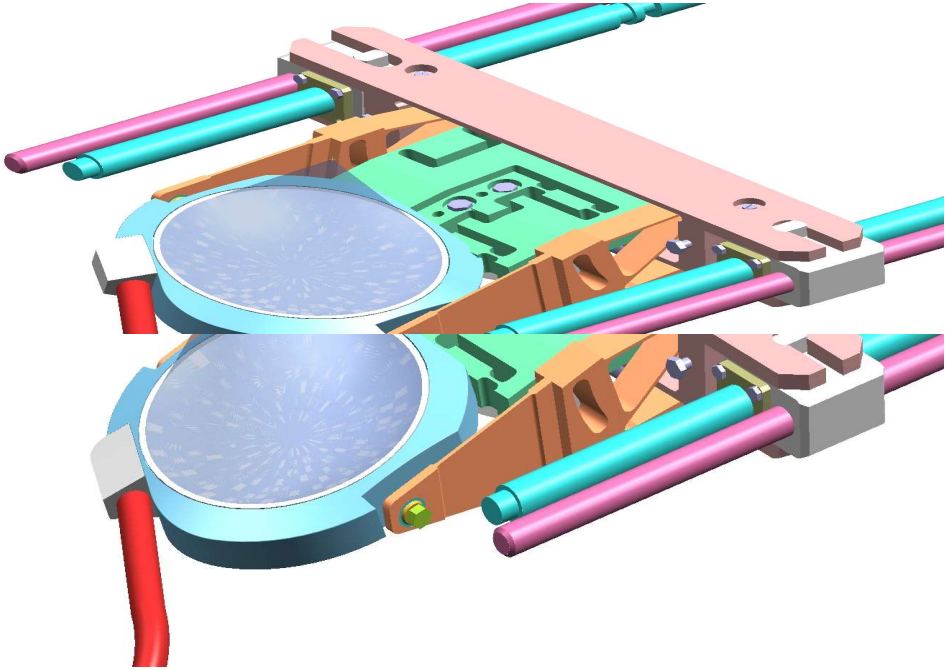
Technically challenging:

- Large volume → mechanical steering & near field heating
- Long duration → field drift & near field heating
- Narrow temperature range → control algorithm
- Large spatial variations in tissue energy absorption rate → control algorithm
- Large variations in cooling rate caused by blood flow → control algorithm

