

HEATING TECHNOLOGY:

- RF & MICROWAVES**
- QUALITY ASSURANCE**

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ESHO School



Erasmus MC
University Medical Center Rotterdam



Cancer Institute

Wave constructive interference



Lets think together

What do we need to achieve an effective hyperthermia treatment?

Introduction Heating technology



<https://youtu.be/OMzguVx5USs>

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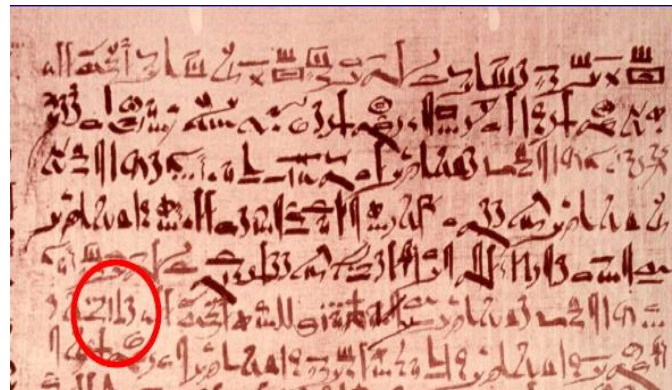
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- WHAT DO WE NEED TO ACHIEVE AN EFFECTIVE HYPERTHERMIA TREATMENT
 - CLINICAL EXAMPLES
- TREATMENT PLANNING
- QUALITY ASSURANCE

HISTORICAL PERSPECTIVE

Historical perspective

- **3000 B.C.** - Egypt (Edwin Smith Surgical Papyrus) (thermal surgery)



Edwin Smith Surgical Papyrus

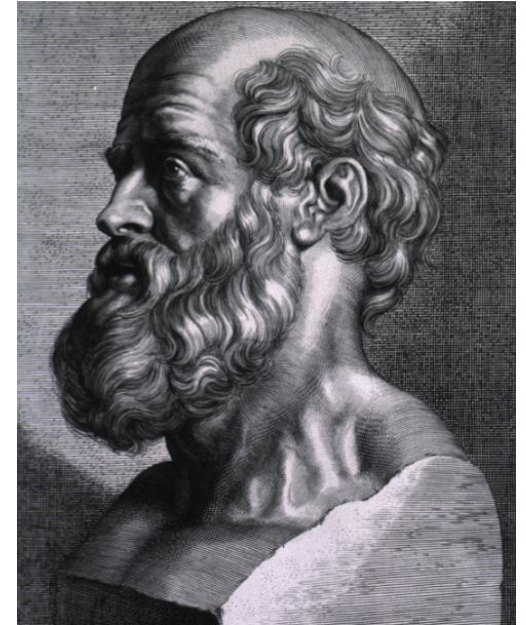
Historical perspective

- Hippocrates (460–370 B.C.)

“Those who cannot be cured by medicine can be cured by surgery.

Those who cannot be cured by surgery can be cured by fire.
[hyperthermia]

Those who cannot be cured by fire, they are indeed incurable.”

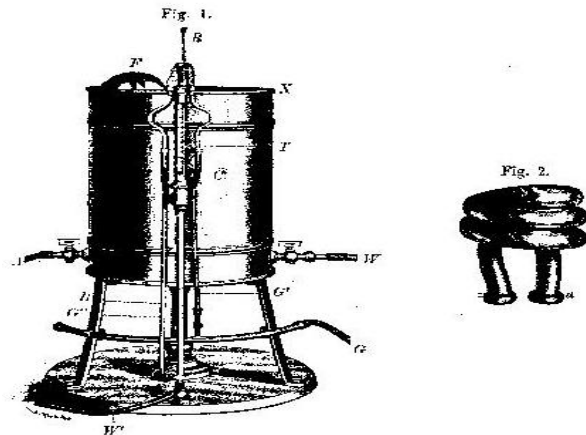


Hippocrates (460-370 B.C.)

Historical perspective

- **19th Century**

Water circulating cisterns to treat carcinoma of the uterus with temperatures of 42-44°C (F.Westermark 1898)



F.Westermark 1898

Historical perspective

- 20th Century

Cavaliere 1967; clinical study: 45% LC leg tumors after chemo perfusion under hyperthermia (41-43°C).

Netherlands first Dutch Cancer Society supported research 1977.

2000 Lancet publication Dutch Deep Hyperthermia Trial.



Dutch Deep Hyperthermia Phase III trial
Locally advanced cervical ca: IIb-d, IIIb, IVa
J van der Zee, D Gonzalez Gonzalez et al.
Lancet 2000;355:1119-1125

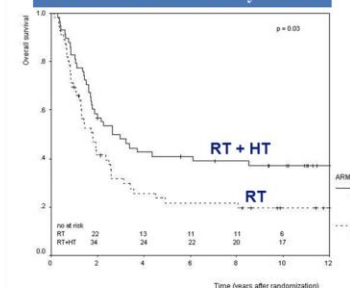
RT+HT significant better than RT-alone!

3-yrs pelvic control 41% → 61%

3-yrs overall survival 27% → 51%

no increase in acute or late toxicity

12 year follow-up
M. Franckena et al.
Int J Radiat Oncol Biol Phys. 2008



DUTCH DEEP HYPERTHERMIA STUDIES

Techniques used for induction of hyperthermia:

- Rotterdam:** BSD-2000 system (70-120 MHz)
- Amsterdam:** AMC Four-waveguide array (70 MHz)
- Utrecht:** Coaxial TEM applicator (70 MHz)

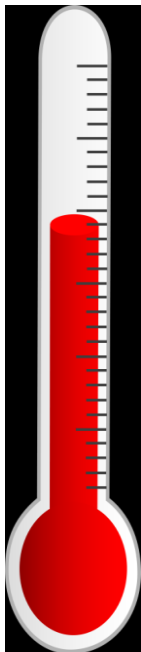
Level 1 clinical evidence.

Randomized trails RT or CT ± HT

27 positive randomized trails RT or CT ± HT

Reference	Treatment	Tumor	Endpoint	Lesions	RT/CT	RT/CT+HT
Van Driel (2018)	CT (hipec)	Ovarian	med Surv.	245	33.9m	45.7m
Issels (2018)	CT	Soft tissue sarcoma	med. Surv.	329	6.2yrs	15.4yrs
Chi (20018)	RT	Painful Bony mets	Time2pain prog	57	55d	>168d
Zhao (2014)	RT	Nasopharynx	3yr OS	83	54%	73%
Kang (2013)	RT+CT	Nasopharynx	5yr OS	154	50%	68%
Hua (2011)	RT+CT	Nasopharynx	5yr PFS	180	63%	73%
Huilgol (2010)	RT	Head and Neck	CR	54	42%	79%
Jones (2005)	RT	Various previously irradiated	CR	109 39	42% 24%	64% 68%
Colombo (2003)	CT	Bladder	2yr OS	75	40%	83%
Verwaal (2003)	CT (hipec)	Colorectal peri. car.	med. Surv.	105	12.6m	22.3m
Harima (2001)	RT	Cervix	CR	40	50%	85%
Van der Zee (2000)	RT	Blad., Cerv., Rect.	3yr OS	358	24%	30%
Sneed (1998)	RT	Glioblas.	2yr S	112	15%	31%
Vernon (1996)	RT	Breast previously irradiated	CR	308 39	41% 39%	59% 79%
Wang (1996)	RT	Oesophagus	3yr S	125	24%	42%
Overgaard (1995)	RT	Melanoma	2 yr NED	134	28%	48%
Kitamura (1995)	RT,CT	Oesophagus	CR	66	6%	25%
You (1993)	RT, surg.	Rectum	pCR	122	5%	23%
Sugimachi (1992)	RT, CT, surg.	Oesophagus	Palliation	53	8%	70%
Strotsky (1991)	RT, surg.	Bladder	3yr S	102	67%	94%
Berdow (1990)	RT, surg.	Rectum	5yr S	115	7%	36%
Kakehi (1990)	RT	Rectum	Response	14	20%	100%
Engelhardt (1989)	CT	Lung	Response	44	36%	60%
Egawa (1989)	RT	Various	Response	92	63%	82%
Valdagni (1988)	RT	Hoofd-hals	CR	44	41%	83%
Datta (1987)	RT	Cervix	CR	64	31%	55%
Kohno (1984)	CT	Vulva/vagina	Response	65	19%	59%

Hyperthermia and ablation



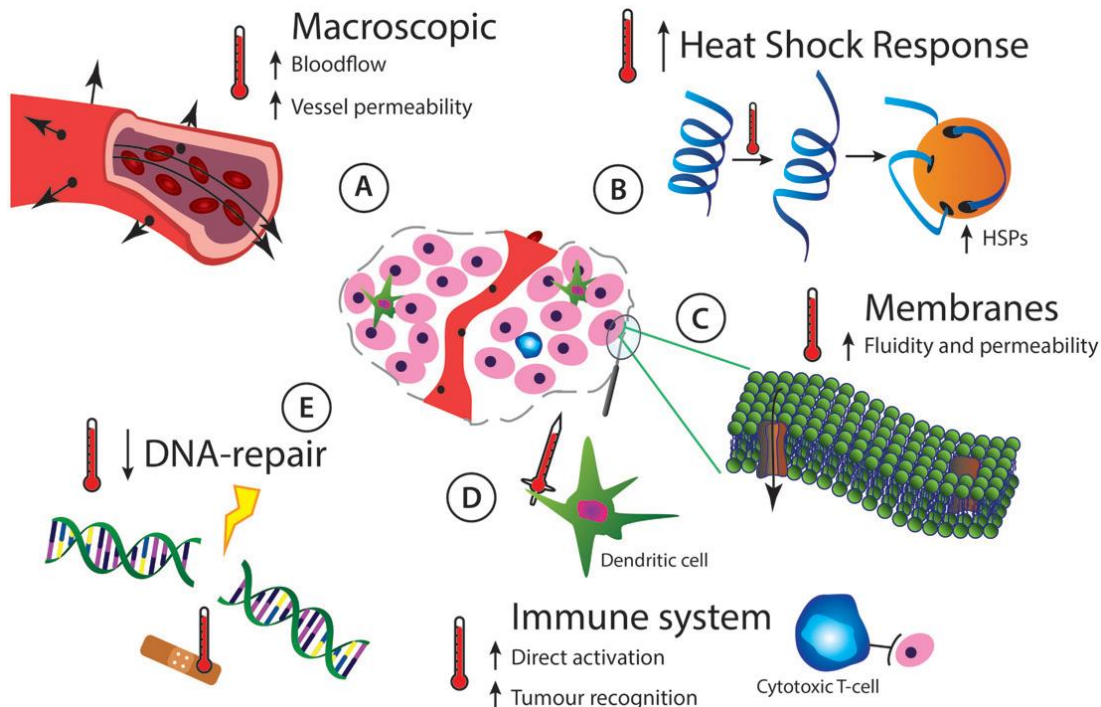
Thermal Ablation: High temperatures $>50\text{ }^{\circ}\text{C}$
Short duration: 5-15 mins
Single fraction

Direct cell kill

Hyperthermia: Mild temperatures $40\text{-}44\text{ }^{\circ}\text{C}$
Duration: 60-90 mins
Multiple (4-6) fraction

