Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

Mild Hyperthermia in Cancer Therapy

Gerard C. van Rhoon
g.c.vanrhoon@erasmusmc.nl

Disclosure of potential conflict of interest

Erasmus MC Cancer Institute

1. Employment or Leadership Position
- Erasmus MC Cancer Institute, Rotterdam

2. Advisory Role or Expert Testimony
- Health Council of the Netherlands
- President of the European Society for Hyperthermic Oncology

3. Stock Ownership
- none of the companies mentioned

4. Patent, Copyright, Licensing
- Erasmus MC Daniel den Hoed Cancer Center, Rotterdam

5. Honoraria
- Speag, Sennewald Medizintechnik

6. Financing of Scientific Research
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- Technology Foundation STW, Netherlands Organization for Health Research and Development,
- Erasmus MC Friends Foundation

7. Other Financial Relationships
- none

Definitions for heating tissue

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

Thermal Ablation: High Temperatures >65 ˚C
Short duration: 5-15 min
Single fraction

Direct Cell Kill

Hyperthermia Works!!

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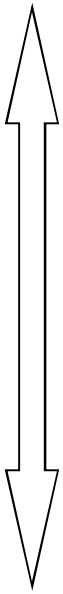
Biology: ***hyperthermia is one of the strongest sensitizers for radiotherapy and chemotherapy***

Hyperthermia Amplifies Radiation and Drugs



43 ºC

42 ºC

41 ºC

40 ºC

39 ºC

38 ºC

37 ºC

36 ºC

Cellular cytotoxicity enhanced at low pH and in S-phase

Heat alone: Direct cell kill

Radiation:
DNA damage repair blocked

RT: more cell kill

Sensitization radiation and drug

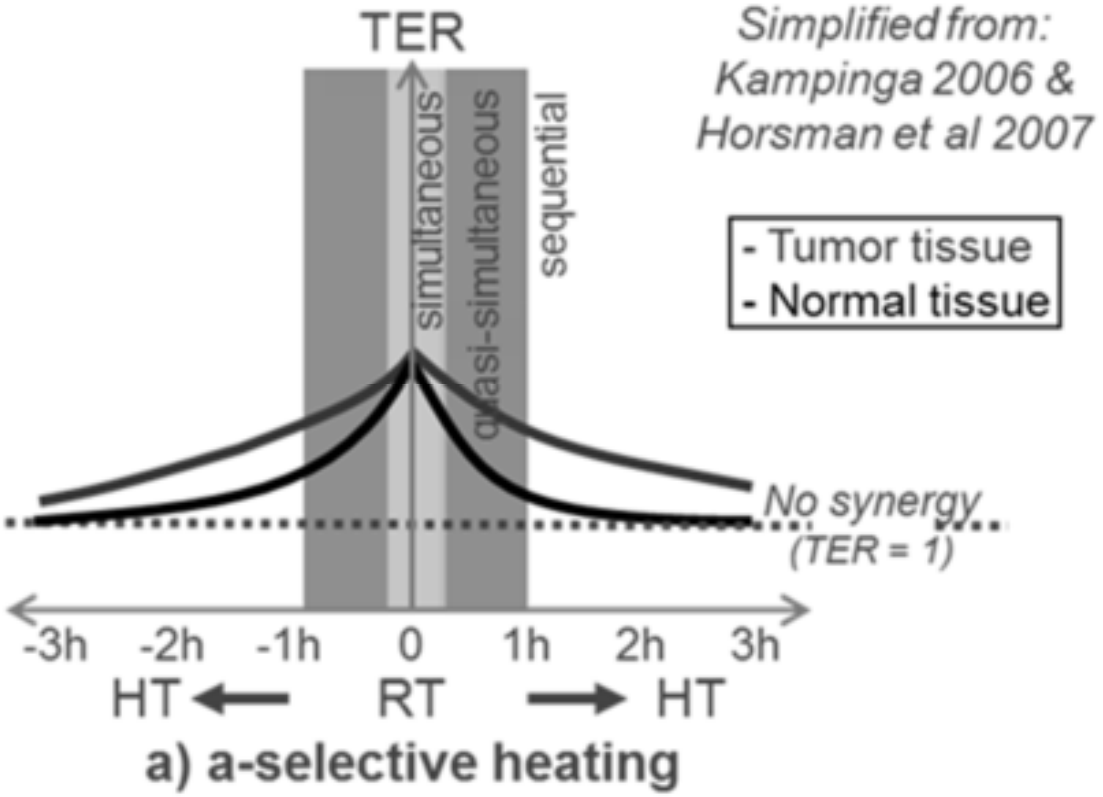
RT & CT more effective

Increased blood perfusion

Better oxygenation
Higher drug concentration
→ RT & CT more effective

Body temperature

Sequential application of Hyperthermia to Radiotherapy: Objective enhance local controle



Impact of sequence & time interval of radiotherapy and hyperthermia on sensitization effect

Hyperthermia Works!!

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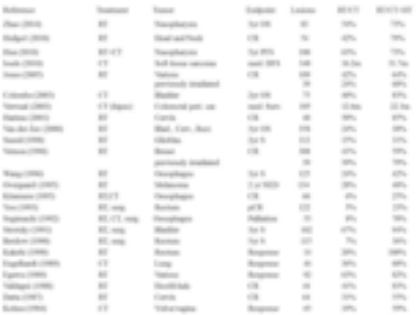
Biology: ***hyperthermia is one of the strongest sensitizers for radiotherapy and chemotherapy***

Has been shown beneficial for patients with

- ***advanced tumors***
- ***recurrent tumors in previously irradiated areas***

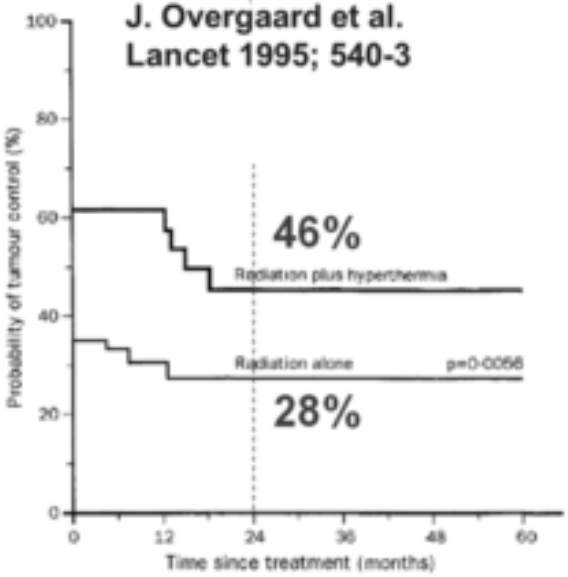
- ***24 positive randomized trails RT or CT ± HT***
- ***10 inconclusive randomized trails on RT or CT ± HT (many of those criticized for low quality of heating)***



