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HYPERBOOST Boosting the effect of Radiotherapy

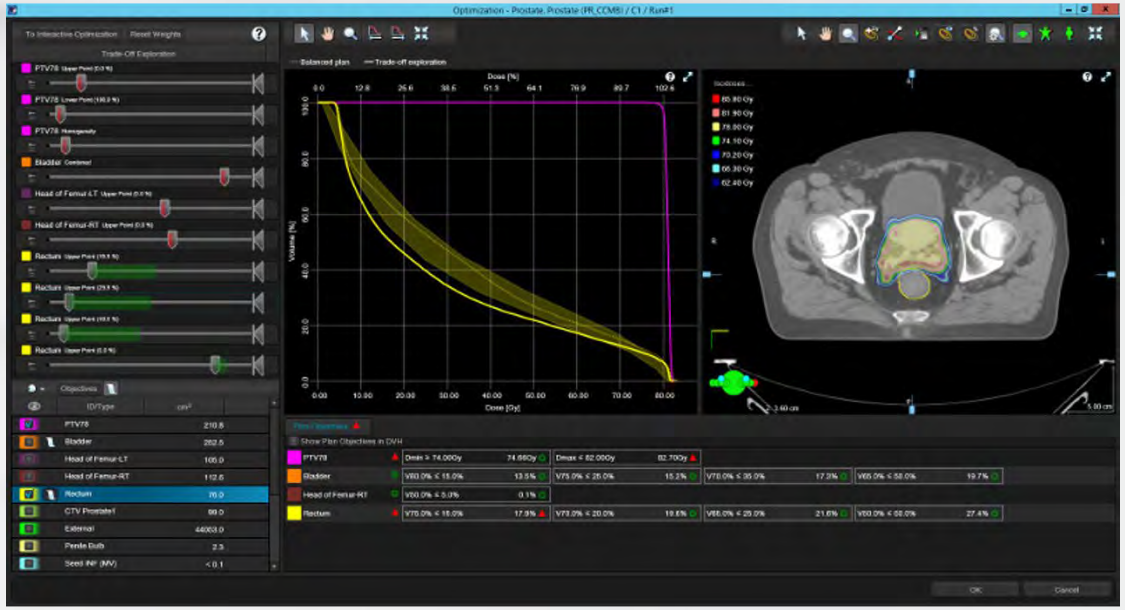
CLINICAL USER INTERFACE FOR HYPERTHERMIA TREATMENT PLANNING SYSTEM (ESR8)

ALBA precision hyperthermia

Artemis Kontogoula
Supervisors: P. Pavoni, P.Kok

TREATMENT PLANNING SYSTEM IN RADIOTHERAPY

A Treatment Planning System (TPS) is **a computer system used to produce a safe and effective dose distribution**



TREATMENT PLANNING SYSTEM IN RADIOTHERAPY

RAYSEARCH
LABORATORIES
STOCKHOLM
2022

TREATMENT PLANNING SYSTEM IN HYPERTHERMIA

TREATMENT PLANNING FACILITATES CLINICAL DECISION MAKING FOR HT TREATMENTS

International Journal of Hyperthermia

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ihyt20

Treatment planning facilitates clinical decision making for hyperthermia treatments

H. P. Kok, J. van der Zee, F. Navarro Guirado, A. Bakker, N. R. Datta, S. Abdel-Rahman, M. Schmidt, P. Wust & J. Crezee

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TREATMENT QUALITY STRONGLY DEPENDS ON THE ACHIEVED TUMOR TEMPERATURES AND TREATMENT PLANNING

↓

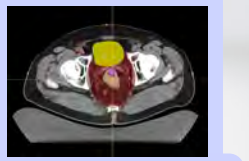
HYPERTHERMIA TREATMENT PLANNING (HTP) CAN BE APPLIED IN CLINICAL DECISION MAKING BOTH FOR **SUPERFICIAL AND LOCOREGIONAL HYPERTHERMIA TREATMENTS**

BASIC HTP CAN FACILITATE CLINICAL DECISION MAKING AND IMPROVING TREATMENT QUALITY

HYPERTHERMIA TPS

ALBA HTPS - PLAN2heat WORKFLOW

PLAN2heat
3D adaptive simulation



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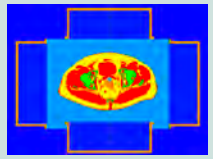


Create Model

CT preprocessing

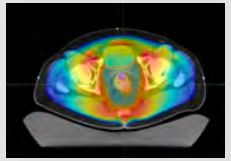
HU automatic segmentation

Segmentation import

Antenna positioning/
Array registration

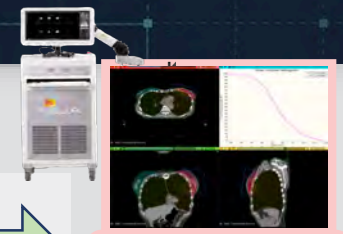
1 2 a b c d e

HT simulation



Computing

3



HT dose comparison

Settings Optimization

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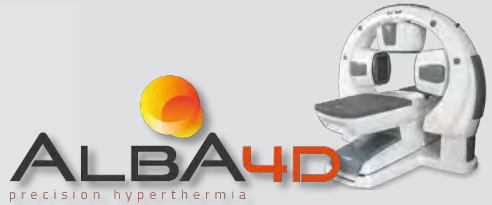
ALBA HTPS - PLAN2heat WORKFLOW

PLAN2heat
3D adaptive simulation



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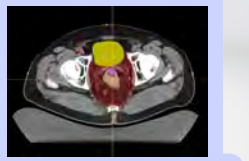
Boosting the effect of Radiotherapy

HYPERBOOST APPROACH

ALBA HTPS - PLAN2heat WORKFLOW

PLAN2heat
3D adaptive simulation



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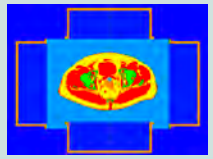