Thermal sensitization

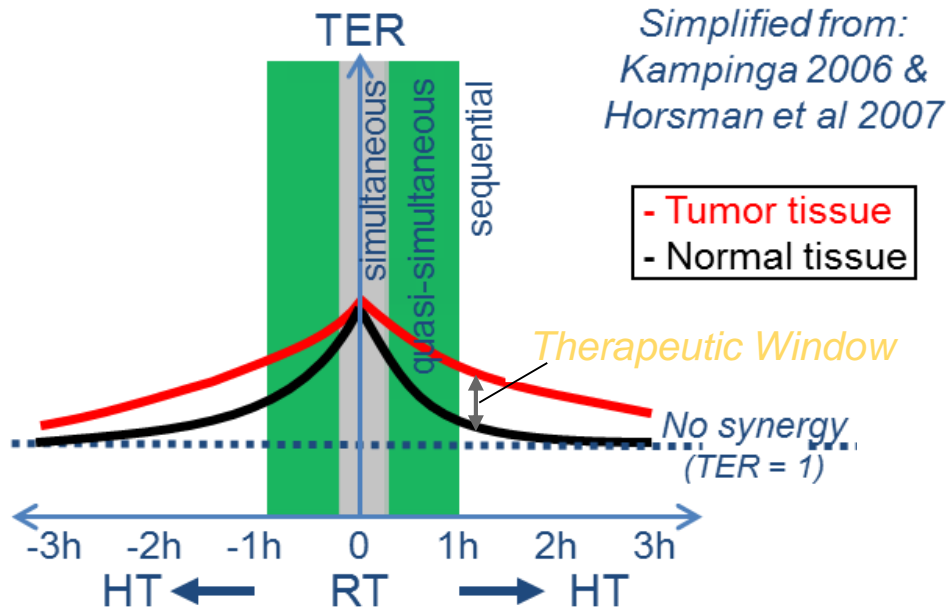
Plethora of biological effects of hyperthermia on tumor cells



Van den Tempel et al.
Int. J. Hyperthermia 2016

Hyperthermia

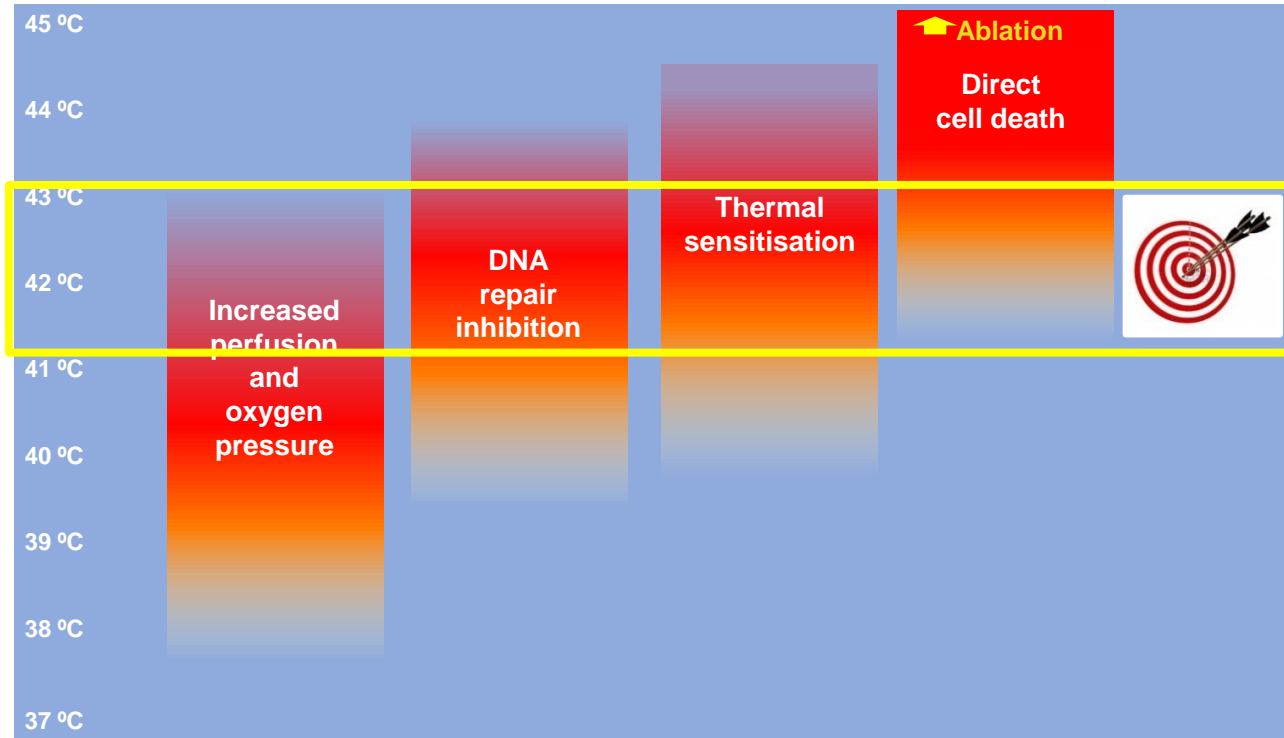
Efficacy depends on time interval between Radiotherapy and hyperthermia



*TER= relative thermal enhancement of the radiotherapy dose

Hyperthermia

The effect depends on the temperature



Thermal dose

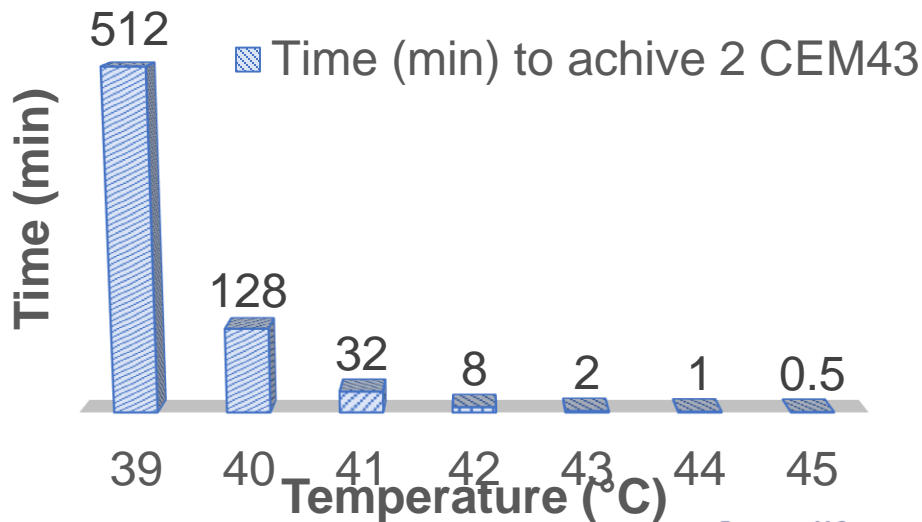
Thermal dose increases in direct proportion with temperature and heating time

Units of “equivalent minutes at 43°C” or CEM43

Concept derived from hyperthermia cytotoxicity, not radio or chemo sensitization

$$TD = \begin{cases} \sum_i \Delta t_i \frac{1}{4^{43-T_i}}, T_i < 43^\circ\text{C} \\ \sum_i \Delta t_i 2^{T_i-43}, T_i \geq 43^\circ\text{C} \end{cases}$$

Temperature T_i (°C)	Thermal dose after 60 min of treatment at T_i (min)
39	0.2
40	0.9
41	3.8
42	15
43	60
44	120
45	240



Summary Temperature matters

- Hyperthermia is used in many target sites
 → **We need target specific applicators**
- The effect depends on temperature, duration and interval between RT/ChT and hyperthermia
 - *Increase perfusion*
 - *Thermal sensitization*
 - *Blocking of DNA damage repair*
 - *Direct cell kill*
 → **We need precise thermometry**

27 positive randomized trials RT or CT ± HT						
Reference	Treatment	Tumor	Intentional	Locoregional	R.F.C.T.	R.F.C.T./HT
Van Derl (2018)	CT (hipoc)	Ovarian	mod. Surv.	245	33.9m	45.7m
Juels (2018)	CT	Soft tissue sarcoma	mod. Surv.	329	6.2yrs	15.4yrs
Chi (20018)	RT	Paclitaxel Body mets	Time2pain prog	57	55d	>60d
Zhao (2014)	RT	Nasopharynx	3yr OS	83	54%	73%
Kang (2013)	RF-CT	Nasopharynx	5yr OS	154	50%	68%
Hsu (2011)	RF-CT	Nasopharynx	5yr PFS	180	63%	73%
Hudgel (2010)	RT	Head and Neck	CR	14	42%	79%
Jones (2005)	RT	Vulvar	CR	109	42%	64%
		previously irradiated		39	24%	68%
Coleman (2003)	CT	Bladder	2yr OS	78	40%	83%
Verwaal (2003)	CT (hipoc)	Colorectal peri. car.	mod. Surv.	105	12.6m	22.3m
Harima (2001)	RT	Cervix	CR	40	50%	85%
Van der Zee (2000)	RT	Blad., Cerv., Rect.	3yr OS	338	24%	30%
Sundt (1998)	RT	Glioblast.	2yr S	112	15%	31%
Verone (1996)	RT	Breast	CR	308	41%	59%
		previously irradiated		39	39%	79%
Wang (1996)	RT	Oesophagus	3yr S	125	24%	42%
Ovgaard (1995)	RT	Melanoma	2 yr NED	134	28%	48%
Khanlou (1995)	RFCT	Oesophagus	CR	66	6%	23%
Yeo (1995)	RE. surg.	Rectum	pCR	122	5%	23%
Sugimachi (1992)	RE. CT. surg.	Oesophagus	Palliation	53	8%	79%
Stetsky (1991)	RE. surg.	Bladder	3yr S	102	67%	94%
Bendow (1990)	RE. surg.	Rectum	5yr S	115	7%	36%
Kakih (1990)	RT	Rectum	Response	14	20%	100%
Engelhart (1989)	CT	Lung	Response	44	36%	66%
Egawa (1989)	RT	Vulvar	Response	92	63%	82%
Valdago (1988)	RT	Head/neck	CR	44	41%	83%
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Kohno (1984)	CT	Vulva/vagina	Response	65	19%	59%



Thermal Ablation: High Temperatures >50 °C
 Short duration: 5-15 min
 Single fraction