THE LANCET Oncology

Inoperable melanoma

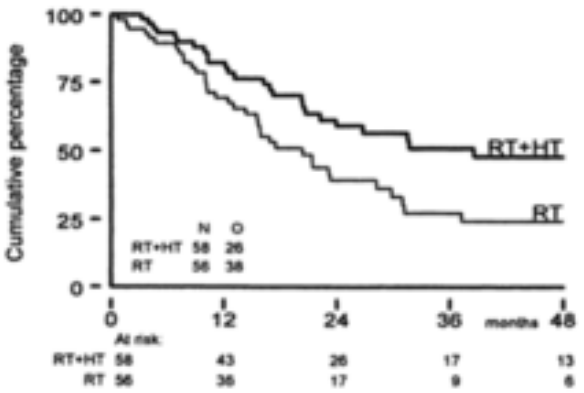
J. Overgaard et al.
Lancet 1995; 540-3



local advanced cervical cancer

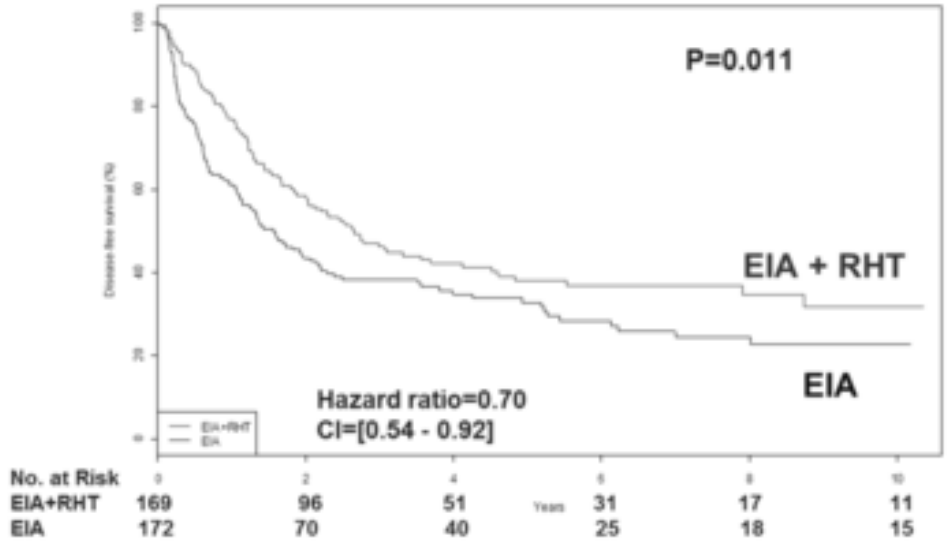
Van der Zee et al. Lancet 2000;355:1119

Cervix 3-yrs overall survival
27% → 51%



localised high-risk soft-tissue sarcoma

Issels et al., Lancet Oncology 2010, 561-70



Hyperthermia Works!!

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- ***advanced tumors***
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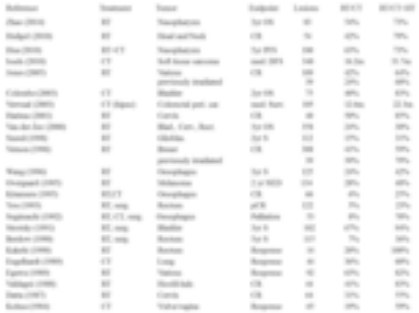

- ***24 positive randomized trails RT or CT ± HT***
- ***10 inconclusive randomized trails on RT or CT ± HT (many of those criticized for low quality of heating)***

- ***In most trials: hyperthermia does not enhance late toxicity***
- ***Clinical experience that it can be applied to frail elderly people (who are excluded for surgery or intolerant for chemotherapy)***

Most common techniques to induce hyperthermia use electromagnetic energy

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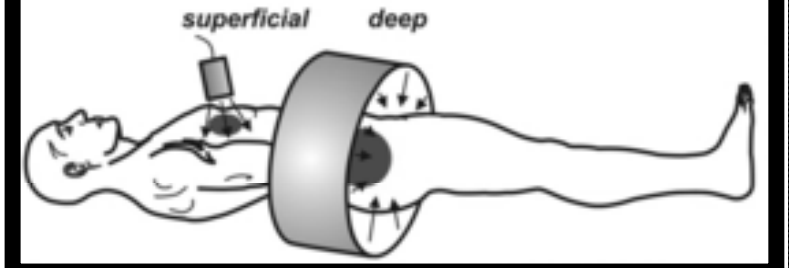
LOCAL EXTERNAL	LOCAL INVASIVE
- radiative 	[redacted]

Other technologies used, are:

- **Ultrasound**
- **Infrared**
- **Laser**
- **Magnetic nano-particles**

Hyperthermie systemen Erasmus MC

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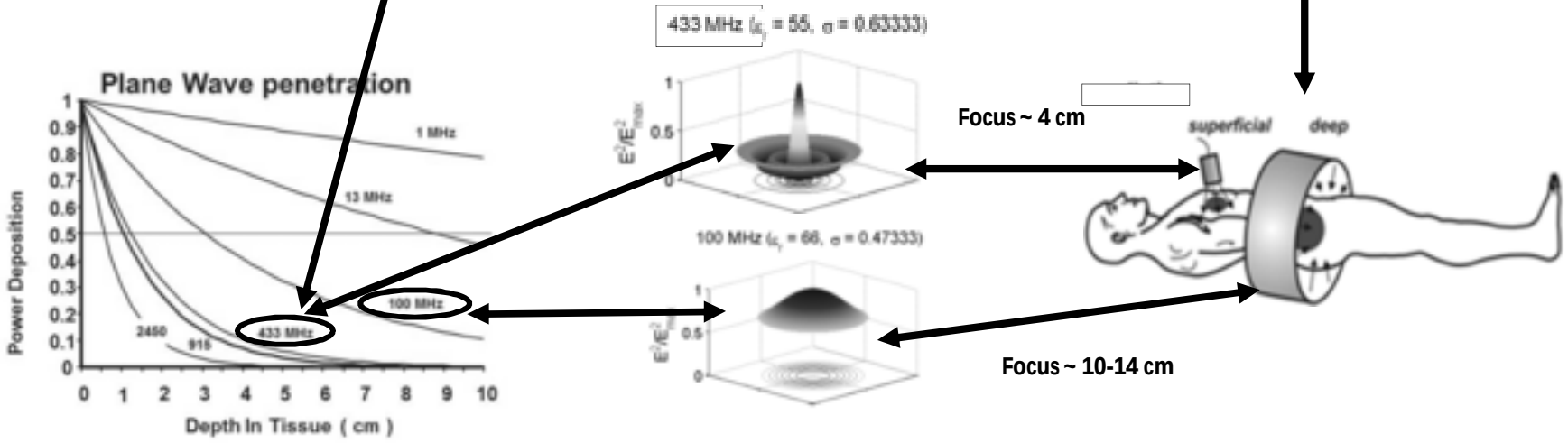
Superficial Hyperthermia:	Loco regional hyperthermia:	Regional deep hyperthermia:
tumors up to 4 cm depth.	Tumor locations in Head and Neck region	Tumor locations at depths > 4cm, i.e. Pelvis, thorax.