Mechanical steering

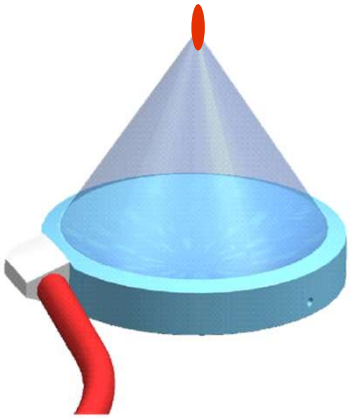


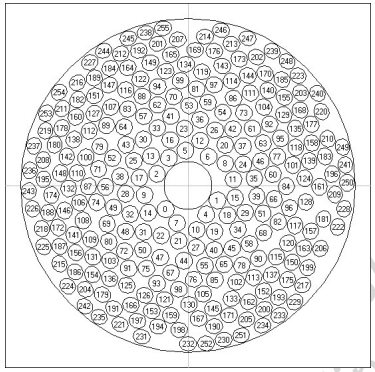




Electronic beam steering

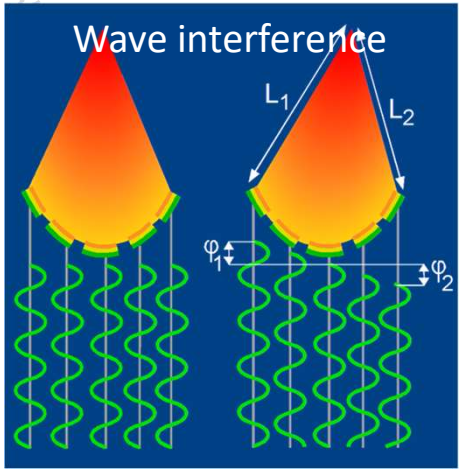
Focal spot size: 2×2×7 mm^3

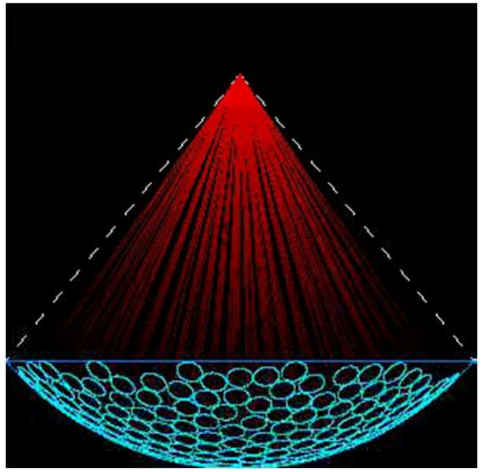




Phased-array transducer:

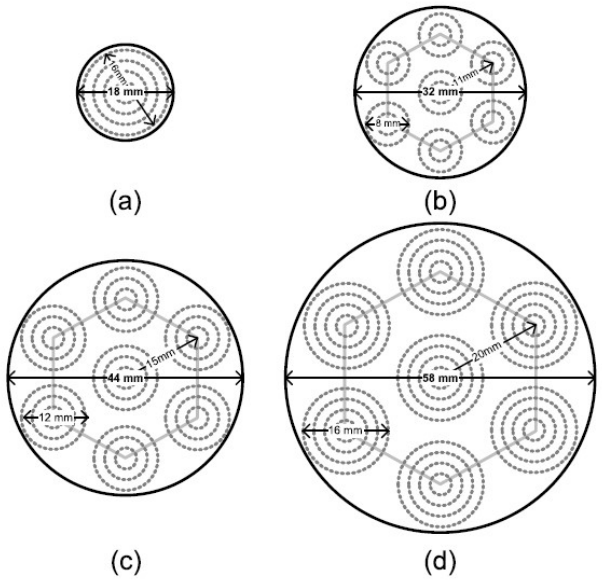
- 256 elements
- Electronic displacement along all directions (about ±2cm)
- Very fast electronic displacement position update < 10ms
- Allow to heat a large area without transducer displacement





$$\varphi_2 - \varphi_1 = 2\pi \frac{L_2 - L_1}{\lambda}$$

Mechanical + electronic steering

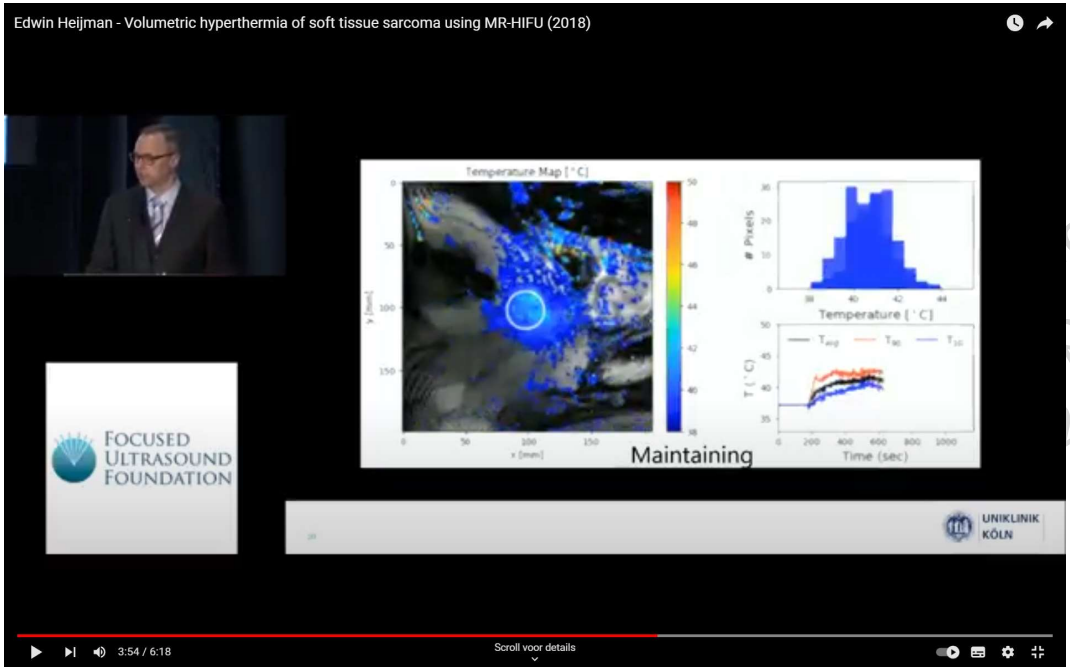


Tillander et al. 2016 Med Phys

- Cell sizes: 18, 32, 44, and 58 mm,
- Predefined set of electronic focus steering points and transducer positions
- Binary feedback algorithm for controlling heating