Direct Cell Kill

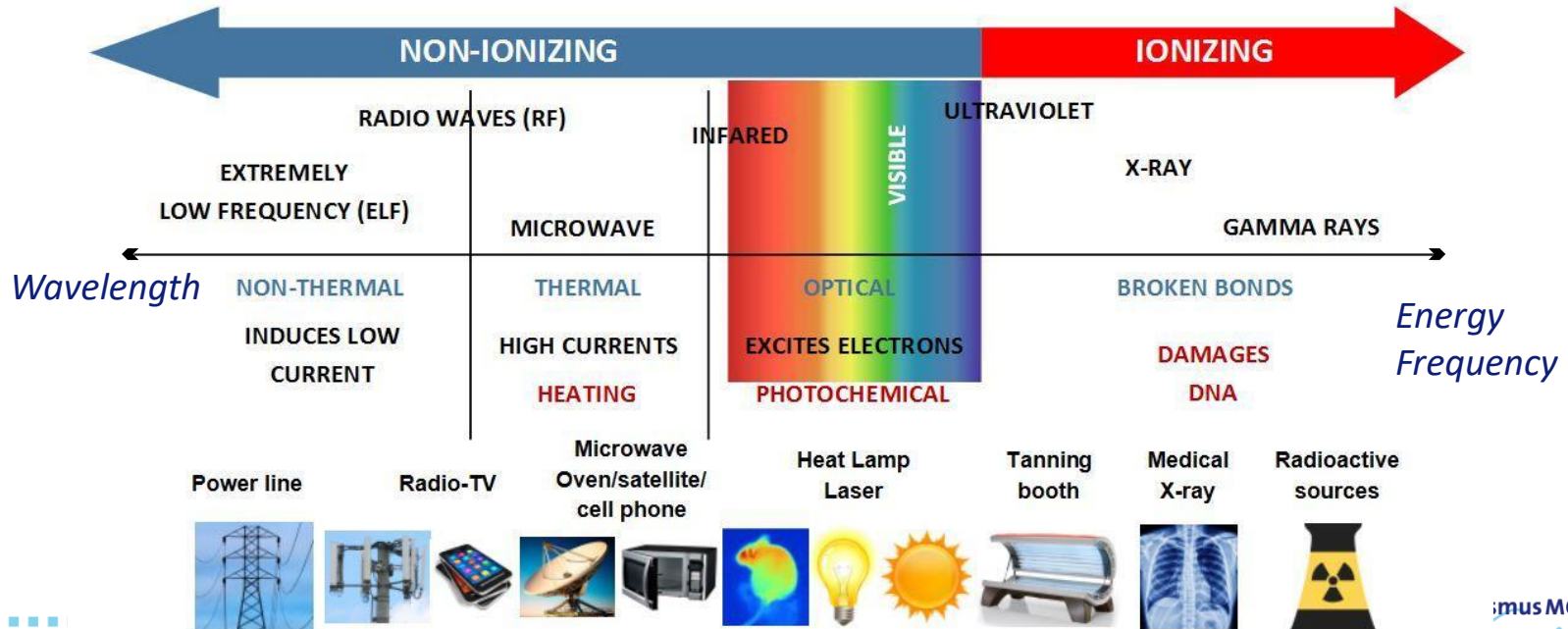
Hyperthermia: Mild Temperatures 40-44 °C
 Duration: 60-90 min
 Multiple (4-6) fraction

Thermal sensitization

MW and RF hyperthermia

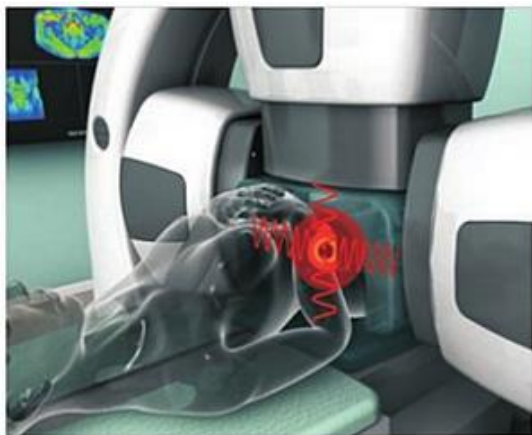
Radiofrequencies (RF, 3 kHz-300 MHz) and Microwaves (MW, 300 MHz-300 GHz) are part of the electromagnetic spectrum

RF/MW waves are still radiation, but with energies that are non-ionizing



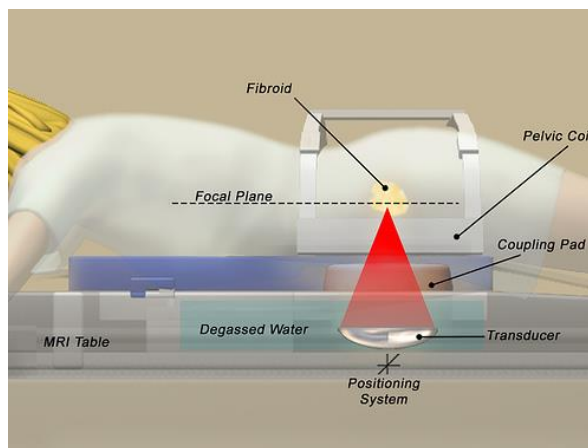
Electromagnetic fields vs US

- Electromagnetic fields
 - Minimal bone absorption
 - Large heating focus
 - Preference for hyperthermia



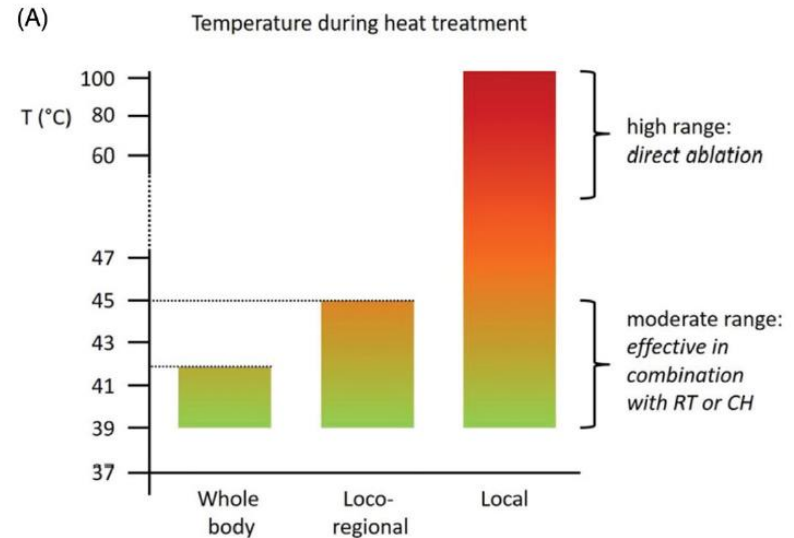
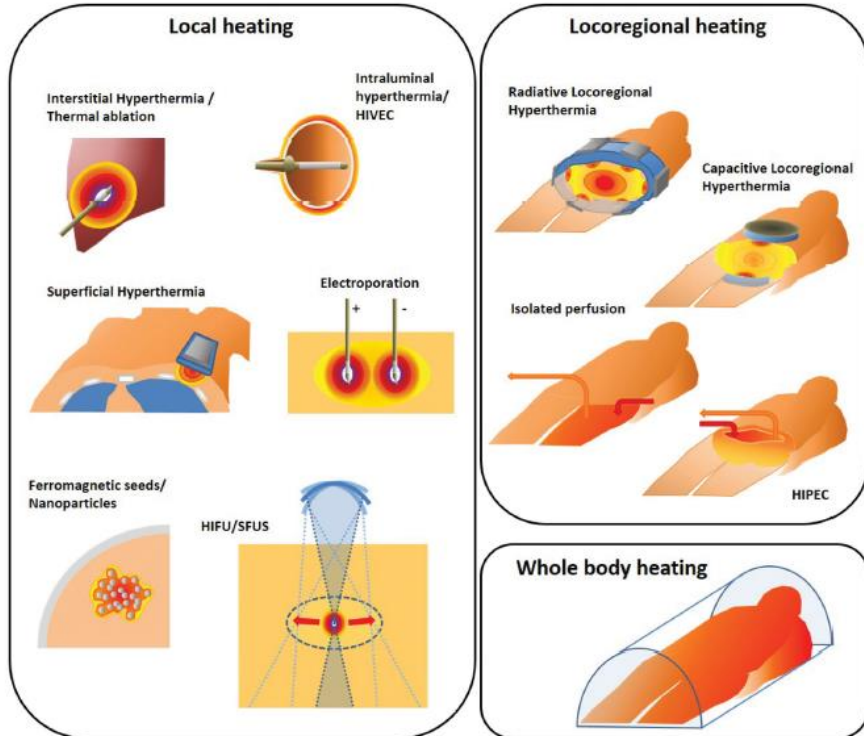
Alba 4D – Deep hyperthermia system

- Ultrasound
 - *High penetration depth*
 - *Small heating focus*
 - *Predominantly thermal ablation*



Ablation cervical Fibroids

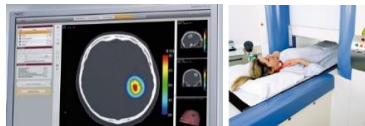
Hyperthermia technologies



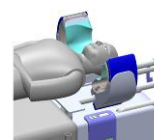
Kok, 2020, Int. J Hyperthermia

Clinical applications

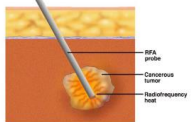
Brain tumors



Head and Neck
MW heating

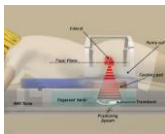


Liver tumours
Thermal ablation

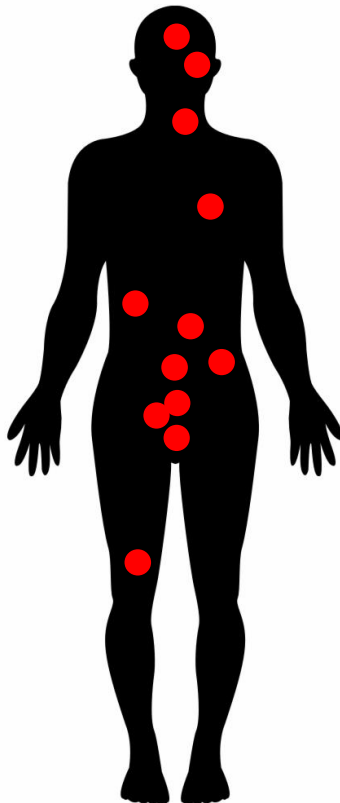
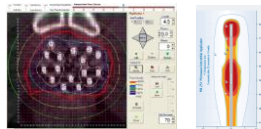


© Society of Interventional Radiology, www.SIRweb.org

Uterine Fibroids
Thermal ablation



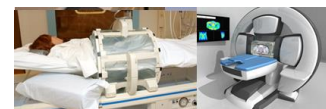
Prostate cancer
Interstitial
Microwaves



Chest wall: MW, Infra-red heating



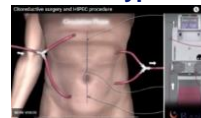
Pelvic, abdomen
Radiofrequency heating



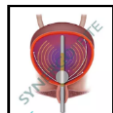
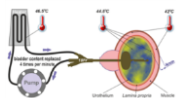
Capacitive heating



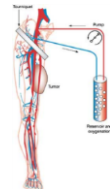
Peritoneal Carcinomatosis
HIPEC - Hyperthermic intraperitoneal chemotherapy



Non-muscle Invasive Bladder Cancer
Conduction and Radiofrequency



Perfusion
extremities



Radiative RF and MW

Non invasive applicators:

- Radiative RF
 - *External applicators*
 - *60MHz – 150 MHz*
 - *Wavelength is 25-60cm in muscle*
 - *Large penetration*
 - *Deep-seated tumor locations (e.g. pelvic tumors)*
- *MW hyperthermia*
 - *Superficial*
 - *433MH, 915 MHz, 2450 MHz*
- *Waterbolus*
 - *Couple the energy into the tissue and cooling / heating the skin*

Radiative RF and MW

Interstitial RF or MW needels

- Minimally invasive ablation as alternative to surgery, also as hyperthermia device
- Insertion under CT, US or MRI
- RF: 350-500kHz
- MW: 915 MHz or 2.450 MHz.
- RF induce areas of high current density, mainly near the electrodes
- MW: dielectric heating in a volume around the applicator
- Interstitial RF or MW needles can be use as single element or in an array

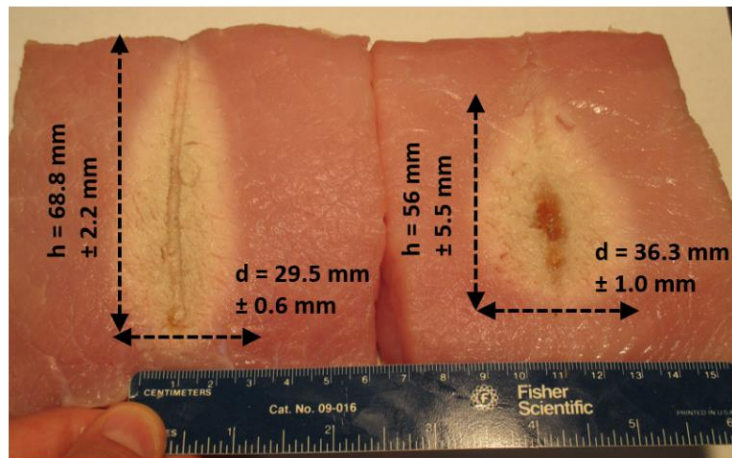


FIG. 5. Experimentally observed ($n = 4$) ablation zones in *ex vivo* pork tissue following 30 W, 10 min ablation with a single microwave antenna operating at 915 MHz (left) and 2.45 GHz (right). Note that the dimensions shown in the figures are the average values of $n = 4$ measurements and standard deviation.