Energy steering to obtain optimal heating

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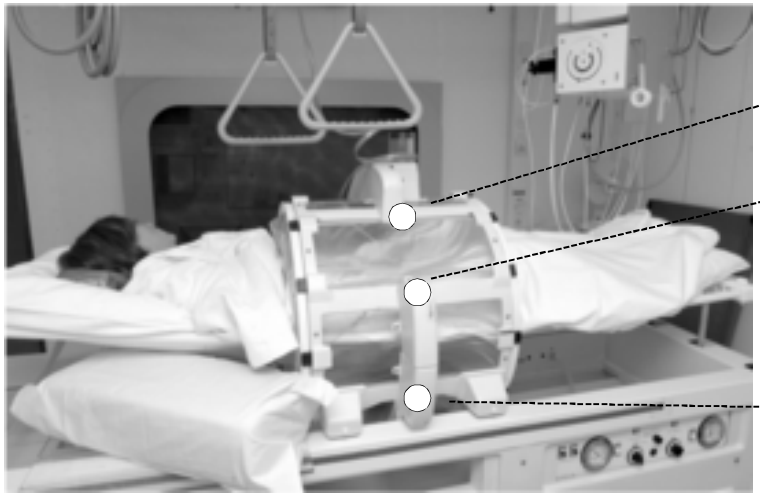
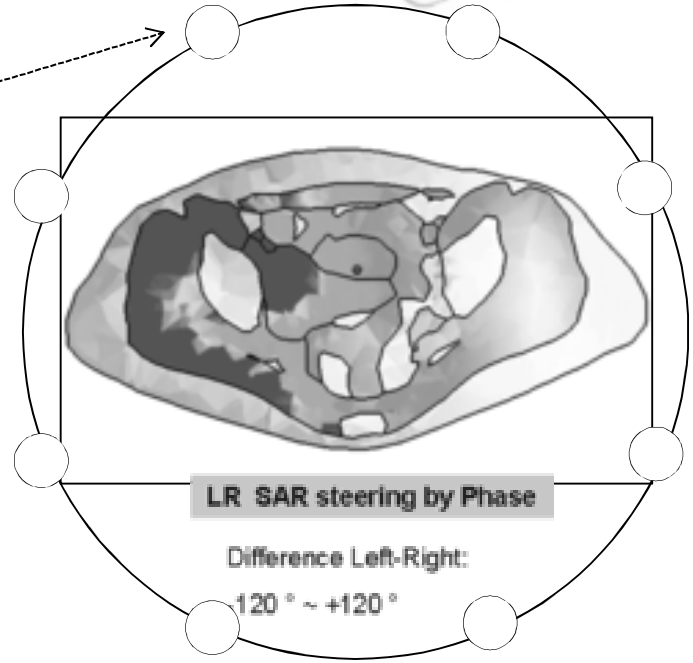


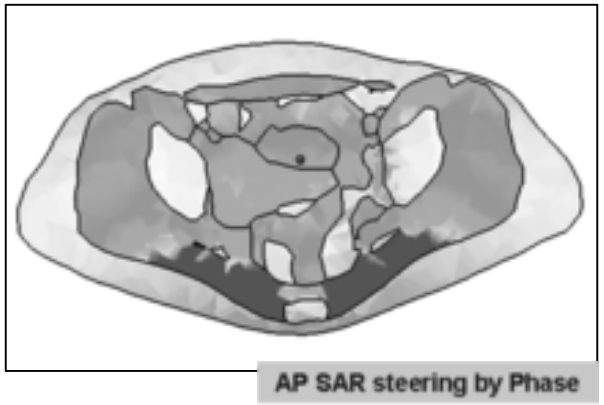


Focused energy deposition at depth: circumferential EM field, constructive interference.

Main challenges

- *Measure temperature at depth*
- *Target energy to the tumor*
- *Prevent acute thermal toxicity*

- *Solutions have been implemented during last decennium.*



Thermal dose effect relationships indicate the need to maximize tumor temperature

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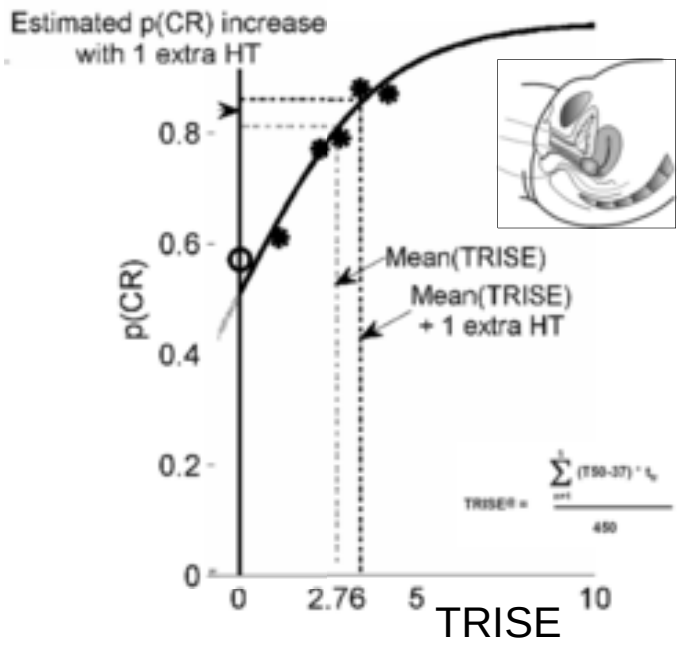
Thermal dose effect relationship

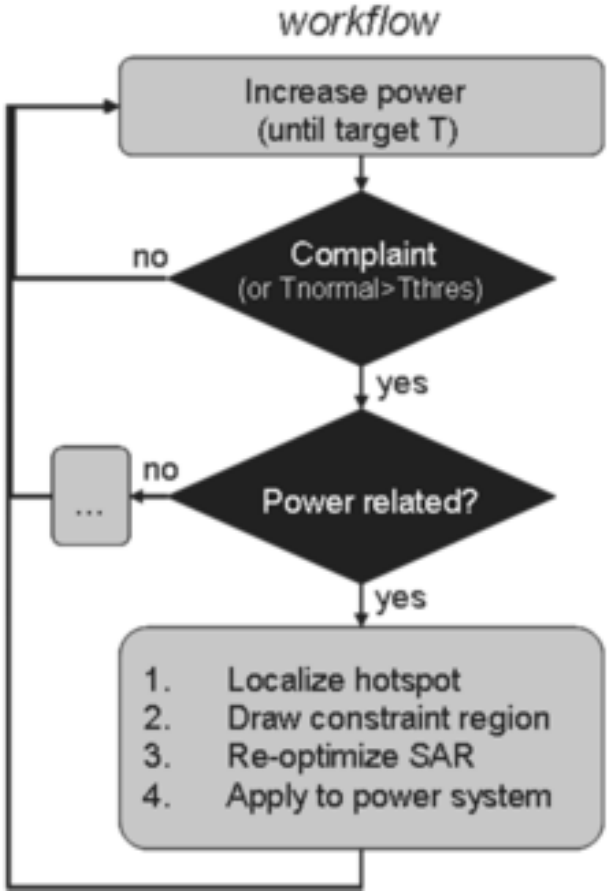
Franckena et al., 2009 European J Cancer



Of 444 patient, 40% showed a positive correlation between T50 and applied energy.

Fatehi et al., 2007 , Int. J. of Hyperthermia

Online Complaint adaptive SAR steering using VEDO



Hyperthermia Treatment Planning (HTP): an essential part for optimal treatment delivery

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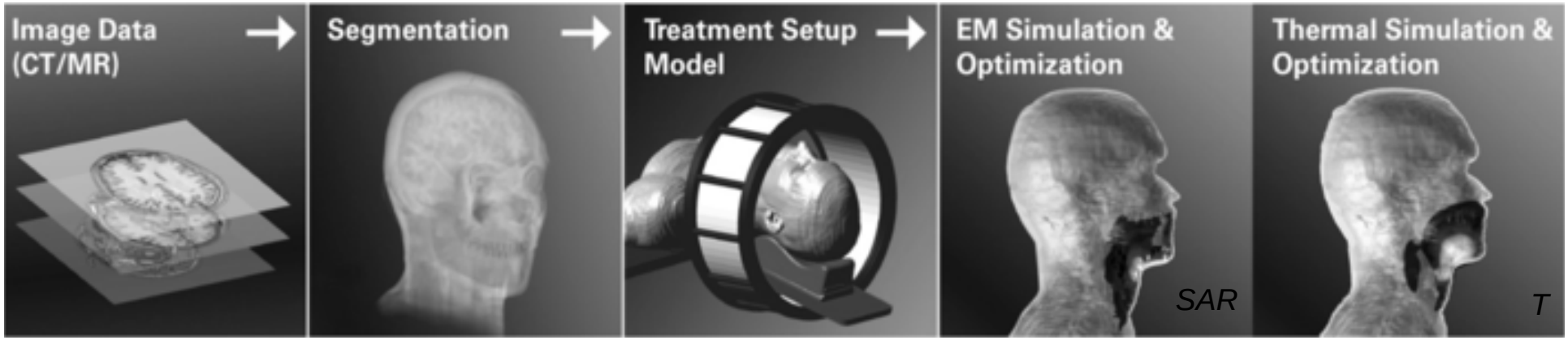
Workflow