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SEGMENTATION IMPORT

Antenna positioning/
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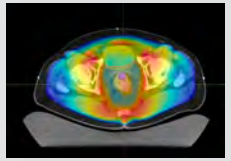
HT simulation



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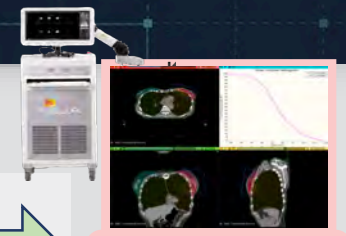

HT dose comparison

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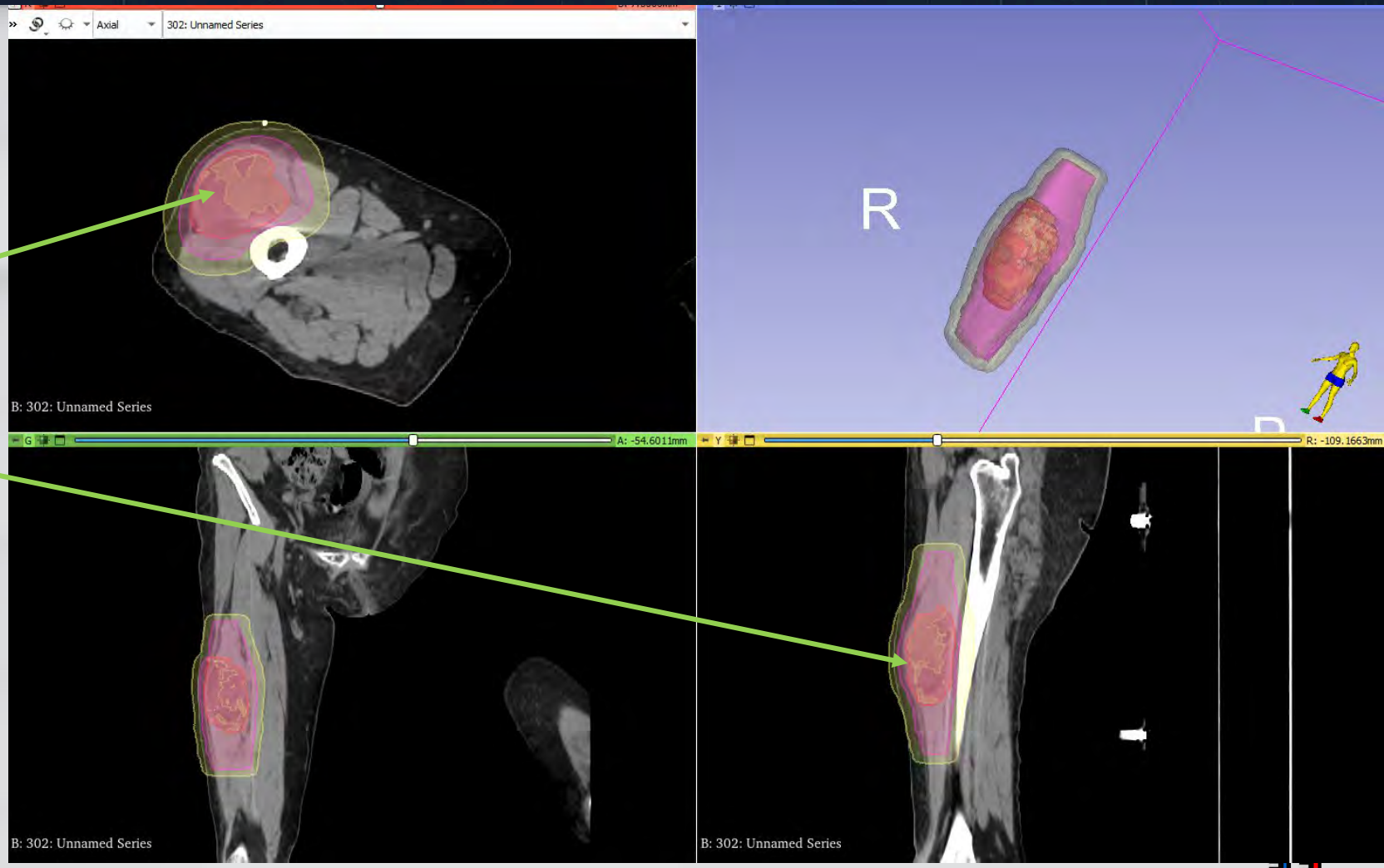
PLAN2heat
3D adaptive simulation

PATIENT-SPECIFIC MR-PERFUSION IMAGING FOR MORE ADVANCED TERMAL MODELLING

Hypoxic area
(MRI image)