Curto et al, Medical Physics, 2015

Lets think together

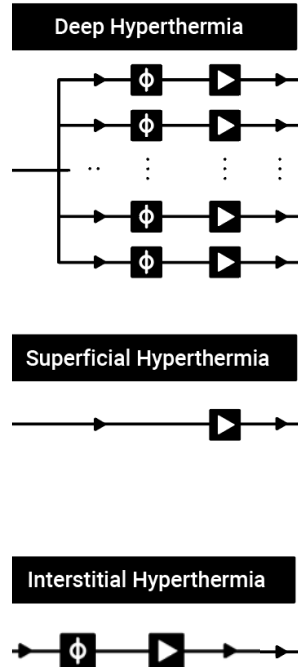
What do we need to achieve an effective hyperthermia treatment?

Lets think together









What do we need to achieve an effective hyperthermia treatment?

1. To know the clinical requirements (dimensions, properties) of the region we want to heat
To know how that region is going to respond
2. *High quality heating equipment*
3. *Power chain*
4. *Treatment planning*
5. *Precise thermal dosimetry system*
6. *Adequate quality assurance*

Radiative hyperthermia techniques



Electromagnetic based HT technologies

Heating approach		Heating region	Typical frequency (f) & number of Antennas	Typical therapeutic heat focus (region at 40–44 °C)	
External	Whole body	Regional	f = 200–375 GHz	Whole body (38.5–40.5 °C for >3 h or 40.5–42 °C for 1–2 h [43,44])	
	Superficial	Local (near the surface)	f = 400–1000 MHz one applicator (single or multi-antenna)	Block-shaped: footprint typically 10 × 10 cm ² Volume: 200–400 cm ³	
			f = 400–1000 MHz Combination of multiple applicators	Block-shaped: footprint typically 20 × 30 cm ² ; Volume: 12050–2400 cm ³	
	Deep	Regional	f ≤ 100 MHz 4 antennas/channels <i>Heat focus steering in radial direction</i>	Ellipsoidal shape: 15–20 cm in the main (patient) axis Volume: 1750–4000 cm ³	
		Locoregional	f = 100–300 MHz, 4–12 antennas/channels <i>Heat focus steering in radial and axial direction</i>	Ellipsoidal shape: 8–15 cm in the main (patient) axis Volume: 250–1750 cm ³	
		Local	f = 300–1000 MHz 12 ≤ antennas/channels <i>Heat focus steering in radial and axial direction</i>	Ellipsoidal shape: 1.5–8 cm in the main (patient) axis Volume: 15–250 cm ³	
Internal	Interstitial (deep)	Local	f = 27, 434, 915 MHz 3–16 antennas/channels	Volume: 30–120 cm ³	
	Intracavitary/Intraluminal (deep)	Local	f = 27, 434, 915 MHz 1 antenna	Volume: 5–30 cm ³ <i>in case of bladder cancer, the complete 400–600 ml volume</i>	

Paulides, Dobsicek Trefna, Curto, Rodrigues, Advanced Drug Delivery Reviews, 2020.

Table 2

List of MW/RF commercial medical devices used in clinical trials that combined adjuvant hyperthermia with chemotherapy. The references listed are the ones that best explain the physical principles of each MW/RF device.

	Device	Manufacturer, country	Applicator	Array description	HT delivery	Frequency (MHz)	Monitoring	References
Radiative	Alba 4D	Medlogix, IT	Alba 4D	1 ring with 4 waveguide antennas	External Deep Locoregional	70	4 or 8 thermocouple multi-sensors (56 sensors total) 1 optical E-field sensor	[88]
	Alba ON4000		Alfa, Beta, Gamma, Delta	1 or 2 contact curved microstrip antennas	External Superficial Local	434	8–32 thermocouples, 1 blood perfusion doppler	[89]
	BSD-500	Pyrexar Medical, US	MA-151, MA-100, MA-120 SA-308, SA-510, SA-812, SA-248 MA-251	1 rectangular waveguide 3, 5, 8, or 24 Archimedean spiral antennas	External Superficial Local	915	8 thermistors	[49]
				1–24 dipole antenna wires driven by 8 channels	Interstitial Deep Local			[91]
	BSD-2000		Σ -30, Σ -60, Σ -Ellipse	1 ring with 4 dipole antenna pairs	External Deep Regional	75–140	8 thermistors, thermal mapping	[92]
			SA-115	1 Archimedean spiral antenna	External Superficial Local	98–140		[93]
	BSD-2000 3D		Σ -Eye	3 rings with 4 dipole antenna pairs per ring	External Deep Locoregional	100	8 thermistors, thermal mapping	[94]
	BSD-2000 3D/MR		Σ -30-MR, Σ -Eye-MR	1 or 3 rings with 4 dipole antenna pairs per ring	External Deep Locoregional	100	8 thermistors, thermal mapping, MR guidance	[95]
	Synergo® RITE	Medical Enterprises, NL	SB-TS 101	1 half wavelength not centrally fed skirt type antenna	Intracavitary Deep Local	915	3 thermocouples	[96]
	Yacht-3	JSC MC SEZ Istok, Fryazino, RU		4 rectangular applicators 1 circular models 3 circular models	External Superficial Local Intracavitary Deep Local	915	Up to 18	N/A
Yacht-4			5 rectangular applicators 3 circular models	External Superficial Local Intracavitary Deep Local	434			

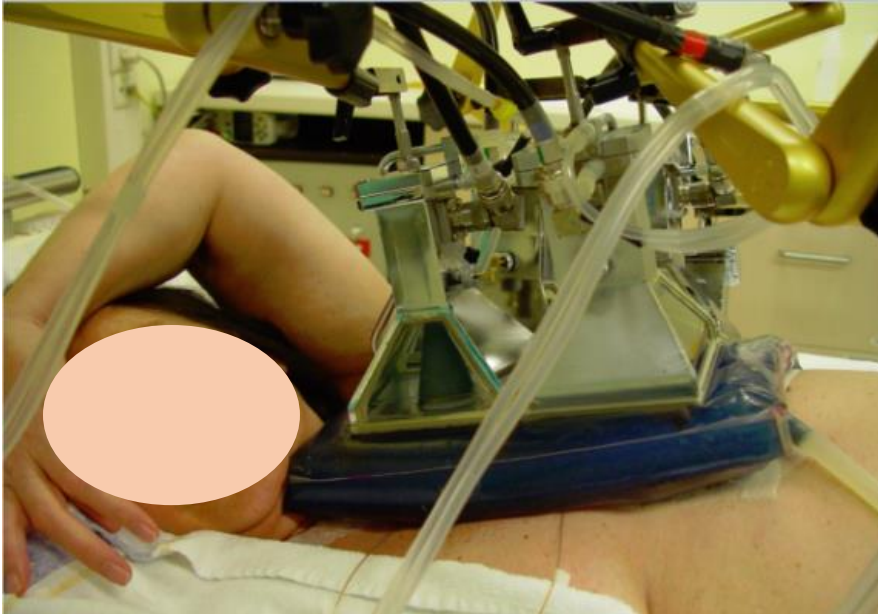
Paulides, Dobsicek Trefna,
Curto, Rodrigues, Advanced
Drug Delivery Reviews, 2020.