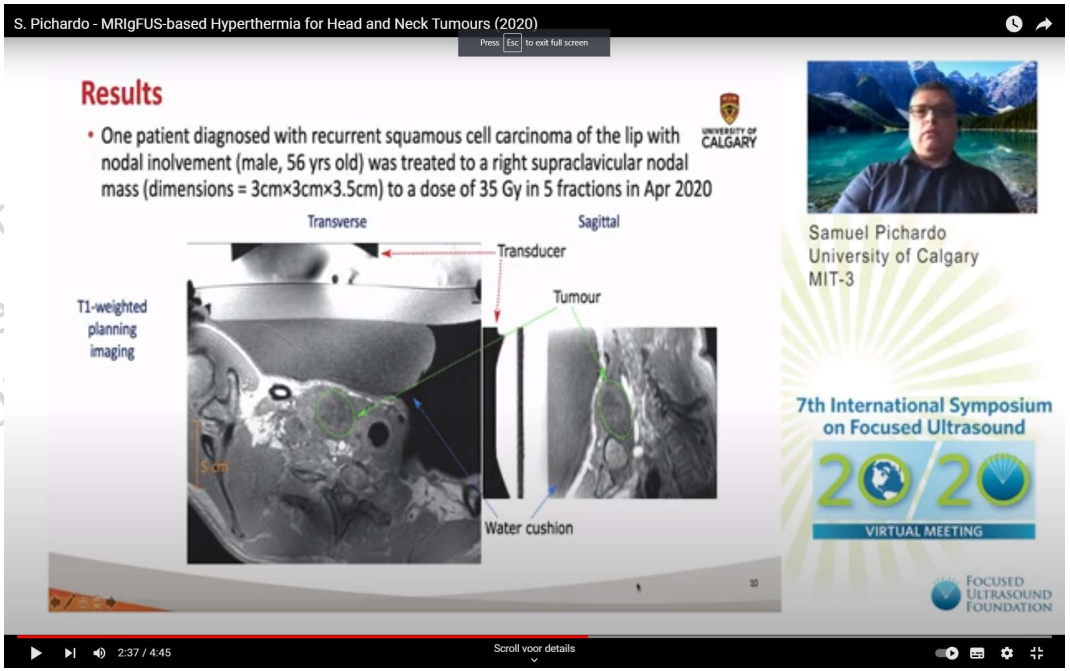
Clinical studies performed with G4 system

Liposarcoma



Heijman et al., FUSF symposium, 2018

Head and Neck tumor



Pichardo et al., FUSF symposium, 2020

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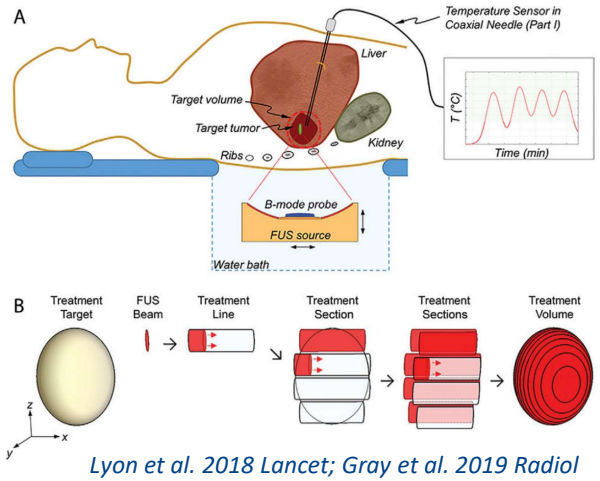
MRgHIFU hyperthermia + TSL