MR modality → RT TPS → HT TPS

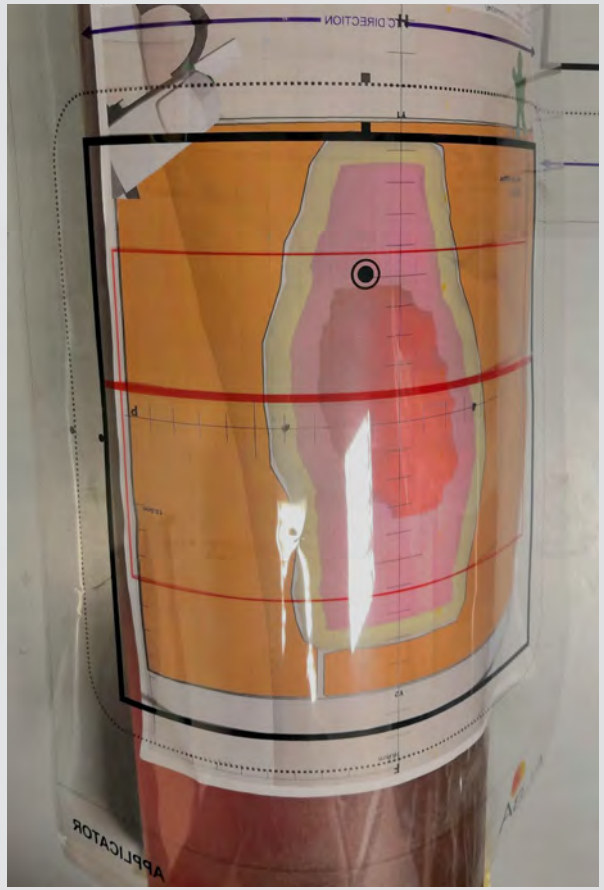


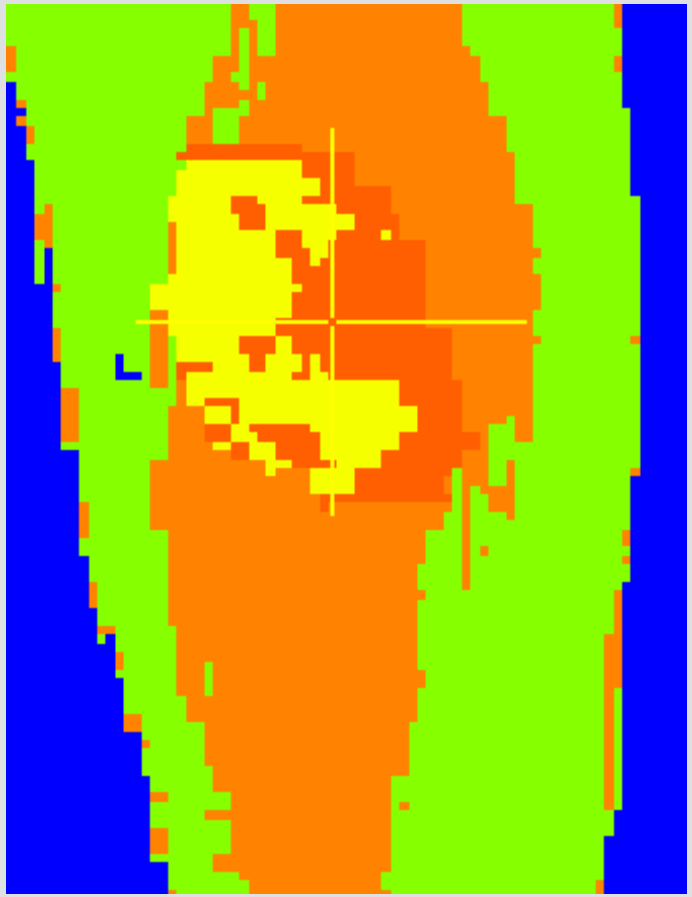
PLAN2heat
3D adaptive simulation

PATIENT-SPECIFIC MR-PERFUSION IMAGING FOR MORE ADVANCED TERMAL MODELLING

Hyperthermia Treatment Planning

1. Antenna selection (tumor size)
2. Configuration selection (antenna positioning)
3. Configuration check
4. Hypoxic area response





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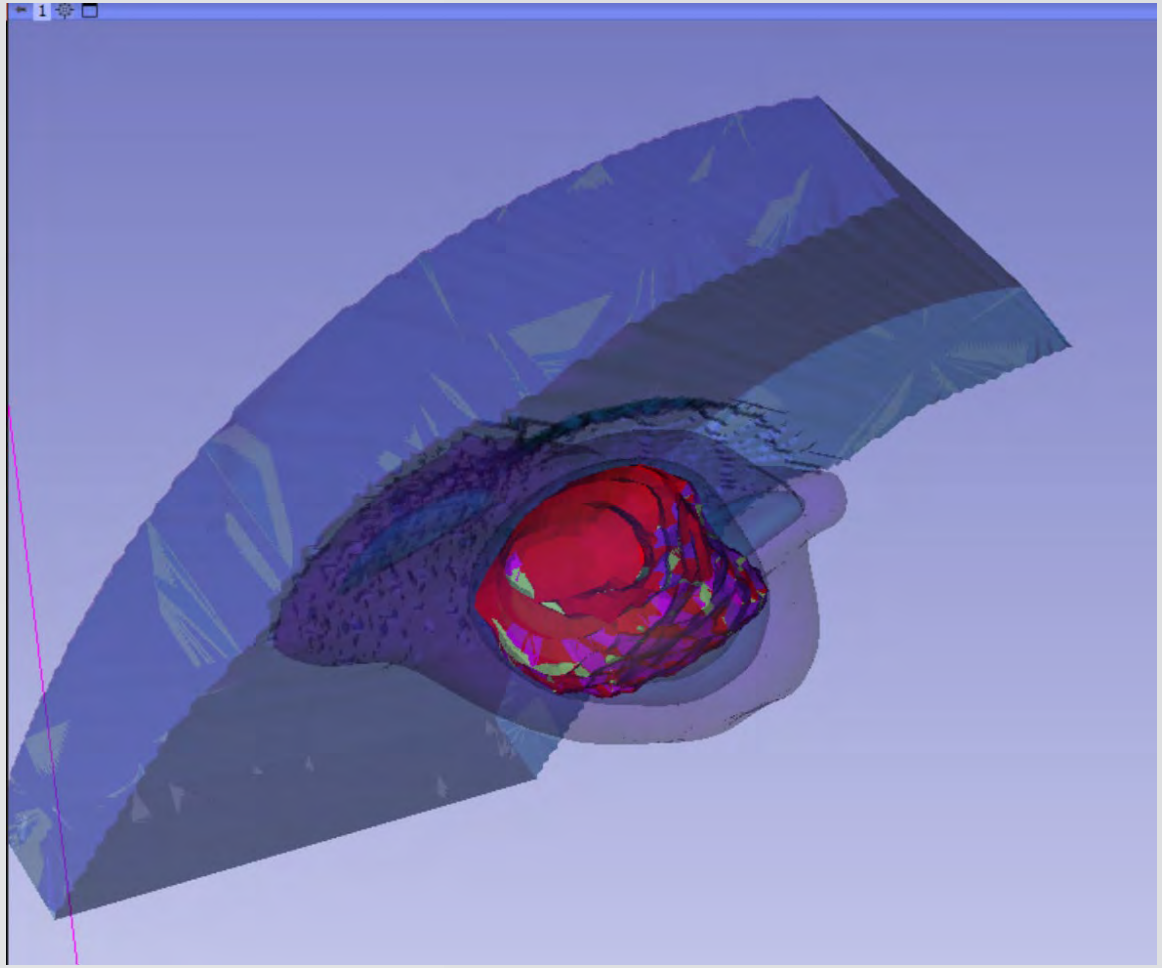