Clinical applications

- Superficial
- Head and neck
- Deep

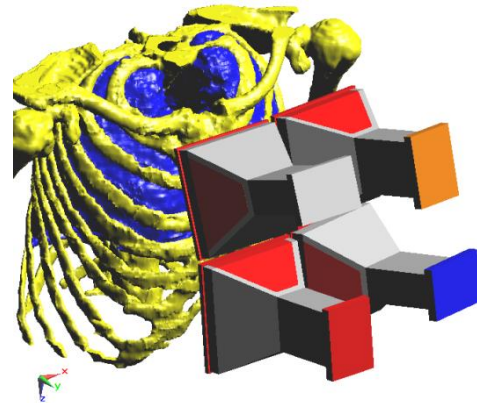
Superficial hyperthermia

Superficial tumours up to 4 cm depth




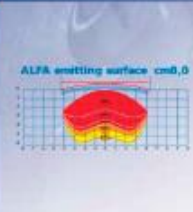



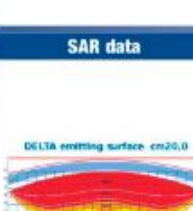
Lucite cone applicators

- 1 to 6 antenna elements
- 433.92 MHz



Water Bag RF Applicators & Tumours

SUPERFICIAL & SEMI-DEEP

Alfa	SAR data	Technical data	Kind of tumours												
		<table border="1"> <tr><td>Size (x-y)</td><td>8 x 20cm</td></tr> <tr><td>Size (x-y)</td><td>160cm²</td></tr> <tr><td>EFS _{10% SAR} (x-y)</td><td>4 x 16cm</td></tr> <tr><td>EFS _{10% SAR} (x-y)</td><td>64cm²</td></tr> <tr><td>DEPTH _{10% SAR} (z)</td><td>43.98±3,41</td></tr> <tr><td>VOLUME _{10% SAR}</td><td>320cm³</td></tr> </table>	Size (x-y)	8 x 20cm	Size (x-y)	160cm ²	EFS _{10% SAR} (x-y)	4 x 16cm	EFS _{10% SAR} (x-y)	64cm ²	DEPTH _{10% SAR} (z)	43.98±3,41	VOLUME _{10% SAR}	320cm ³	<ul style="list-style-type: none"> ■ Head & Neck Tumours ■ Superficial recurrences of malignant lymphoma ■ Melanomas ■ Breast carcinoma
Size (x-y)	8 x 20cm														
Size (x-y)	160cm ²														
EFS _{10% SAR} (x-y)	4 x 16cm														
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VOLUME _{10% SAR}	320cm ³														
Beta	SAR data	Technical data	Kind of tumours												
		<table border="1"> <tr><td>Size (x-y)</td><td>15 x 16cm</td></tr> <tr><td>Size (x-y)</td><td>240cm²</td></tr> <tr><td>EFS _{10% SAR} (x-y)</td><td>8 x 12cm</td></tr> <tr><td>EFS _{10% SAR} (x-y)</td><td>96cm²</td></tr> <tr><td>DEPTH _{10% SAR} (z)</td><td>43.98±3,41</td></tr> <tr><td>VOLUME _{10% SAR}</td><td>480cm³</td></tr> </table>	Size (x-y)	15 x 16cm	Size (x-y)	240cm ²	EFS _{10% SAR} (x-y)	8 x 12cm	EFS _{10% SAR} (x-y)	96cm ²	DEPTH _{10% SAR} (z)	43.98±3,41	VOLUME _{10% SAR}	480cm ³	<ul style="list-style-type: none"> ■ Recurrences breast carcinoma on thoracic wall ■ Melanomas ■ Breast carcinoma
Size (x-y)	15 x 16cm														
Size (x-y)	240cm ²														
EFS _{10% SAR} (x-y)	8 x 12cm														
EFS _{10% SAR} (x-y)	96cm ²														
DEPTH _{10% SAR} (z)	43.98±3,41														
VOLUME _{10% SAR}	480cm ³														
Delta	SAR data	Technical data	Kind of tumours												
		<table border="1"> <tr><td>Size (x-y)</td><td>20 x 21cm</td></tr> <tr><td>Size (x-y)</td><td>420cm²</td></tr> <tr><td>EFS _{10% SAR} (x-y)</td><td>12 x 18cm</td></tr> <tr><td>EFS _{10% SAR} (x-y)</td><td>216cm²</td></tr> <tr><td>DEPTH _{10% SAR} (z)</td><td>43.98±3,41</td></tr> <tr><td>VOLUME _{10% SAR}</td><td>1.400cm³</td></tr> </table>	Size (x-y)	20 x 21cm	Size (x-y)	420cm ²	EFS _{10% SAR} (x-y)	12 x 18cm	EFS _{10% SAR} (x-y)	216cm ²	DEPTH _{10% SAR} (z)	43.98±3,41	VOLUME _{10% SAR}	1.400cm ³	<ul style="list-style-type: none"> ■ Large recurrences breast carcinoma on thoracic wall ■ Various origins adenopathy ■ Melanomas ■ Superficial relapses of soft tissue sarcomas
Size (x-y)	20 x 21cm														
Size (x-y)	420cm ²														
EFS _{10% SAR} (x-y)	12 x 18cm														
EFS _{10% SAR} (x-y)	216cm ²														
DEPTH _{10% SAR} (z)	43.98±3,41														
VOLUME _{10% SAR}	1.400cm ³														

@ALBA HYPERTHERMIA

Water bolus

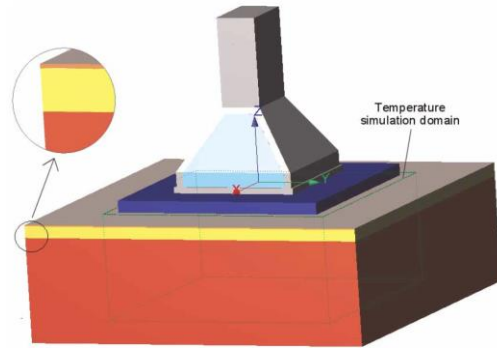


Figure 1. 3-D model used for simulating the superficial hyperthermia treatment. It employs an LCA, a water bolus and a block of tissue consisting of a skin, fat and muscle layer.

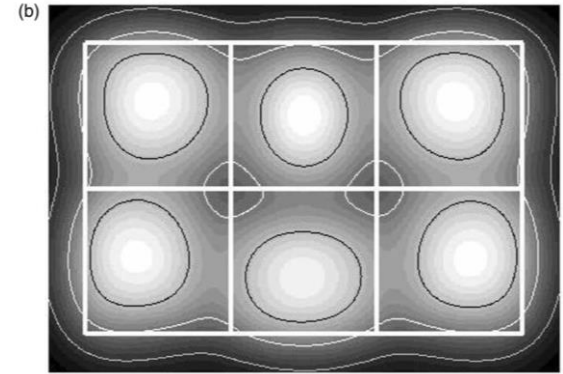
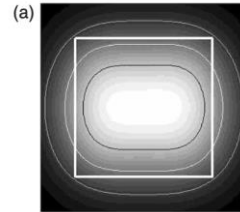


Figure 7. Illustration of increased SAR coverage below the footprint of an (a) 1×1 array and (b) 3×2 array of LCAs. Normalized SAR plots 12.5 mm below the skin surface. The thick white lines indicate the applicator footprint (aperture dimensions: 10×10 cm). The thin contours indicate 25% (grey), 50% (white), and 75% (black) SAR.

Water bolus

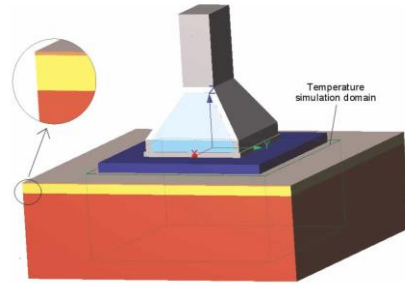


Figure 1. 3-D model used for simulating the superficial hyperthermia treatment. It employs an LCA, a water bolus and a block of tissue consisting of a skin, fat and muscle layer.

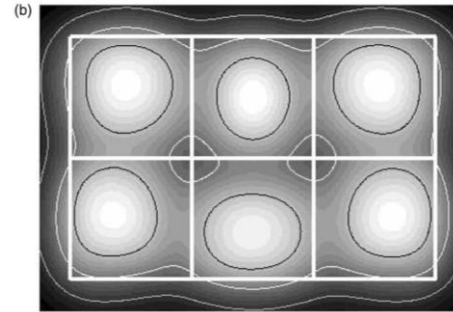


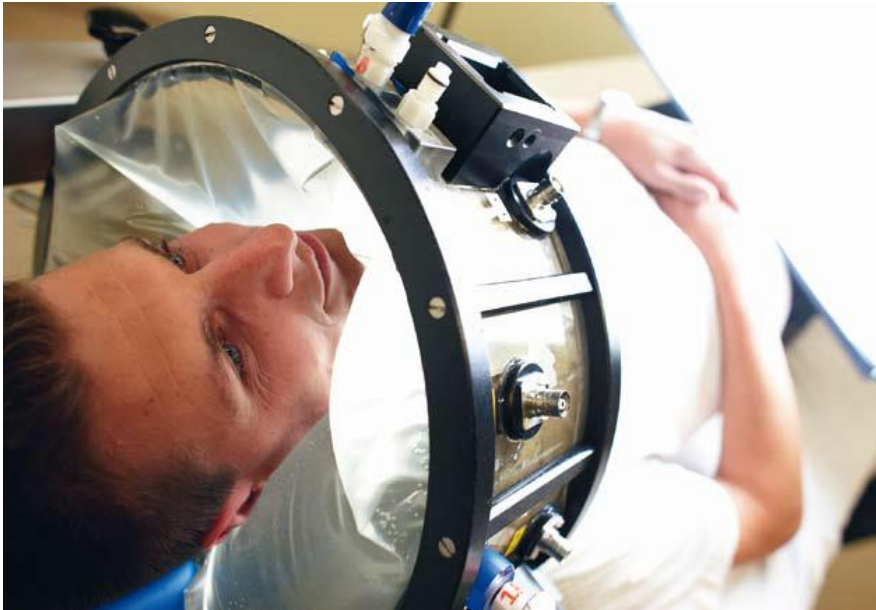
Table IV. Guideline temperatures for the water bolus for specified antenna array and target depth.

Target depth (cm)	1 antenna array	2 antenna array	4 antenna array	6 antenna array
0–1	42°C	41°C	41°C	41°C
0–2	41°C	39°C	39°C	38°C
0–3	41°C	39°C	39°C	38°C
0–4	41°C	39°C	39°C	38°C
1–3	39°C	37°C	36°C	36°C
1–4	37°C	37°C	36°C	36°C
2–4	37°C	34°C	33°C	32°C

Head and Neck hyperthermia

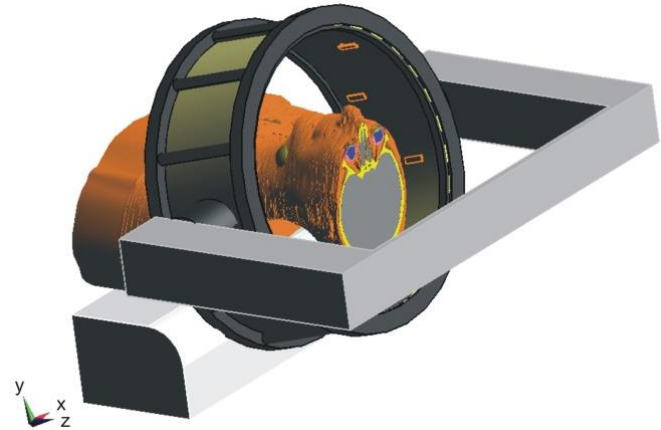
Loco regional hyperthermia:

Tumour locations in Head and Neck region



HYPERcollar applicator

- 12 patch antennas (2x6ant's)
- 433.92 MHz (~3.5cm focus in muscle)



Deep hyperthermia

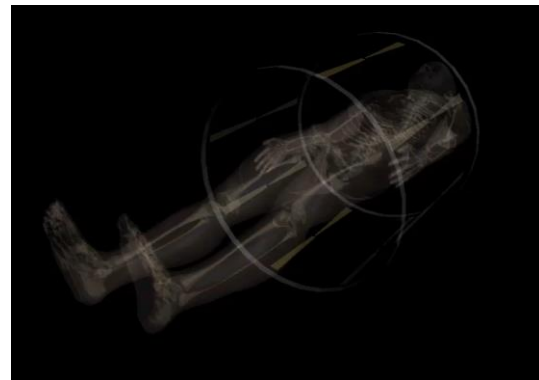
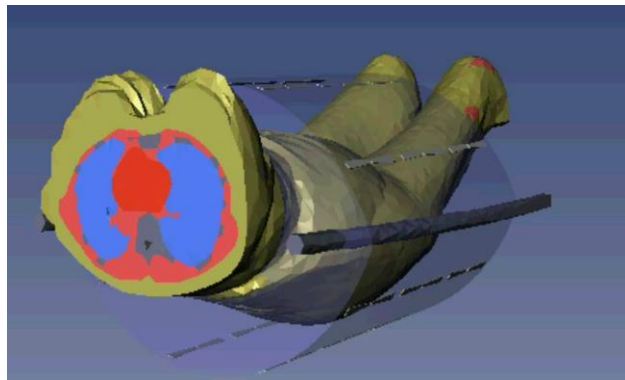
Regional deep hyperthermia:

Tumor locations at depths $> 4\text{cm}$, i.e.

Pelvis, thorax.