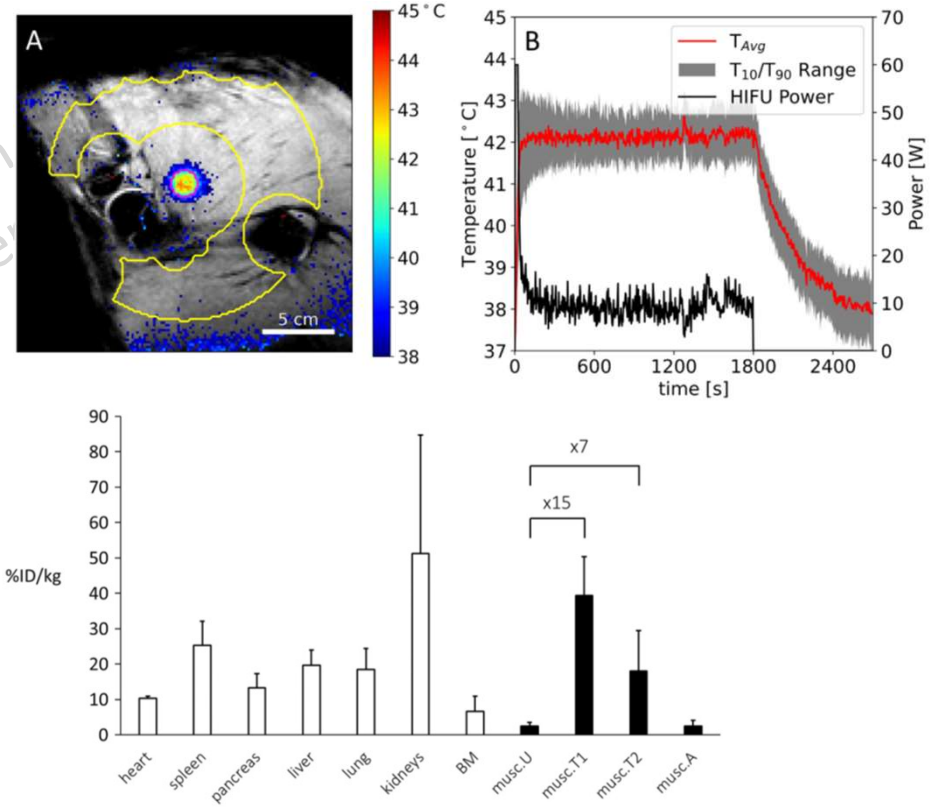
TARDOX-study



Lyon et al. 2018 Lancet; Gray et al. 2019 Radiol

- No MRI-guidance
- Avg. increase of 3.7 times in intratumoural biopsy doxorubicin concentrations
- Clinically feasible, safe, and able to enhance intratumoural drug delivery

MR-HIFU + $DPPG_2$-TSL in pigs



Sebeke et al. 2022 JCR

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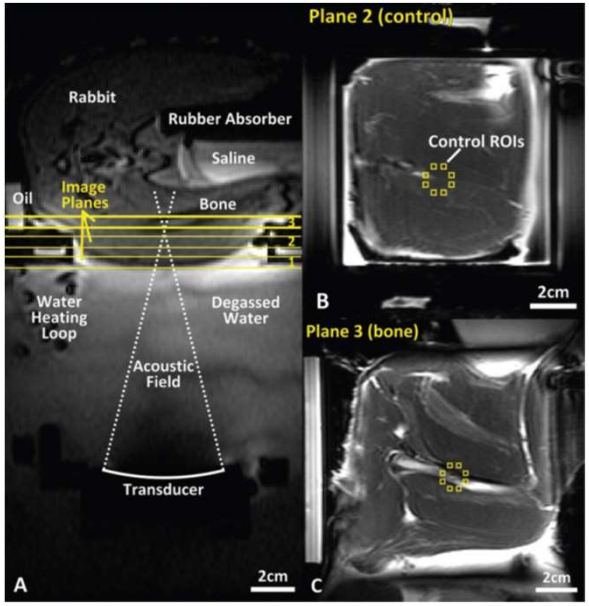
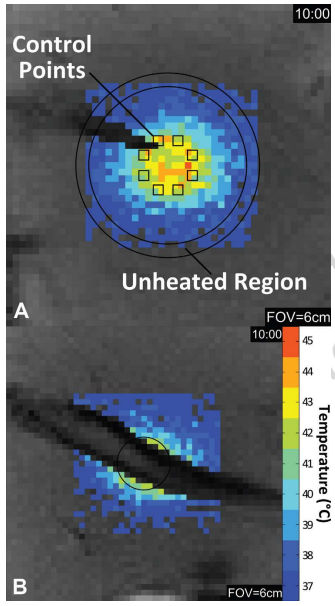
Treatment site feasible for HIFU?