VEDO is an online HTP-GUI to guide energy steering during actual treatment delivery

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VEDO is an online HTP-GUI to guide energy steering during actual treatment delivery

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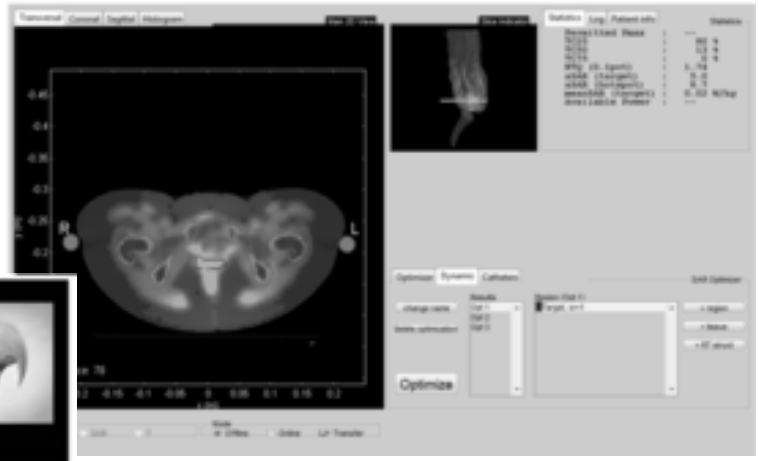

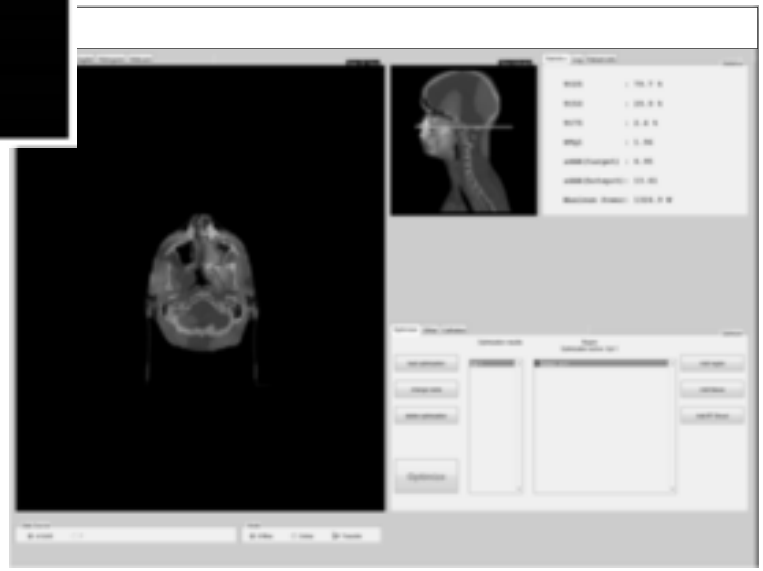

Pre-treatment plan

Real-time adapted plan

Clinical experience from hyperthermia

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- ***The human body has an efficient physiological defense mechanism to limit temperature increase under thermal stress (despite a high RF-power input it is hard to increase the average temperature)***

Variable thermal regulation response within a patient after a deep hyperthermia treatment for 90 minutes at 40-42 ºC

Clinical experience from hyperthermia

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- ***The human body has an efficient physiological defense mechanism to limit temperature increase under thermal stress (despite a high RF-power input it is hard to increase the average temperature)***
- ***High temperatures at the skin are sensed as burning pain***
- ***High temperatures at depth are sensed as pressure pain, urging, period pain, etc.***
- ***Responding to pain complaints can adequately confine thermal toxicity***
- ***Areas with reduced sensitivity have a high risk for burns (skars have also a reduced perfusion making them extra vunerable to thermal damage)***
-

Loco-regional deep heating
Typical values

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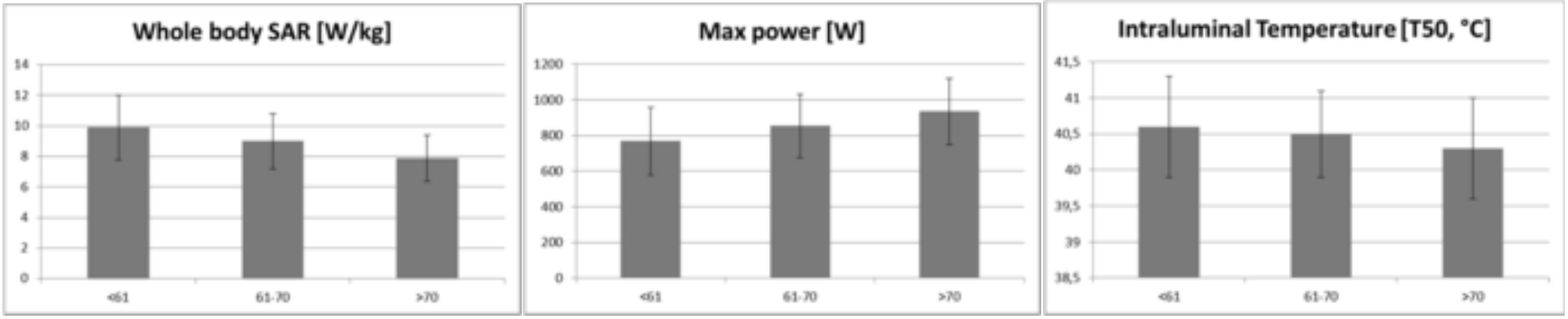
RF-power and temperature data analysis of 444 patients with primary cervical cancer
Fatehi et al., 2007 , Int. J. of Hyperthermia

Whole body SAR for therapeutic temperatures: 9-10 (± 2) W/kg
Max. Forward power applied: 768-934 (± 185) W

More power is needed for heavier patients though average temperature is lower.



Three weight groups

Acute hyperthermia toxicity to subcutaneous tissue

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Grade	Description	Number
0	No symptoms	267
1	Symptoms lasting less than 3 days	80
2	Symptoms lasting 3-14 days	60
3	Symptoms lasting 3-14 days, or causing a delay or interruption of treatment	16
4	Symptoms requiring surgery	1

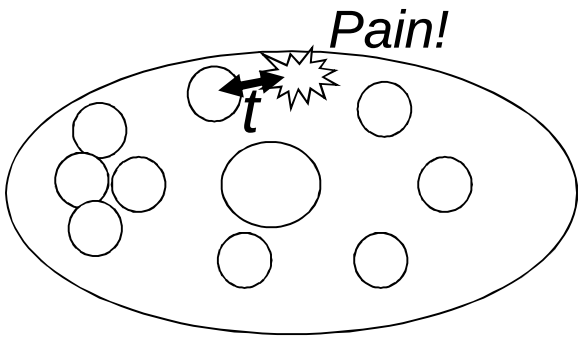
Patients with toxicity had:

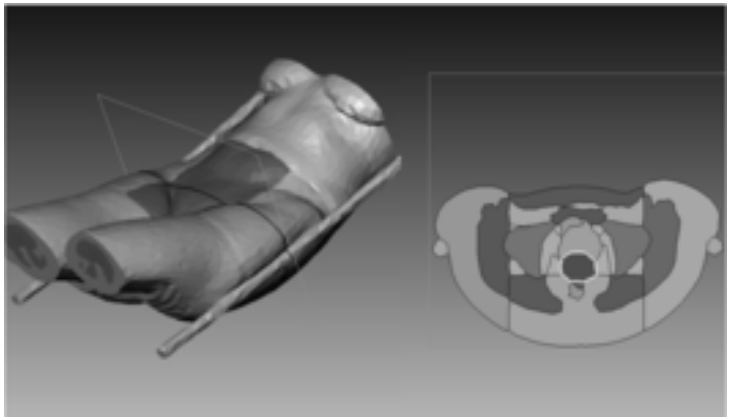
- **thicker (0.7 cm) dorsal subcutaneous fat**
- **were larger in anterior-posterior (0.9 cm) and lateral (1.5 cm) directions.**

After adjustment for these factors, only the average intraluminal TRISE increase correlated with toxicity probability
(TRISE 1.7 ºC higher, p = 0.010)

Five patients developed grade 3 neurotoxicity

Location complaints matches with predicted location hot-spot





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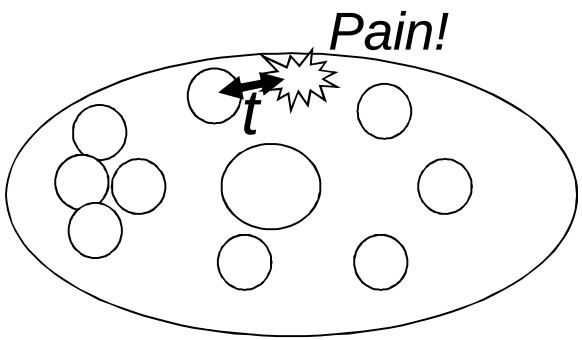
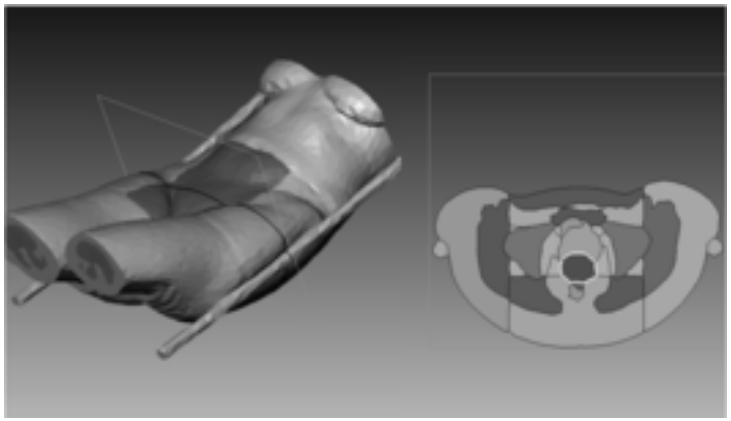
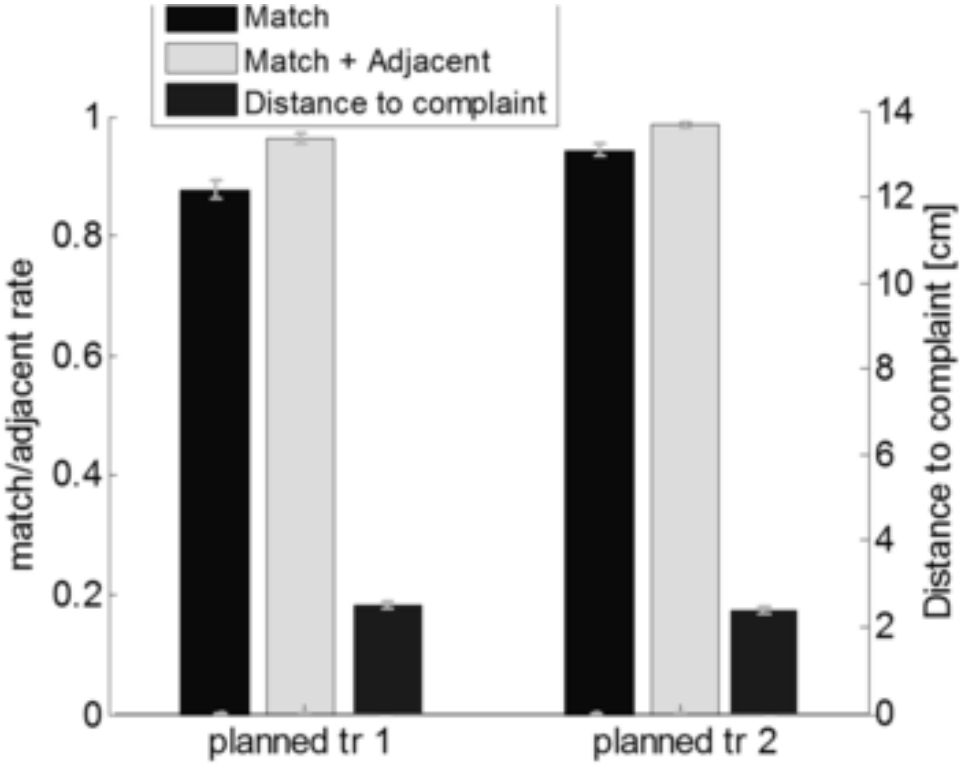




Closest HS in model



~90% of complaints have a predicted hotspot in the same region as the actual complaint

No clear relation between max SAR values (10ml) during treatment and complaints

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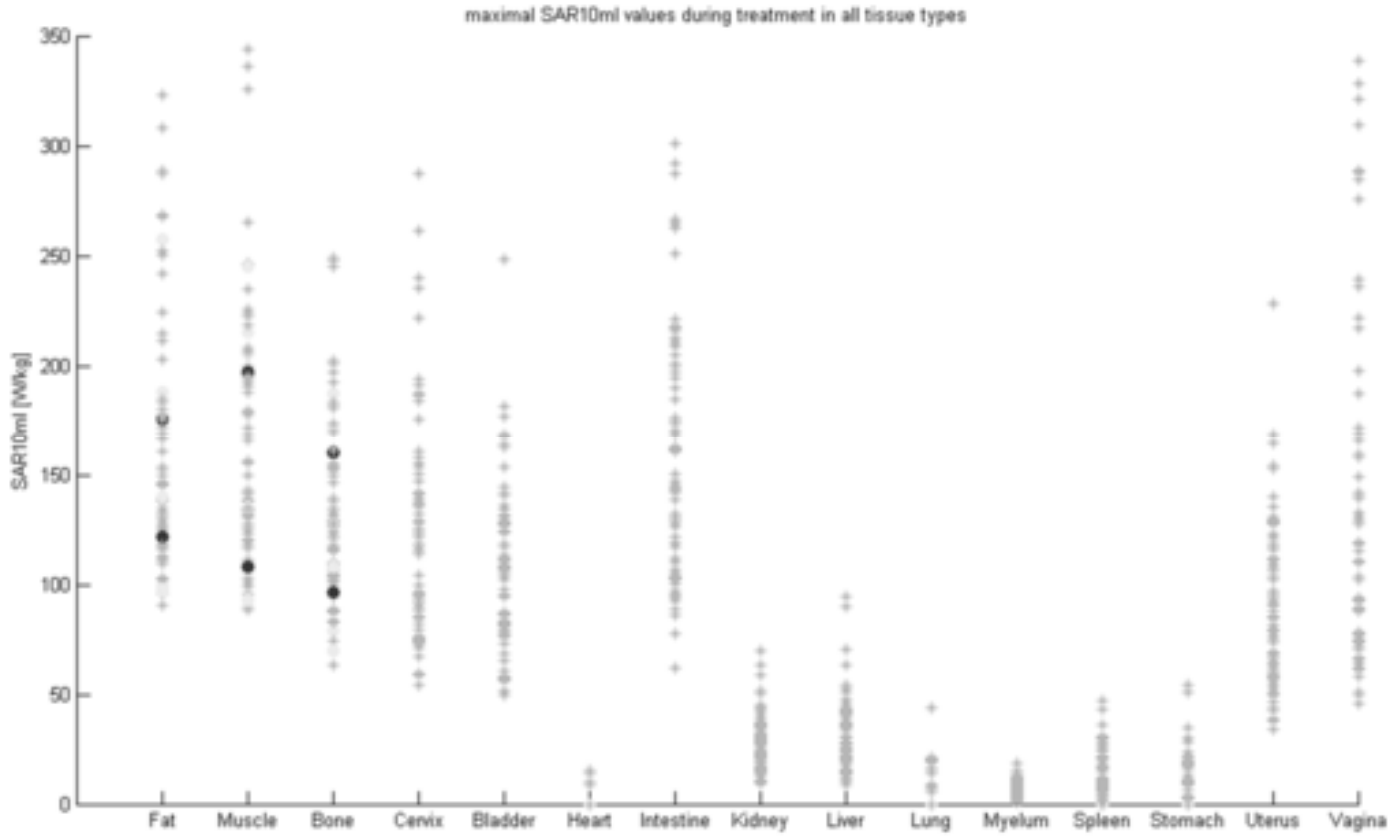