HYPERBOOST
Boosting the effect of Radiotherapy

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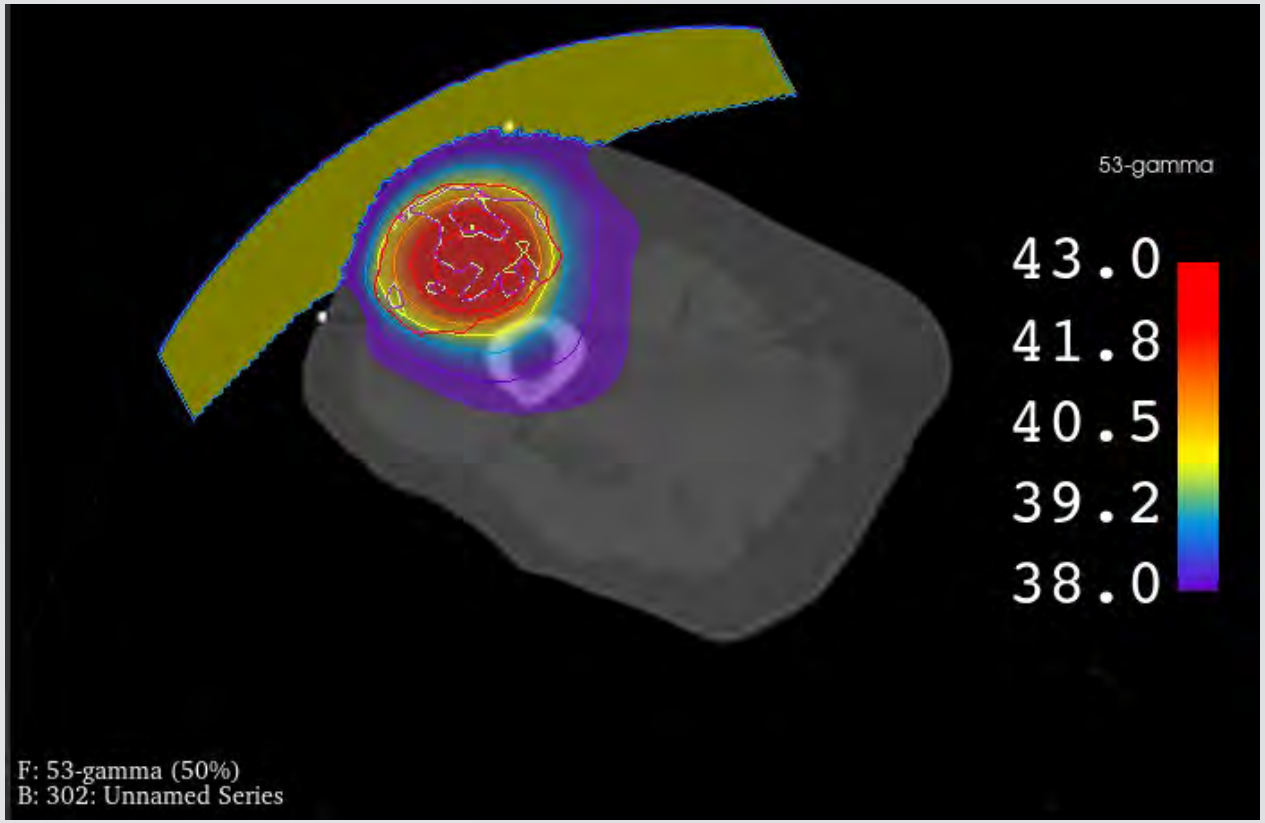