	MR thermometry quality	Accessibility using MR-HIFU	HIFU ablation
Bladder	Kothapalli2018		?
Bone	Staruch2012; Guillemin2019	Bing2018	Yes, FDA approved
Breast	UMCU	UMCU	Yes
Cervix/ovary		Zhu2021; Giles2019	
Chest (wall)	Kothapalli2018; Bing2019		
Glioblastoma			
Head & neck			?
Limb	Kothapalli2018; Bing2019		
Liver			Yes
Lung			Case report in 2018
Melanoma			?
Neuroblastoma		Shim2016	
Pelvis	Bing2019		
Rectum	Chu2016	Chu2016	
Soft tissue sarcoma		Shim2016	Yes

Bone

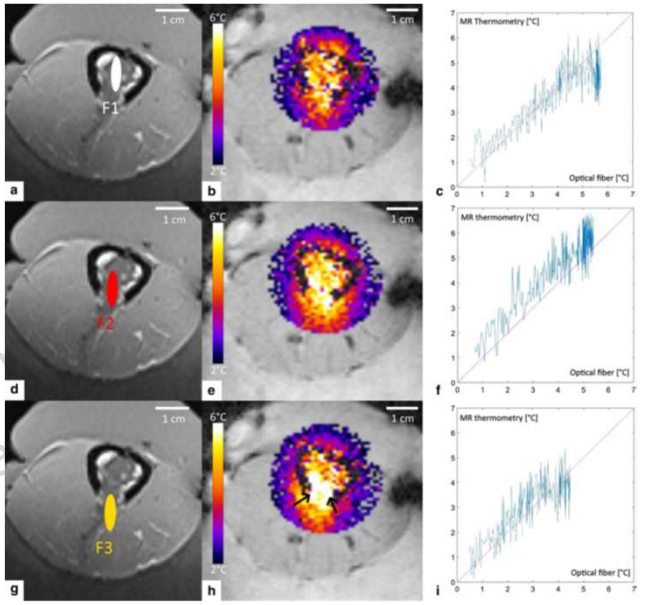
Problem: Temperature control in bone is difficult
Solution: MR thermometry at muscle bone interface + simulation