○ *No complaints* ○ *Complaints* ○ *Toxicity*

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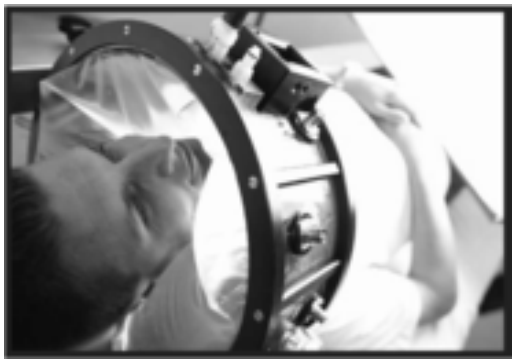

Exposure of the brain during deep microwave hyperthermia in the Head and Neck region has been accessed for 16 patients

Fatemeh Adibzadeh*, R.F. Verhaart, G.M. Verduijn, V. Fortunati, M. Franckena, G.C. van Rhoon, M.M. Paulides

*f.adibzadeh@erasmusmc.nl

Hyperthermia Unit, Departement of Radiation Oncology,

Erasmus MC- Cancer Center, Rotterdam, The Netherlands

This work is supported by: ZonMw

HT treatment planning

overview

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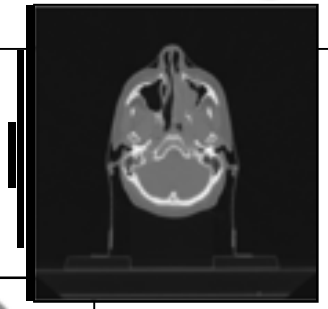
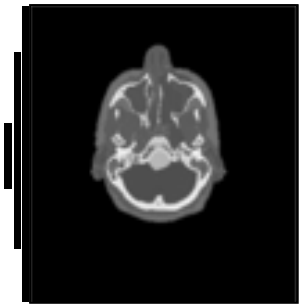
CT scan

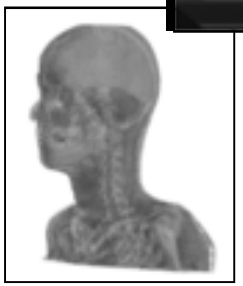
~200 slices



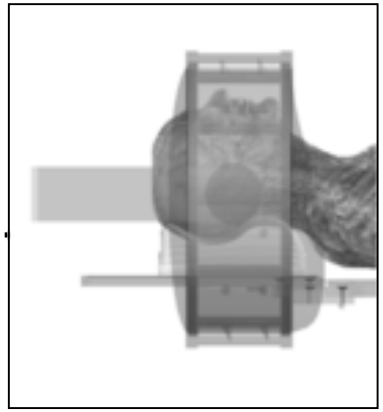


segmentation

Patient model



Applicator model



EM simulation & optimization

T simulation & optimization

Purposes: decision making, optimization, analyses

HT treatment planning

overview

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CT scan

segmentation

Patient model

Applicator model

EM simulation & optimization

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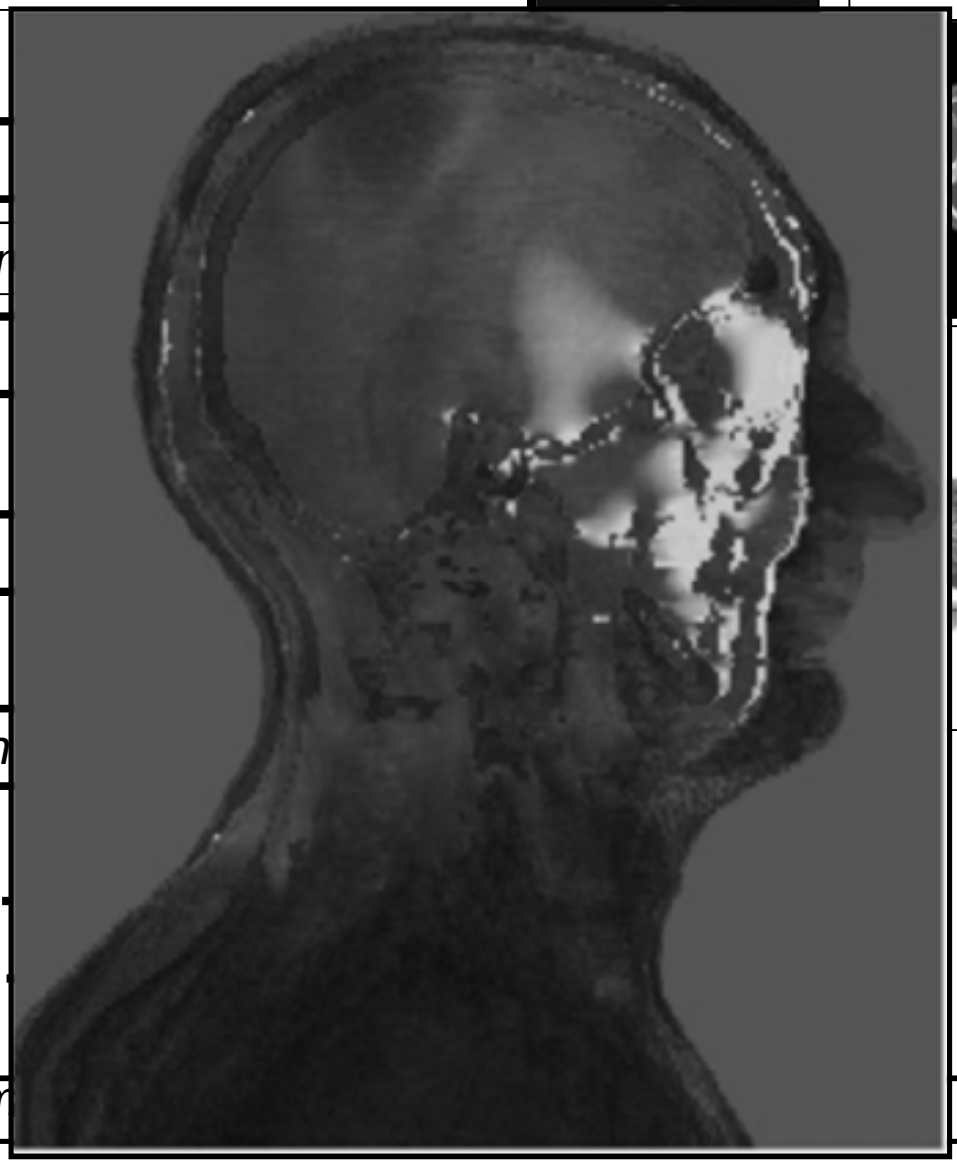
Purposes: decision making, optim