PLAN2heat
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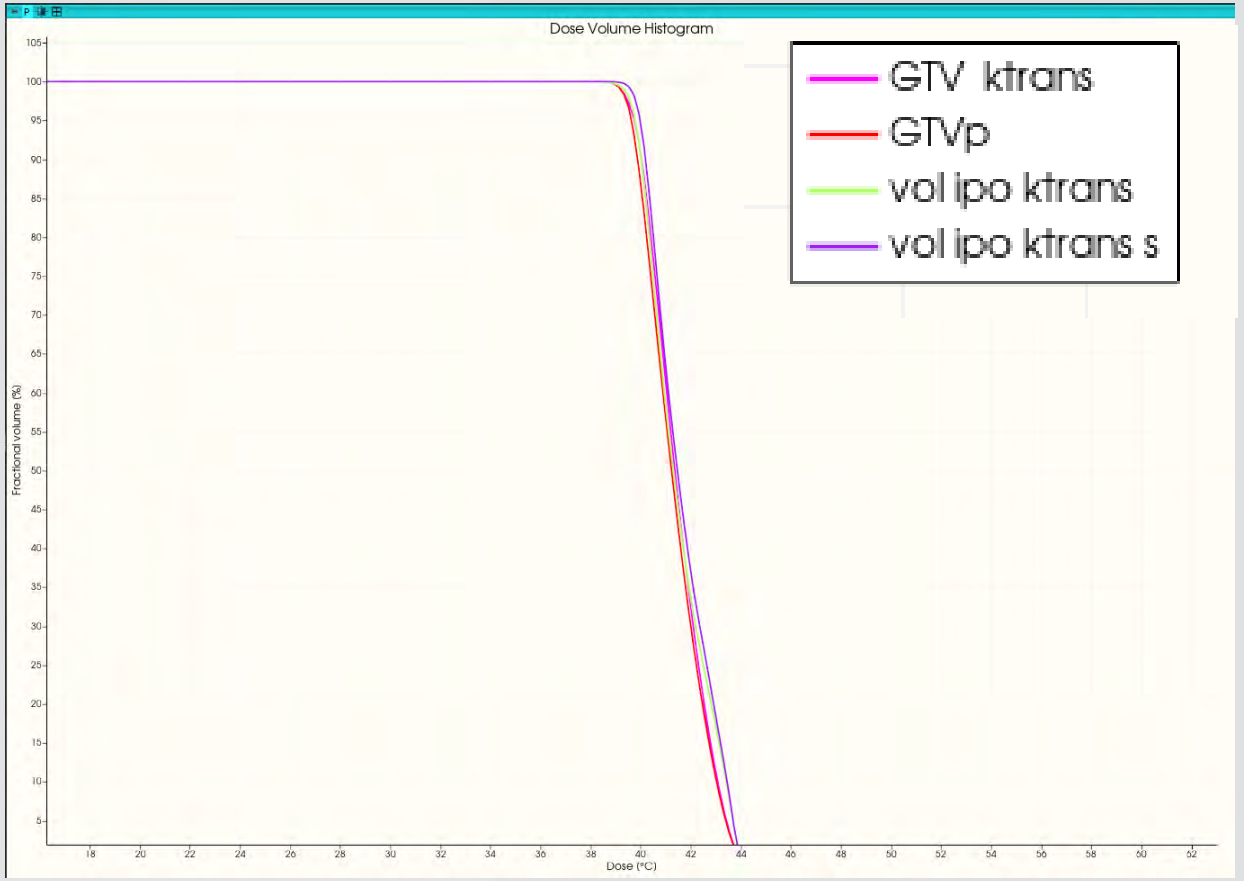

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FIRST TREATMENT FACILITATED BY PLAN2HEAT

GAMMA antenna
216 cm^2

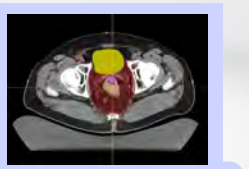
TEMPERATURE ACHIEVED 41°C

No invasive thermometry was performed

National Cancer Center Rome

HYPERBOOST
Boosting the effect of Radiotherapy

ALBA HTPS - PLAN2heat WORKFLOW



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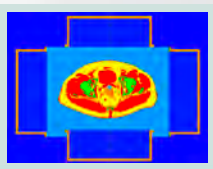

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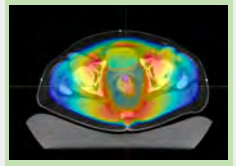
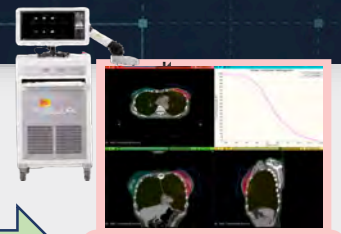


Computing

3

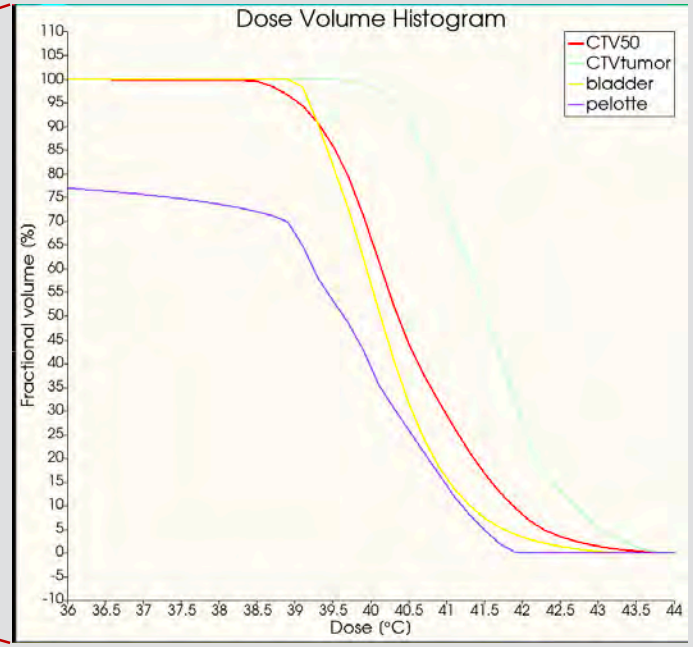


HT DOSE COMPARISON

SETTINGS OPTIMIZATION

EVALUATION TOOLS FOR THE EFFECTIVE DOSE DISTRIBUTIONS OF HT(DVH)

HT DOSE



PLAN2heat
3D adaptive simulation

ONLINE ADAPTIVE HT PLANNING BASED ON TEMPERATURE AND BED(RT+HT)


International Journal of Hyperthermia

3D radiobiological evaluation of combined radiotherapy and hyperthermia treatments