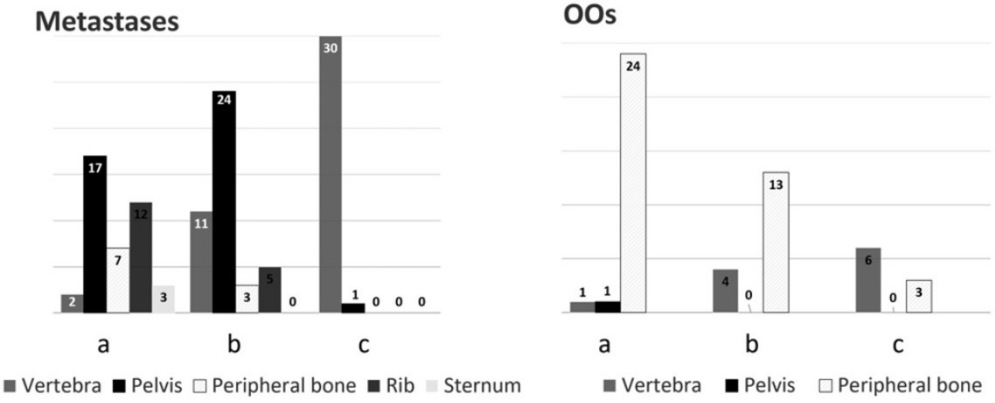


Staruch, 2012, Radiology

Positioning of the focal point is critical



Guillemin 2019, J Transl Med



Bing, 2018, Radiology

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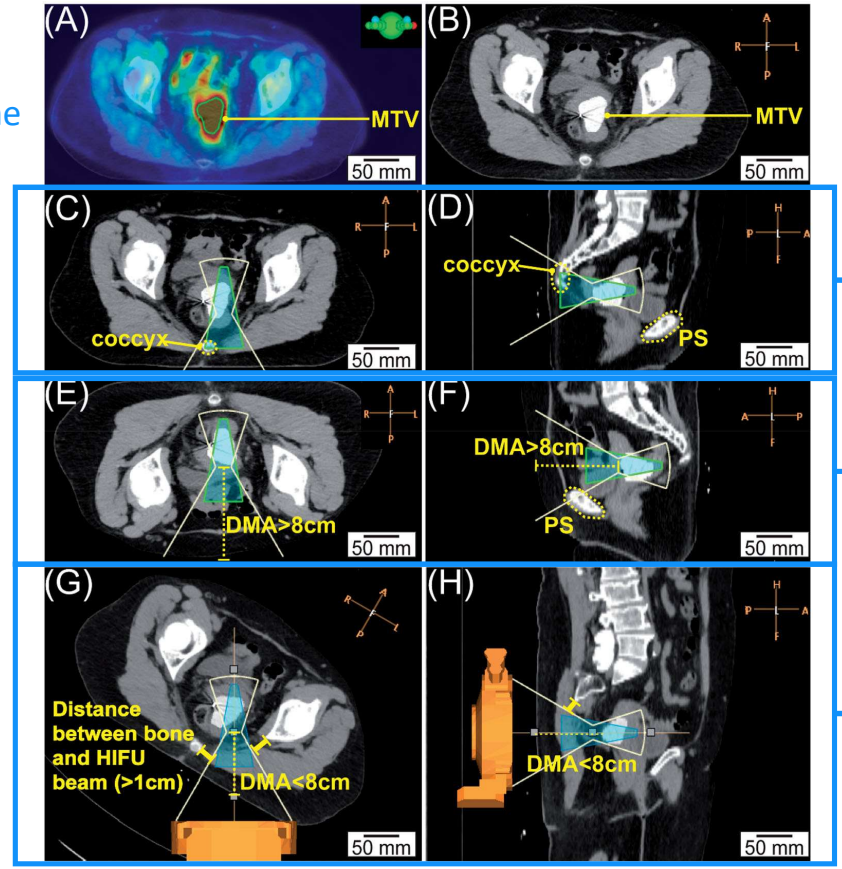
Cervix

Zhu, 2021, IJH

Metabolic Tumor Volume



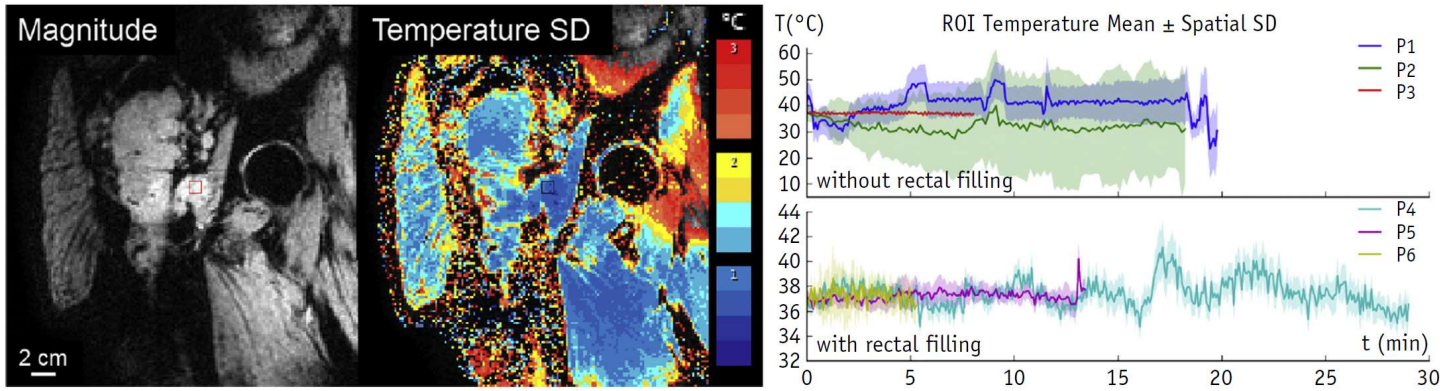
targeting posteriorly → Coccyx blocked the HIFU beam-path