Pyrexar applicators

- 1 to 3 rings of antennas
- 70-140MHz



Deep Hyperthermia



Pyrexar BSD 2000

- 1 ring of 4 dipole antenna pairs
- 2D heating steering
- 77 MHz



ALBA 4D

- 1 ring of 4 waveguide
- 2D heating steering
- 70 MHz



Pyrexar BSD 2000-3D

- 3 rings of 4 dipole antenna pairs per ring
- 3D heating steering
- 100 MHz

Deep Hyperthermia

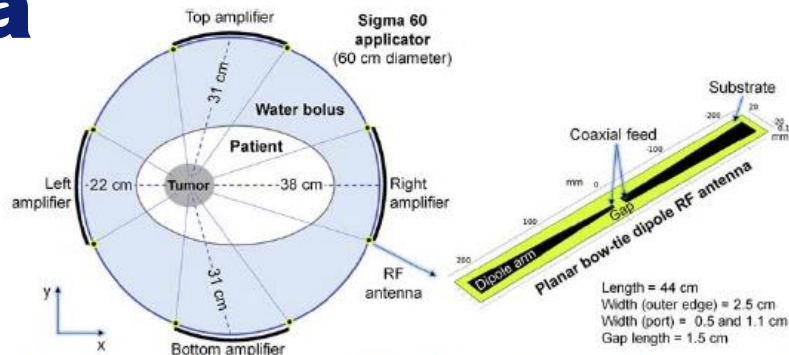


Figure 9.5 Cross section of the Sigma 60 applicator (Pyrexar Medical, Salt Lake City, UT, USA) consisting of four pairs of dipole antennas (shown on the right) in an annular phased array configuration. The patient is represented with a simplified ellipse with dimensions of $40 \times 24 \text{ cm}^2$. Adapted with permission from Pyrexar Medical Inc. SIGMA 60 and Sigma Ellipse hyperthermia treatment applicator operator manual, part # 10-16401, Rev. H, 2016. [Pyrexar Medical: Salt Lake City, UT].

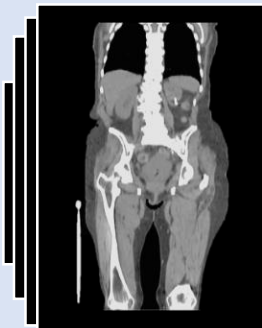
Table 9.1 Phase calculation for the BSD Sigma 60 applicator: target located 8 cm to the left from the center of the applicator, frequency = 90 MHz. Note that each amplifier controls an antenna pair.

Amplifier	Amplifier coordinates (cm)	Distance to target, R (cm)	Amplifier phase ($^\circ$)
Right, $i = 1$	(30, 0)	38	0
Top, $i = 2$	(0, 30)	31	67
Left, $i = 3$	(-30, 0)	22	154
Bottom, $i = 4$	(0, -30)	31	67

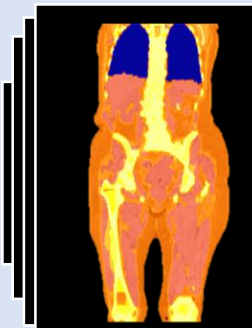
Rodrigues et al. Elsevier 2021

Treatment planning

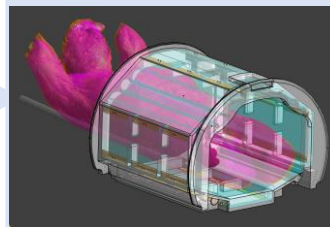
CT / MR scan



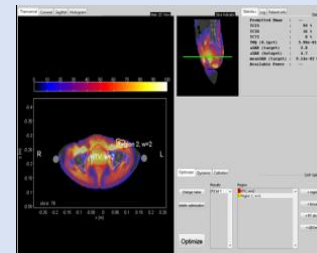
Segmentation



3D
Electromagnetic
simulations



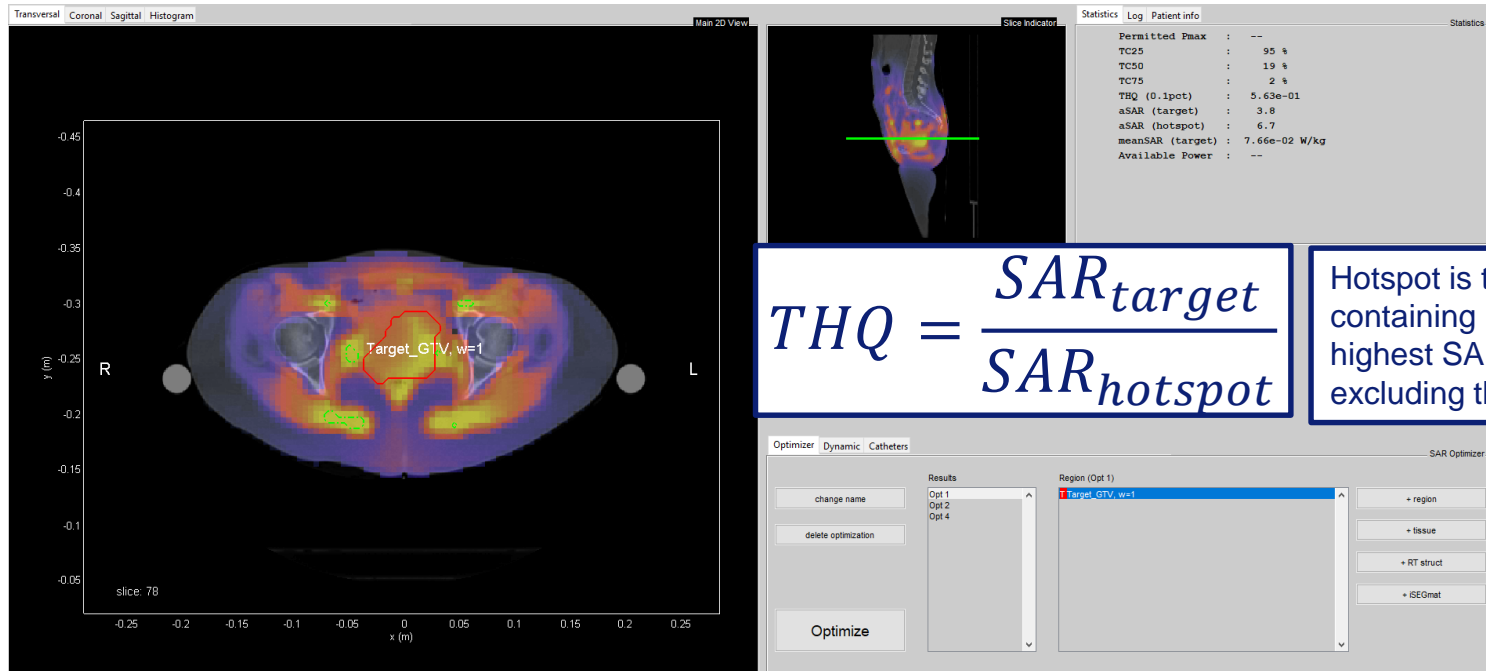
Optimization



VEDO

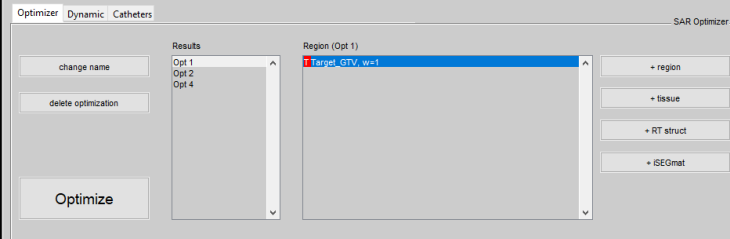
VEDO – fields optimization

Amplitude and phase settings of each antenna



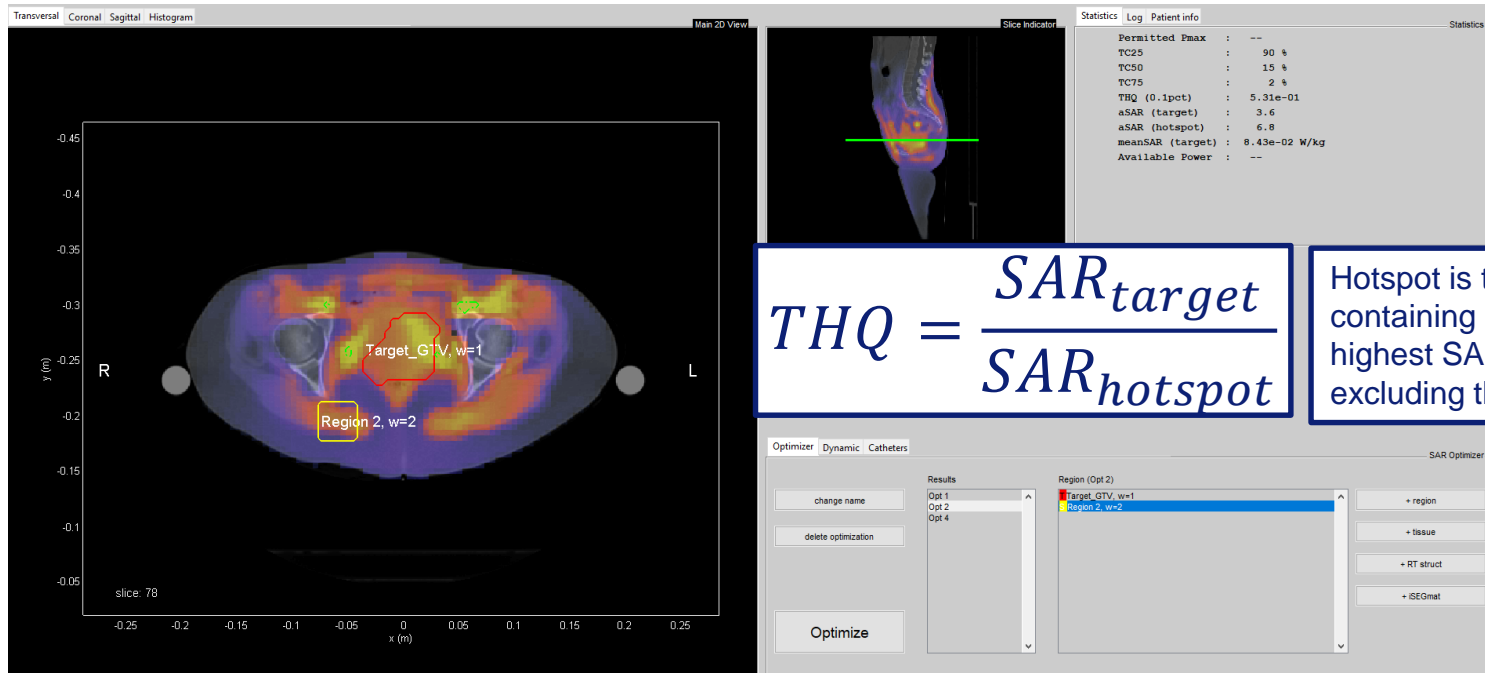
$$THQ = \frac{SAR_{target}}{SAR_{hotspot}}$$

Hotspot is the volume containing 1 percentile of the highest SAR in the total body excluding the target