C. M. van Leeuwen, J. Crezee, A. L. Oei, N. A. P. Franken, L. J. A. Stalpers, A. Bel & H. P. Kok

LQ RT+HT equivalent

$$SF(D,T,t_{int}) = \exp[-[\alpha(T,t_{int})\cdot D + G\cdot\beta(T,t_{int})\cdot D^2]]$$

$$EQD2_{RT+HT} = \frac{\sum_{i=1}^{n}\alpha(T_i,t_{int,i})\cdot d_i + \beta(T_i,t_{int,i})\cdot d_i^2 + c(T_i)}{\alpha 37 + 2\cdot\beta 37}$$

$$\alpha(T,t_{int}) = \alpha_{37}\cdot\exp\left[\frac{T-37}{T_{ref}-37}\cdot ln[\frac{\alpha_{41}}{\alpha_{37}}]\cdot\exp[-\frac{|t_{int}|}{\tau}]\right]$$

$$\alpha_{37} = \alpha(37,0)$$
$$\alpha_{41} = \alpha(41,0)$$

$$\beta(T,t_{int}) = \beta_{37}\cdot\exp\left[\frac{T-37}{T_{ref}-37}\cdot ln[\frac{\beta_{41}}{\beta_{37}}]\cdot\exp[-\frac{|t_{int}|}{\tau}]\right]$$

$$\beta_{37} = \beta(37,0)$$
$$\beta_{41} = \beta(41,0)$$

→ Exponential **increase** with temperature **T > 37°C**
Exponential **decreasing** exponent with **t_{int} > 0 h**

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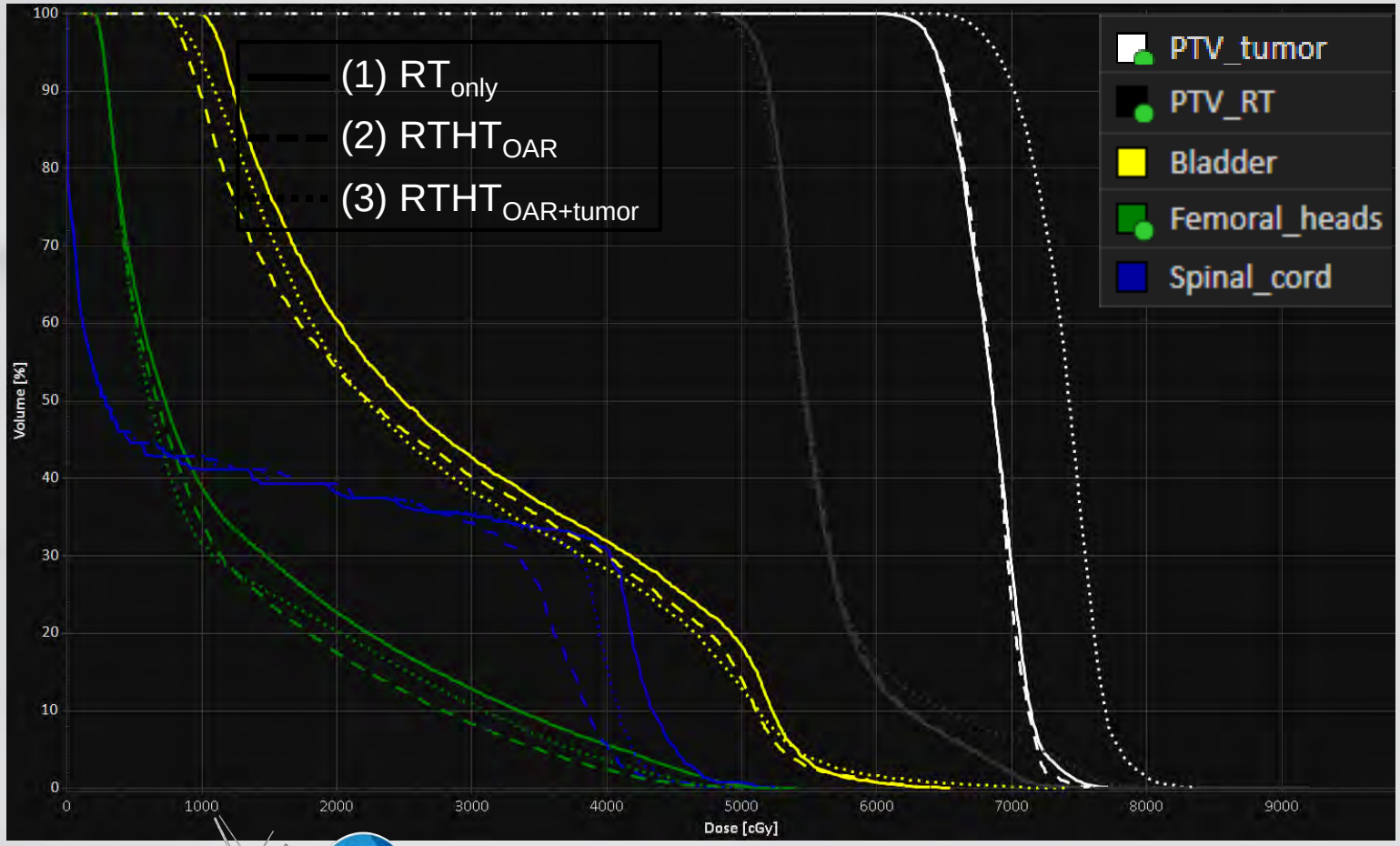
EVALUATION TOOLS OF THE EFFECTIVE DOSE DISTRIBUTIONS OF HT, RT, AND THE COMBINATION OF RT+HT

EQD(RT+HT)