Induced psSAR in the brain: Influence of brain tissue segmentation

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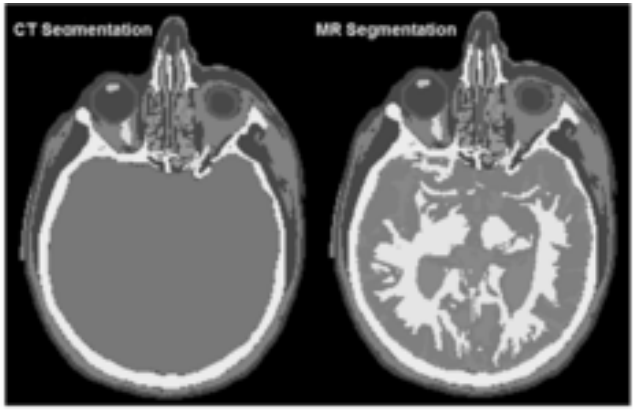
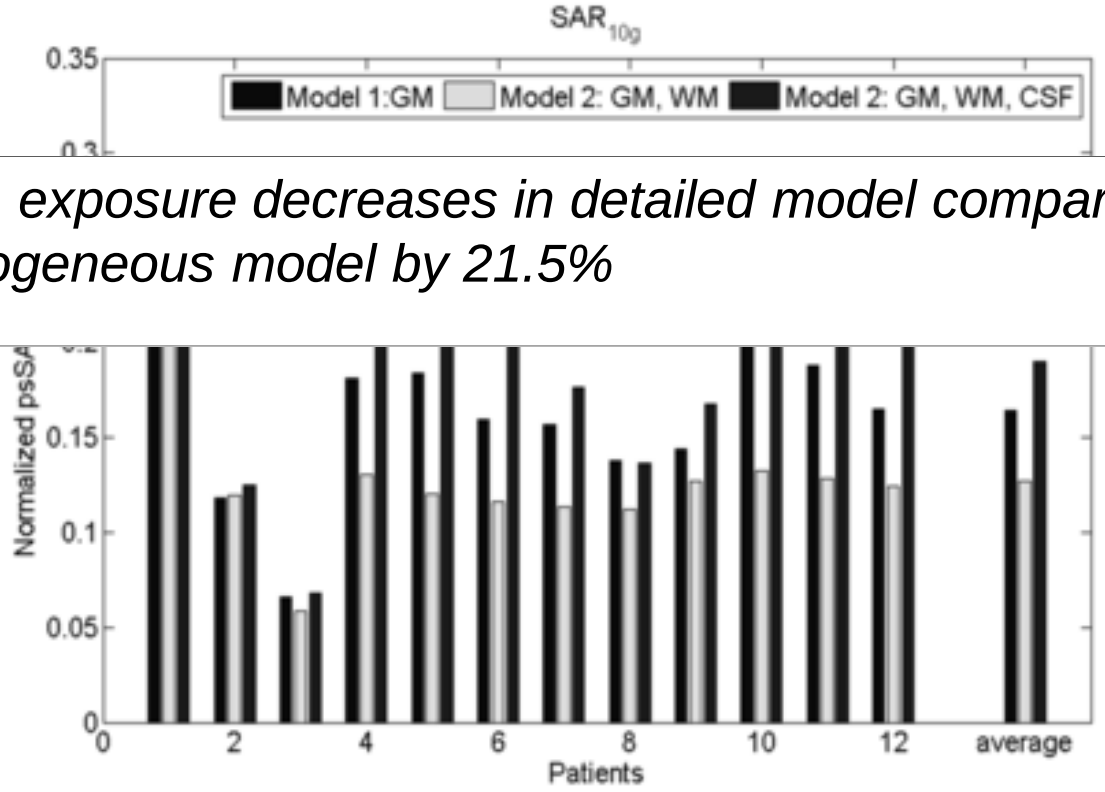
- Segmentation details:





Brain exposure decreases in detailed model compared to homogeneous model by 21.5%

Induced psSAR in the brain (10 g)

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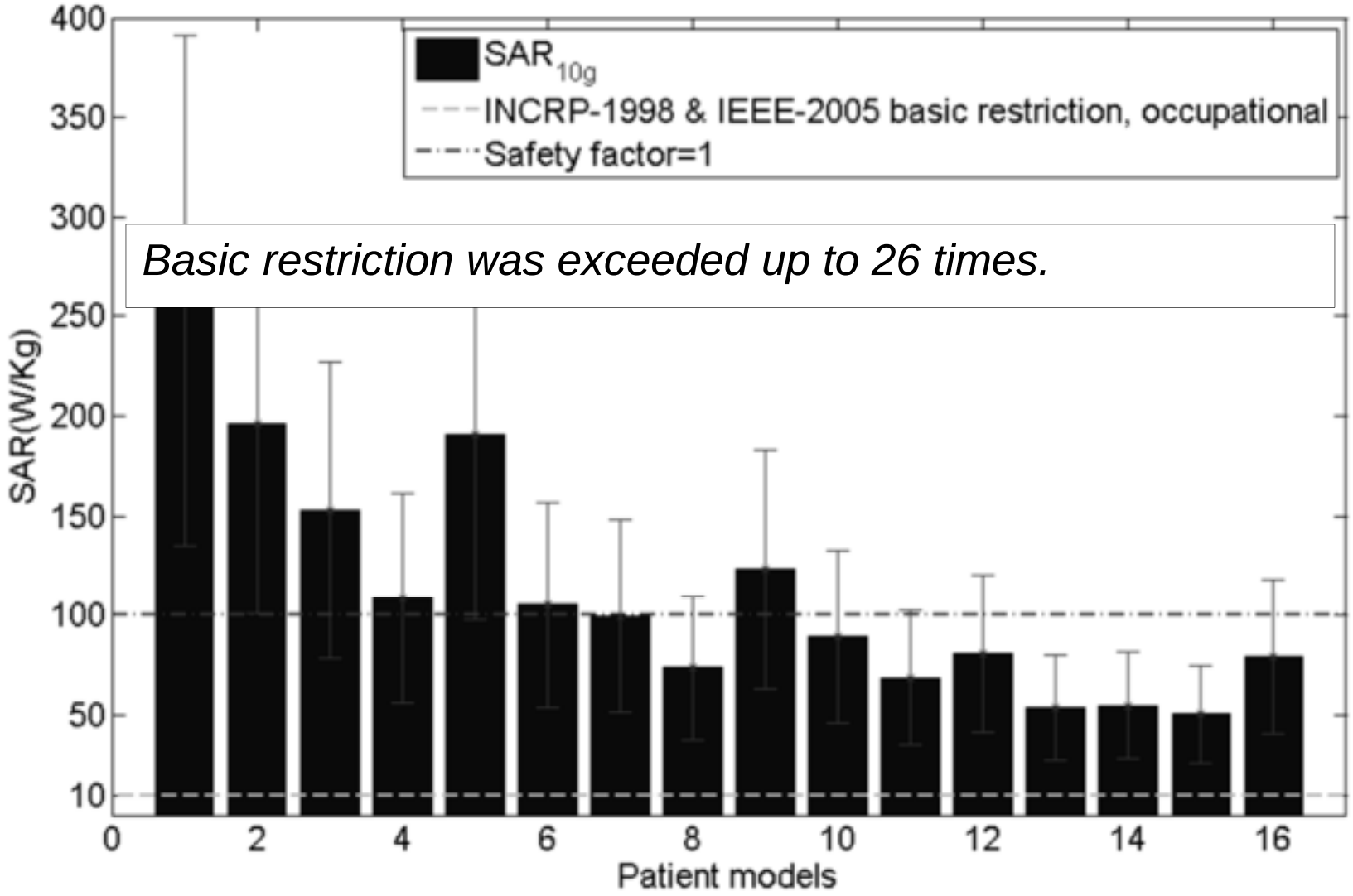

Basic restriction was exceeded up to 26 times.