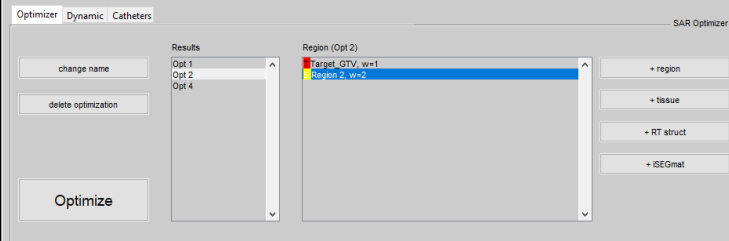
VEDO – fields optimization

Amplitude and phase settings of each antenna

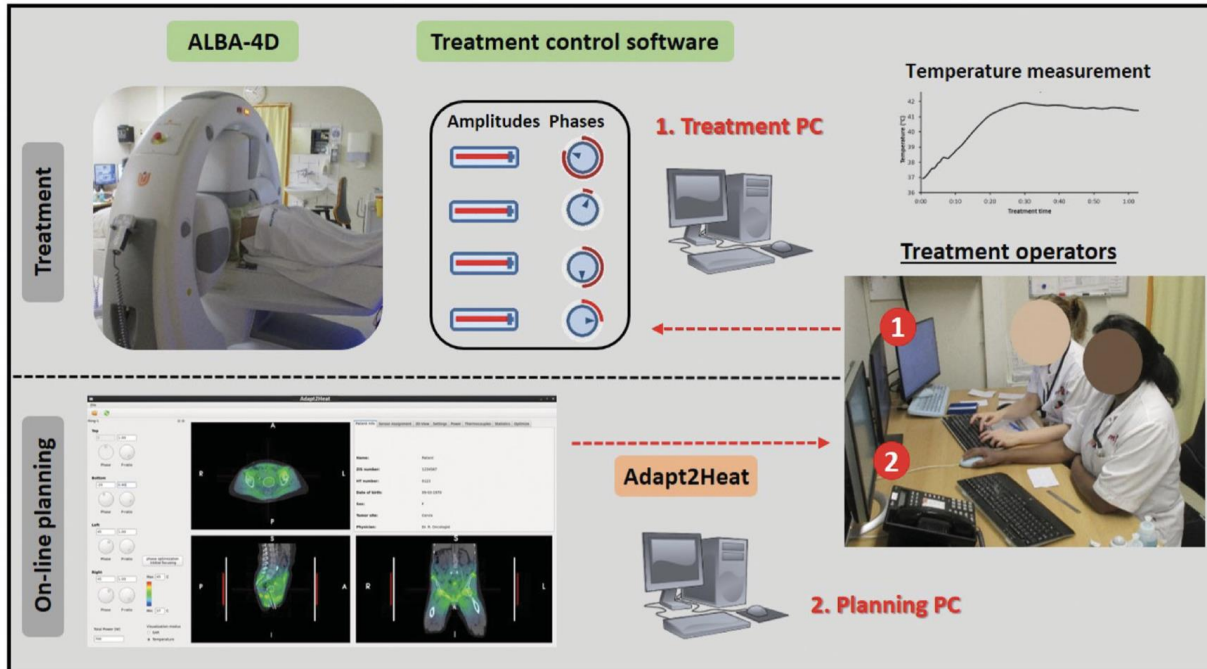


$$THQ = \frac{SAR_{target}}{SAR_{hotspot}}$$

Hotspot is the volume containing 1 percentile of the highest SAR in the total body excluding the target



ADAPT2HEAT

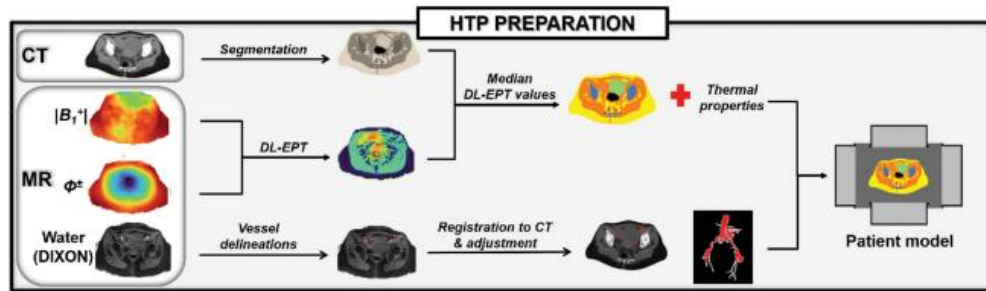


Kok and Crezee, Int J Hyp, 2022

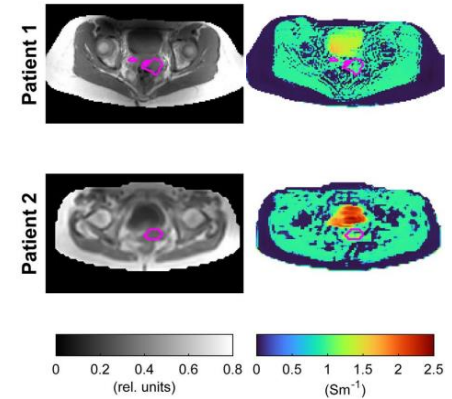
Figure 2. Situation during a hyperthermia treatment, where Adapt2Heat is used as an assistance tool. There is no direct connection between Adapt2Heat and the treatment control software, which avoids any risk of inadvertently affecting the actual treatment when using the treatment planning. The operators remain responsible for changing the system settings via the treatment control software.

Treatment planning

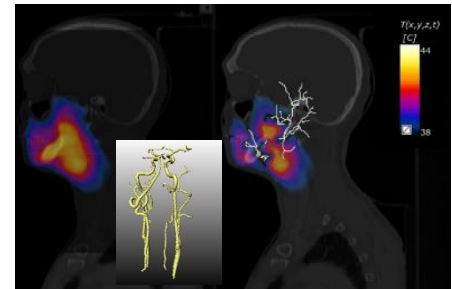
- EM patient model: segmentation + dielectric properties
Electrical properties tomography (EPT)
- T patient model: PBHE (+ discrete vasculature modelling - DIVA)
discrete vasculature in clinical practice



Soraya Gavazzi, et al. "Advanced patient-specific hyperthermia treatment planning", *IJH* 2020, 37: 1; 992-1007.

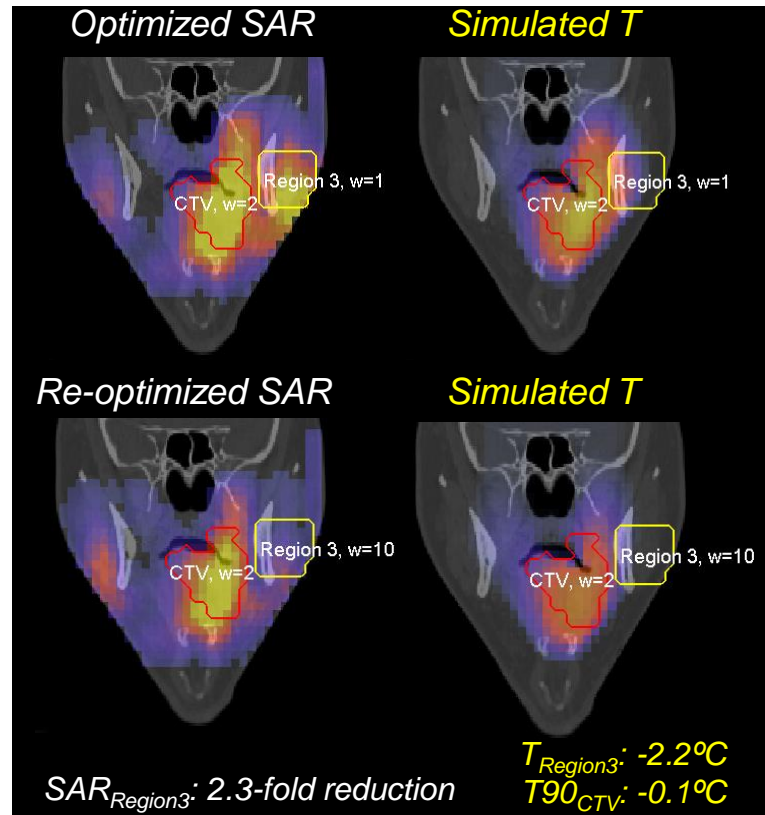
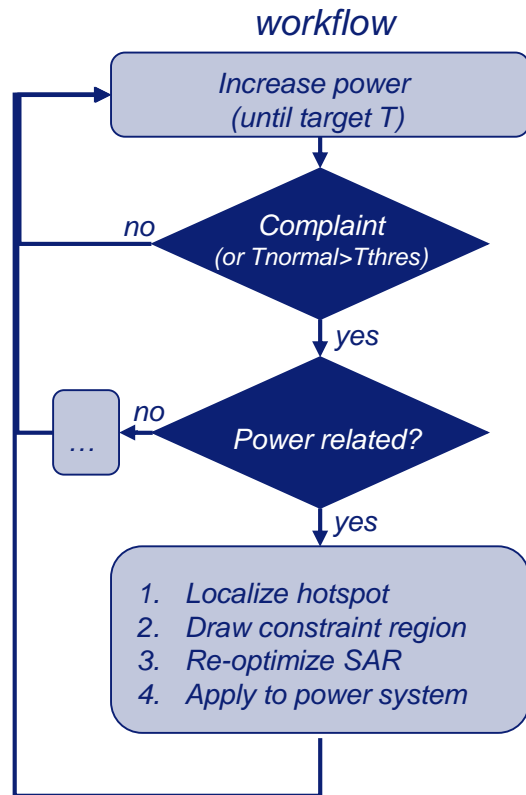


Soraya Gavazzi et al. "Deep learning-based reconstruction of in vivo pelvis conductivity with a 3D patch-based CNN trained on simulated MR data", *MRM* 2020: 2772-2787.



Kemal Sumser, et al. "Feasibility and relevance of DIVA modeling in routine HTP", *IJH* 2019, 36:1 ; 800-810.

Complaint adaptive steering using VEDO



Quality Assurance

- **Quality assurance (QA)**
- Process to assure that an efficient hyperthermia treatment is delivered
- Involve:
 - *Pre-treatment evaluations*
 - *During treatment measurements*
 - *Post treatment evaluations*

Quality Assurance Guidelines

Deep Hyperthermia

- Bruggmoser, G., et al., *Quality Assurance for Clinical Studies in Regional Deep Hyperthermia*. Strahlentherapie Und Onkologie, 2011. **187**(10): p. 605-610.
- Bruggmoser, G., et al., *Guideline for the clinical application, documentation and analysis of clinical studies for regional deep hyperthermia*. Strahlentherapie Und Onkologie, 2012. **188**: p. 198-211.

Superficial Hyperthermia

- Dobsicek Trefna, H., et al., *Quality assurance guidelines for superficial hyperthermia clinical trials: I. Clinical requirements*. Int J Hyperthermia, 2017. **33**(4): p. 471-82.
- Dobsicek Trefna, H., et al., *Quality assurance guidelines for superficial hyperthermia clinical trials : II. Technical requirements for heating devices*. Strahlenther Onkol, 2017. **193**(5): p. 351-66.

Interstitial Hyperthermia

- Dobšiček Trefná, H., et al., *Quality assurance guidelines for interstitial hyperthermia*. International Journal of Hyperthermia, 2019. **36**(1): p. 277-294.