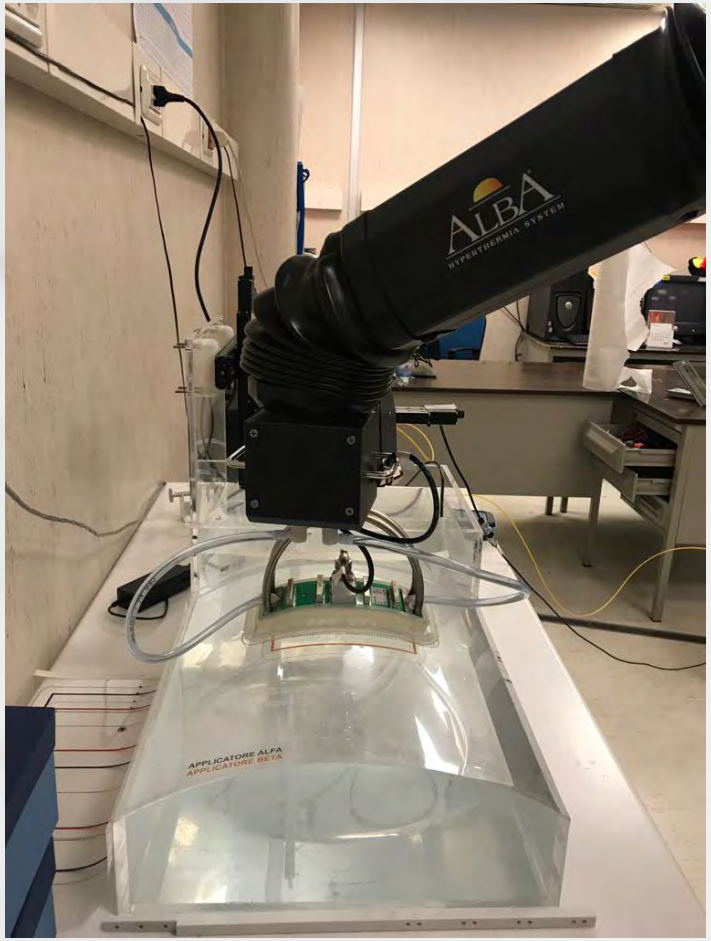


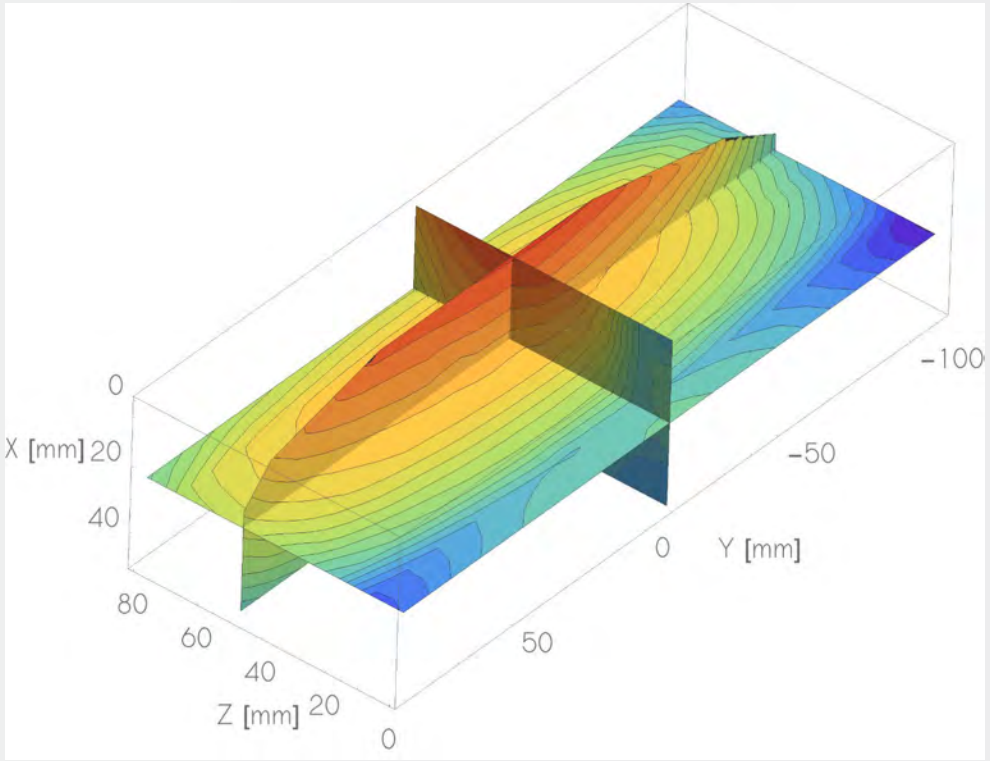
SIDE PROJECTS

ANTENNA MODEL VALIDATION

ALFA ANTENNA

E-FIELD MEASUREMENTS

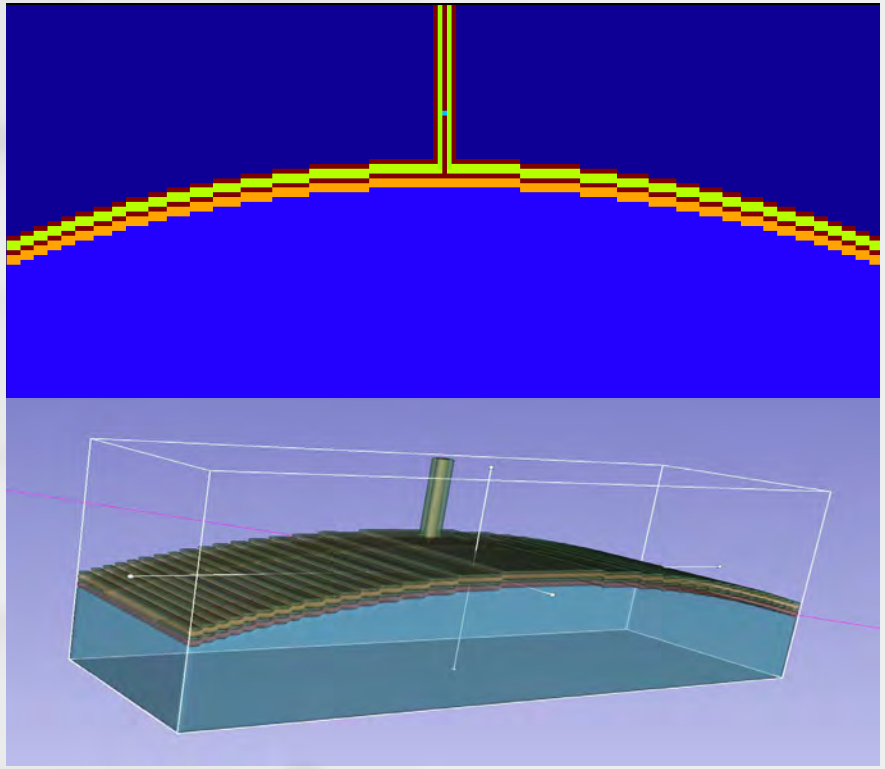




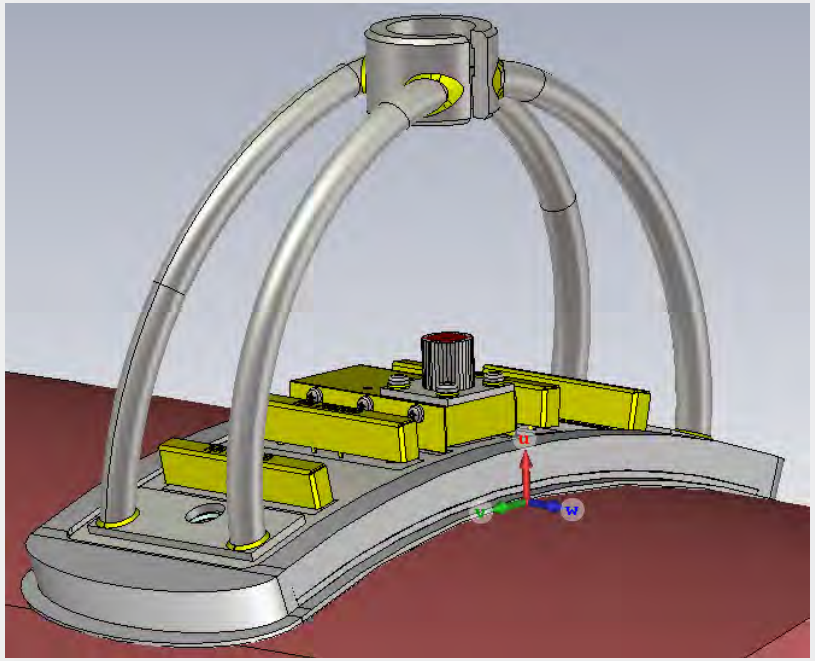
ANTENNA MODEL VALIDATION

Validation of the PLAN2heat antenna models with a second simulator:

CST STUDIO SUITE



PLAN2heat
3D adaptive simulation



CST STUDIO SUITE

POST-PLANNING METHOD FOR VALIDATION OF TEMPERATURE DATA

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TUMOR TYPES