HT-related acute health effect

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- Common Toxicity Criteria (CTC) is a standardized classification of adverse effects used in cancer therapy evaluation, developed by National Cancer Institute.

CTC Grades definition:

Grade	Definition
1	Mild adverse event; asymptomatic or mild symptoms; Clinical or diagnostic observations only; intervention not indicated.
2	Moderate adverse event; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event

Activities of Daily Living (ADL)
**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*
***Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

Observed acute toxicity for the 16 selected patients

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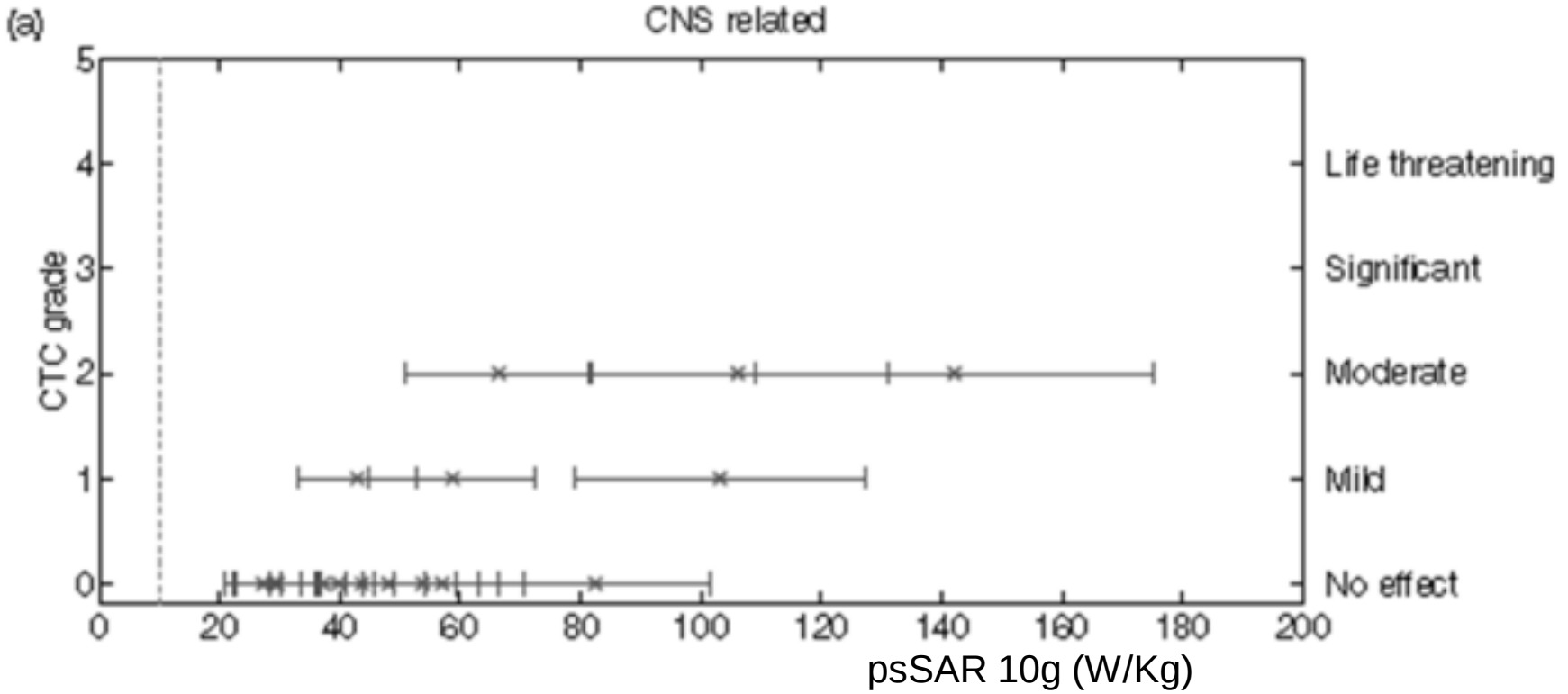
Table 3. Observed acute toxicity for the selected HT patients. Note that the number of incidents were counted, i.e. not just one incident per patient, so every treatment session always led to one score.

	Nr of patients: 16 Total Nr of HT sessions:74						
	CTC-grade	0	1	2	3	4	5
CNS-related	Pns motory	74	0	0	0	0	0
	Pns sensory	71	1	2	0	0	0
	Headache	73	1	0	0	0	0
	Pain in Eye	73	1	0	0	0	0
	Dizziness	73	1	0	0	0	0
	Nausea[a]	71	2	1	0	0	0
	Vomiting[a]	72	2	0	0	0	0
Subcut burns	Subcut skin	70	2	0	2	0	0
	Subcut fat	72	0	2	0	0	0
	Subcut muscle	72	0	2	0	0	0
	Subcut bone	69	1	3	1	0	0

[a] Nausea and vomiting may stem from reactions in the CNS but also from many other causes. In this study they are considered as CNS-related acute effects.

Observed acute toxicity for the 16 selected patients versus psSAR

Adibzadeh F., PMB, 2015



Evaluation of acute adverse effects from prolonged exposure to deep RF head and neck hyperthermia reveals that although the brain was exposed up to 14 times the common basic restriction on psSAR10g, there is no indication of any induced serious neurological adverse effect. This study provides initial data that enables to determine the basic restrictions based on the functional change that is to be prevented and the level of safety to ensure prevention.

Temperature simulations in hyperthermia treatment planning of the head and neck region: Rigorous optimization of tissue properties

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Verhaart R, Strahlenther Onkol 2014

Table 3 Literature values for baseline [13–16] and thermal stress [17], as well as the optimized patient group values from this study for perfusion (ω) and thermal conductivity (k) in tumor, muscle, and fat tissue

	ω_{Tumor}	ω_{Muscle}	ω_{Fat}	k_{Tumor}	k_{Muscle}	k_{Fat}
	[ml min^{-1} kg^{-1}]			[W m^{-1} °C^{-1}]		
Literature: baseline	400.0	39.1	32.7	0.51	0.49	0.21
Literature: thermal stress	80.0	300.0	200.0	0.64	0.64	0.21
Optimized (this study)	1146.0	563.6	76.7	0.97	5.75	0.38

Perfusion (ω) and thermal conductivity (k) were simultaneously optimized for muscle, fat, and tumor by minimizing the cumulative error between measured and simulated temperature points at steady state Temperature (Tss) in a group of 17 patients.

Summary

Hyperthermia is valuable adjuvant to radiotherapy and chemotherapy in the treatment of cancer.

Toxicity associated with hyperthermia is mainly acute and consists of thermal burns, mostly of grade 1-2.

The high energy exposue levels of EMF for hyperthermia can be informative for potential assessment of threshold levels for EMF effects in critical tissues, such as brain, as this is one of the few occasions where human tissue is exposed above the ICNIRP guidlines.
First analysis of such human data have not shown adverse, acute effects at levels 14 times of the common basic restriction guideline of ICNIRP.

Acknowledgements.

Dept. of Radiation Oncology
- Radiation Oncologists

www.erasmusmc.nl/radiotherapie

Members of the Rotterdam Hyperthermia group

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TNO-FEL Netherlands

ITIS & Speag, Zurich, Swiss

Dutch National Aerospace laboratorium

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- Utrecht
- Amsterdam
- Duke
- San Francisco

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