Quality Assurance Guidelines

MAINTENANCE SCHEDULE DEEP HYPERTHERMIA 2022 – ERASMUS MC

Acties per maand	jan	feb	mrt	apr	mei	jun	jul	aug	sep	okt	nov	dec
Control door Faraday cage + cleaning strips												
Measuring electrical conductivity BSD water bath												
Security updates W10												

Acties per 3 maanden	jan	feb	mrt	apr	mei	jun	jul	aug	sep	okt	nov	dec
Applicator E-field sheet												
Hardware / software updates (??)												
Maintenance BSD system												
Refresh BSD water bath												
Refresh water baths BIORAD												
Stock control demi-NaCl water bolus												

Acties per 6 maanden	jan	feb	mrt	apr	mei	jun	jul	aug	sep	okt	nov	dec
Applicator reflection S11												
Change CT hammock												
MMS power verification												
Multipoint temperature calibration FISO												
Replace laser battery												

Acties per 12 maanden	jan	feb	mrt	apr	mei	jun	jul	aug	sep	okt	nov	dec
Calibration RF cables												
Maintenance saturation meter												
Maintenance ear thermometer												
Maintenance blood pressure monitor												
Defrost freezer												



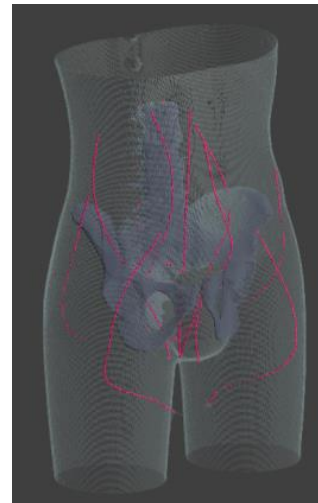
Not execute	Done	Dees not apply	Open	To be done
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Quality assurance Examples

Probe measurements



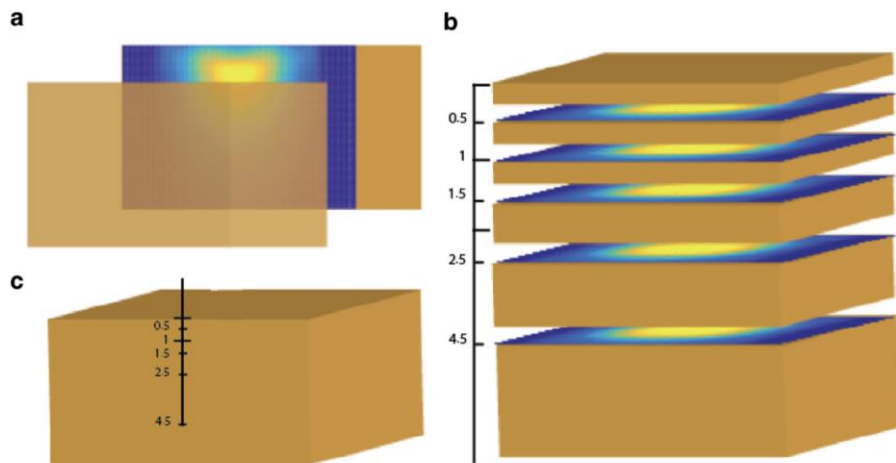
Cylindrical



Human representative anthropomorphic

Quality assurance Examples

Infrared measurements



LED / LAMP phantoms



Dobšićek Trefná et al, Strahlenther Onkol, 2017

Quality assurance Examples

MR Thermometry

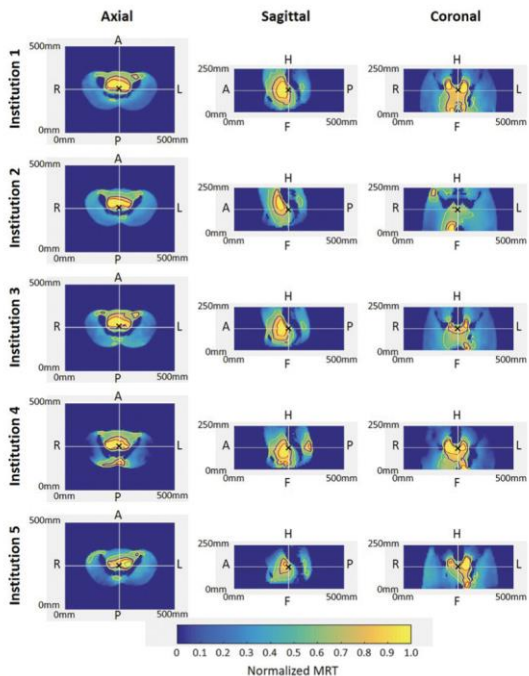


Figure 3. Normalized MRT distribution for centric targets. Axial, sagittal, and coronal cross-sections are plotted at the center of the field of view (white lines), iso-contours at 90% (red), 75% (blue), and 50% (yellow) are shown. The center of the heating target is indicated with 'x' in all cross-sections.

Centric target

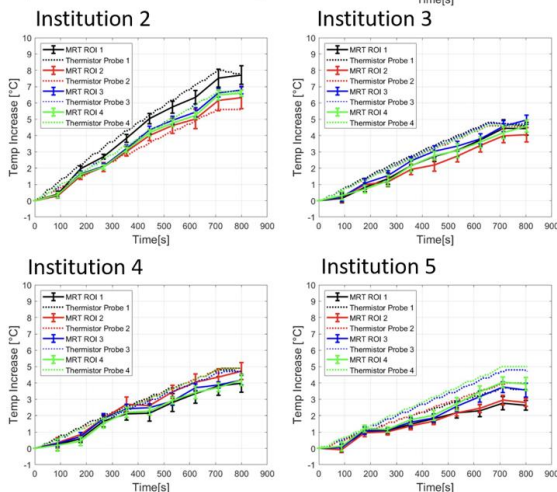
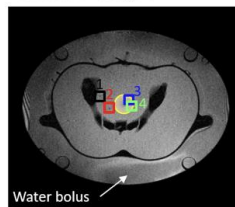


Figure 2. Temporal evolution of temperature increase determined by high resistance thermistor probes and by computed MRT for centric heating target (yellow circle). The position of probes and ROIs in the phantom are indicated by numbers and coloured squares in the MR image showing the cross-section of the phantom and the surrounding water bolus. Measurements were performed at five different institutions.

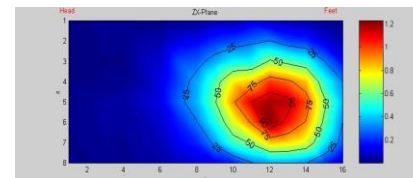
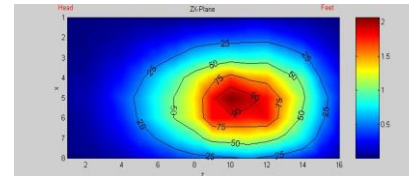
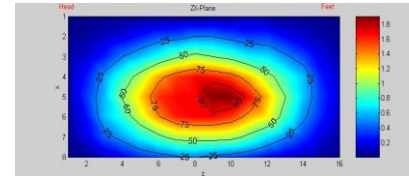
Applicator characterization / QA

E-field sheet



Using array of Schottky diode E-field sensors.

- accurate
- fast, but only in 1 plane
- only 1 field direction
- homogeneous phantom

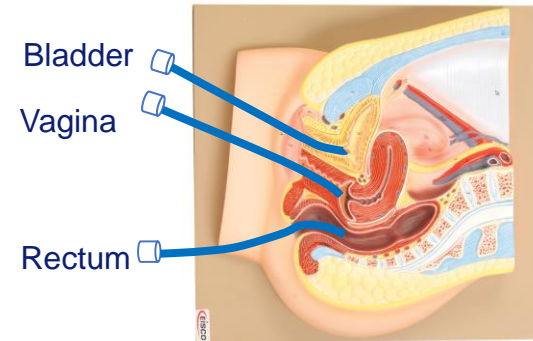


Accurate Thermometry is highly important

- Dose effect has been demonstrated, but quantification difficult
- Temperature increase in target area in practice limited by hotspots



Superficial Hyperthermia.
Bakker et al. 2020



Schematic for cervical carcinoma Hyperthermia.

Accurate Thermometry is highly important, Many parameters affect interpretation

Thermometry

invasive / superficial / non-invasive

Thermometry technique

thermocouple / thermistor / fibreoptic

Invasive or minimally invasive thermometry placement

intratumour / intraluminal / interstitial

Temperature acquisition

not continuous / mapping / continuous

Temperature acquisition rate (min)

Number of probes and sensors

State of the art hyperthermia technology: the hybrid system



State-of-the-art Pyrexar ARCH applicator. Recently installed in Erasmus

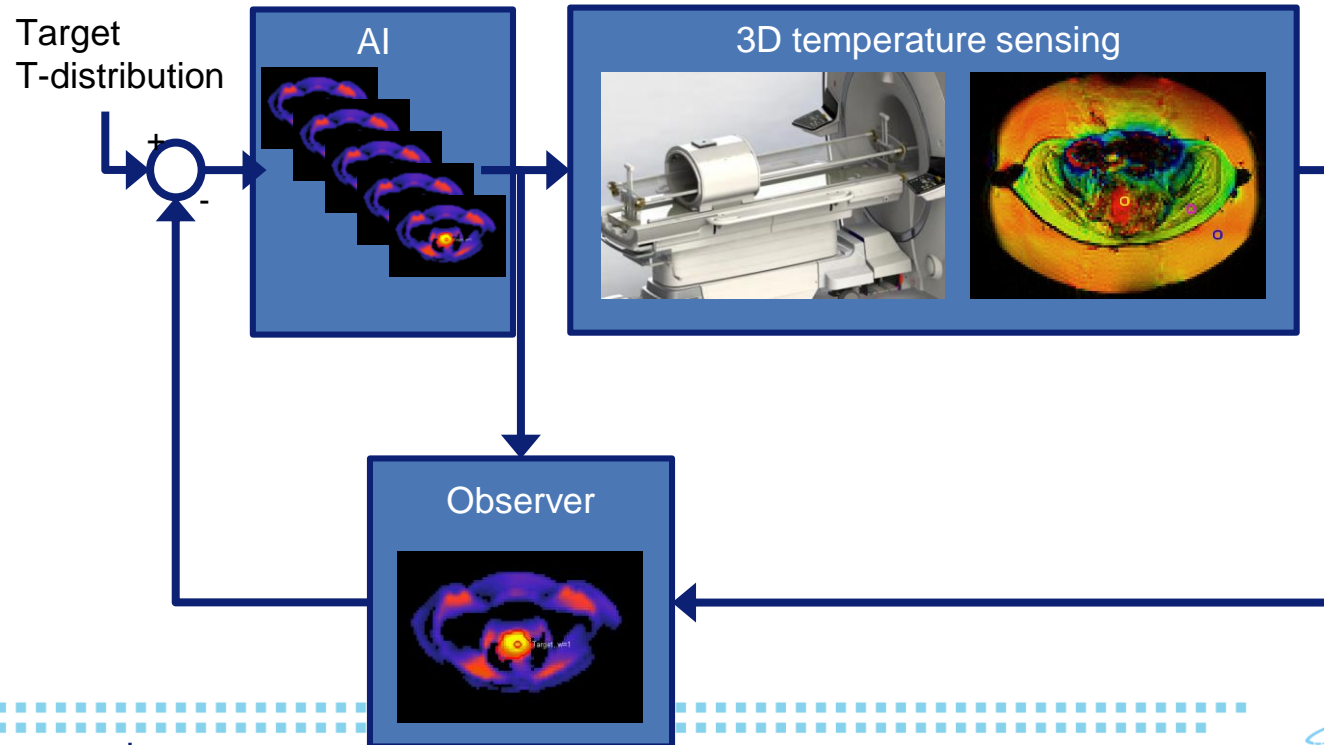
3D measurement in the tumor

3D measurement in the surrounding

Potential automatic optimization

(Detect hotspots before they are a complaint for the patient)

Closing the loop simulations /measurements: Artificial Intelligence



Conclusions

To achieve an effective hyperthermia treatment, we need

1. To know the clinical requirements (dimensions, properties) of the region we want to heat
2. *High quality heating equipment*
3. *Power chain*
4. *Treatment planning*
5. *Precise thermal dosimetry system*
6. *Adequate quality assurance*

We should follow established QA guidelines when evaluating or systems and delivery treatments.

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Erasmus MC

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