targeting anteriorly → Too deep
PS blocked the HIFU beam-path

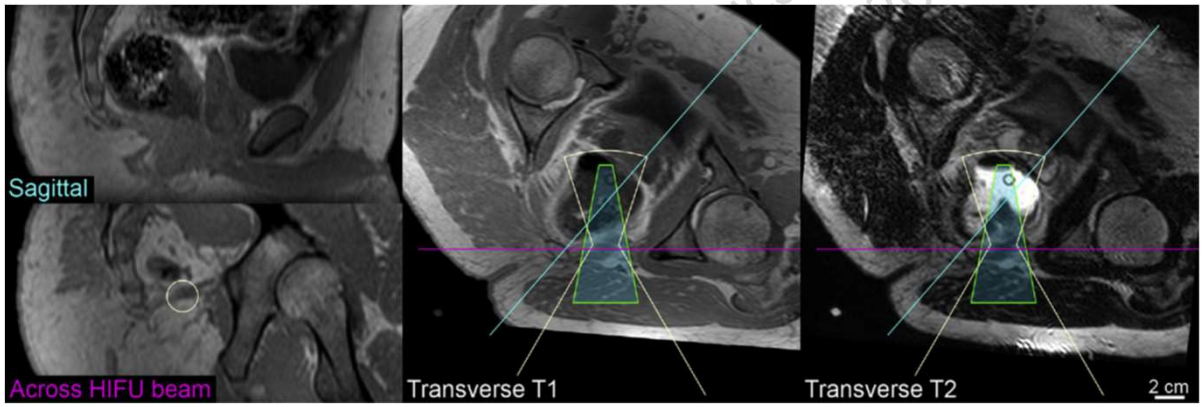
rotated clockwise for 30° → Potential targetable

- 57/79 patients (72.15%) were targetable from at least one angle
- 39/79 (49.37%) were targetable posteriorly and 31/79 (39.24%) were targetable anteriorly

Rectal cancer



→ Temperature mapping stability and precision were acceptable only in volunteers who had rectal filling



→ Target tumors up to 8 cm from the skin

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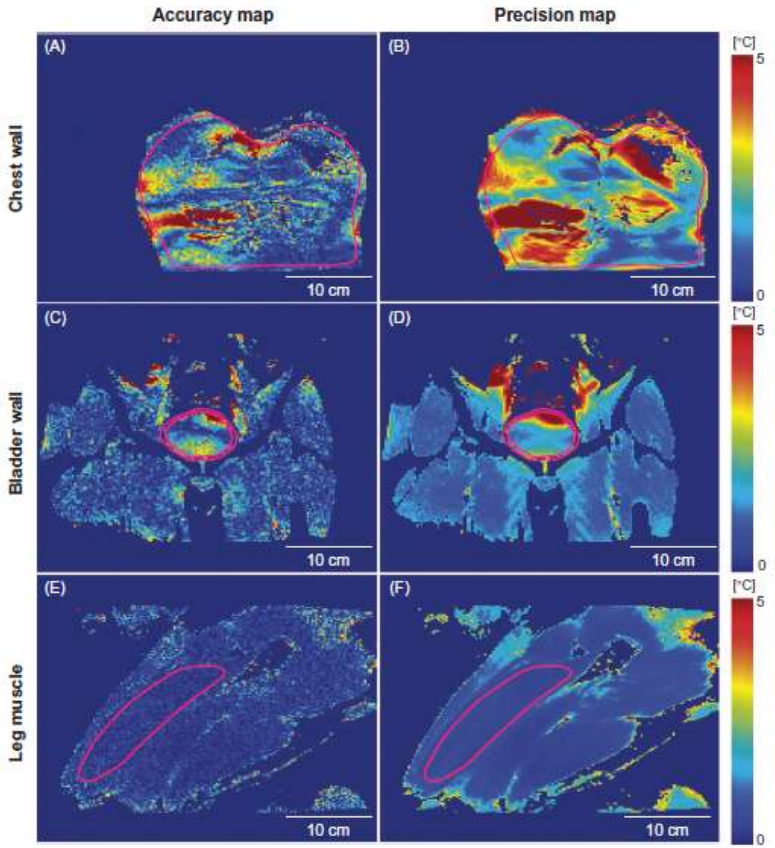
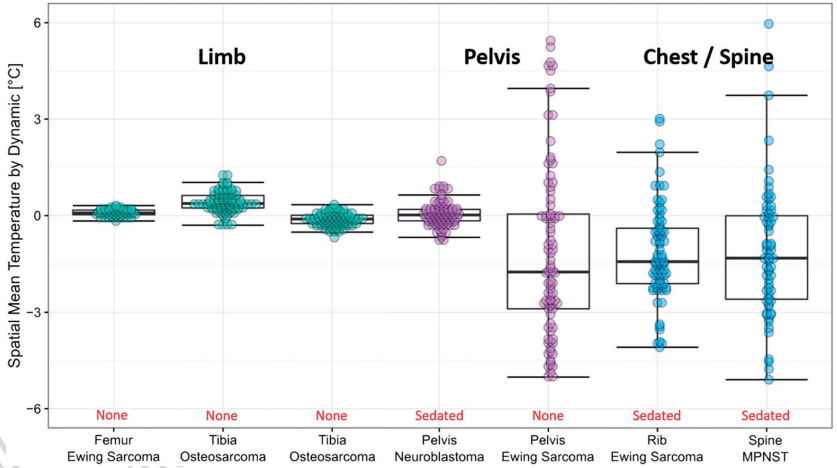
Chu, 2016, IJROBP

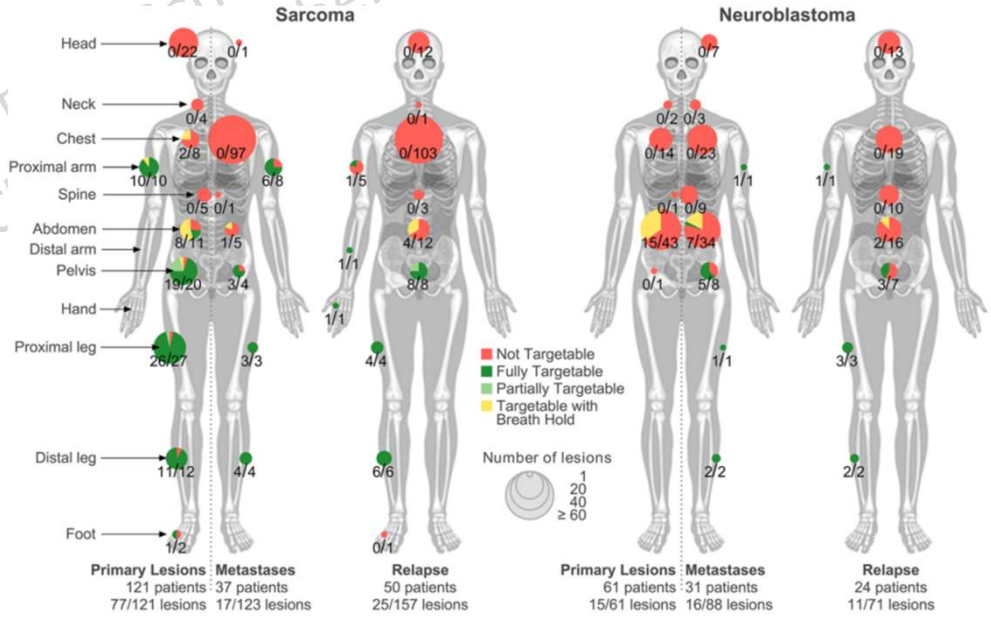
Other target sites



Kothapalli, 2018, IJH



Bing, 2019, IJH



Shim, 2016, Pediatr Blood Cancer

UMC Utrecht

Homework assignment

- Why is (MR-guided) focused ultrasound currently not used for hyperthermia treatments in the clinic?
- What is the best application for MR-guided FUS induced HT to start with?

Answers can be mailed to: r.deckers-2@umcutrecht.nl