- *Locally Recurrent Rectal Cancer (LRRC)*
- *Locally Advanced Rectal Cancer (LARC)*

TREATMENT SETTINGS

Power Phase

TREATMENT DATA

Temperature

PLAN2heat
3D adaptive simulation

SIMULATION SETTINGS

Power Phase

SIMULATION DATA

Temperature

Hospital Universitario de Gran Canaria Doctor Negrín

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POST-PLANNING METHOD FOR VALIDATION OF TEMPERATURE DATA

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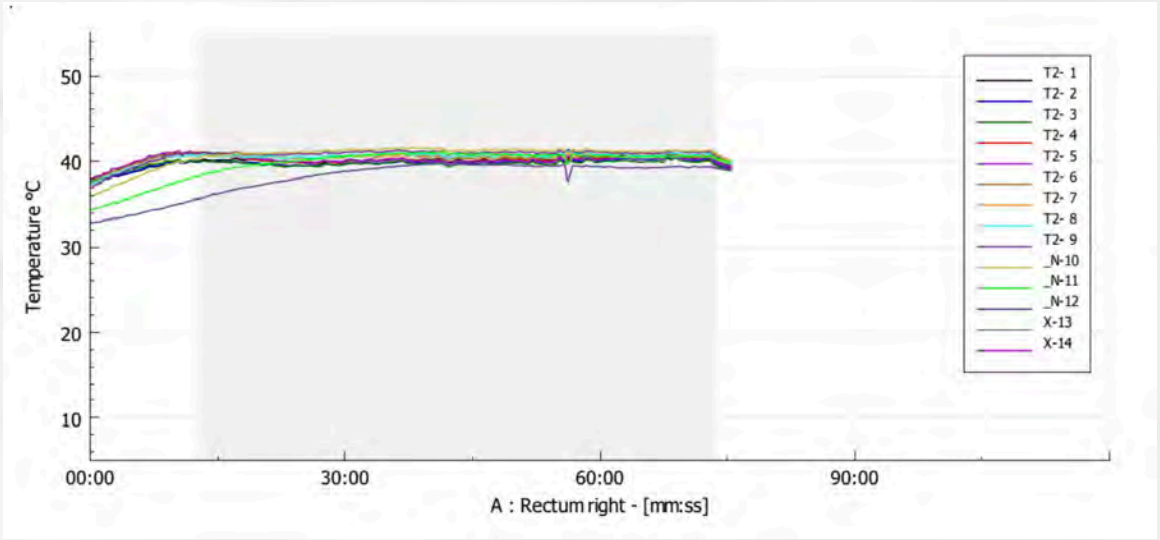
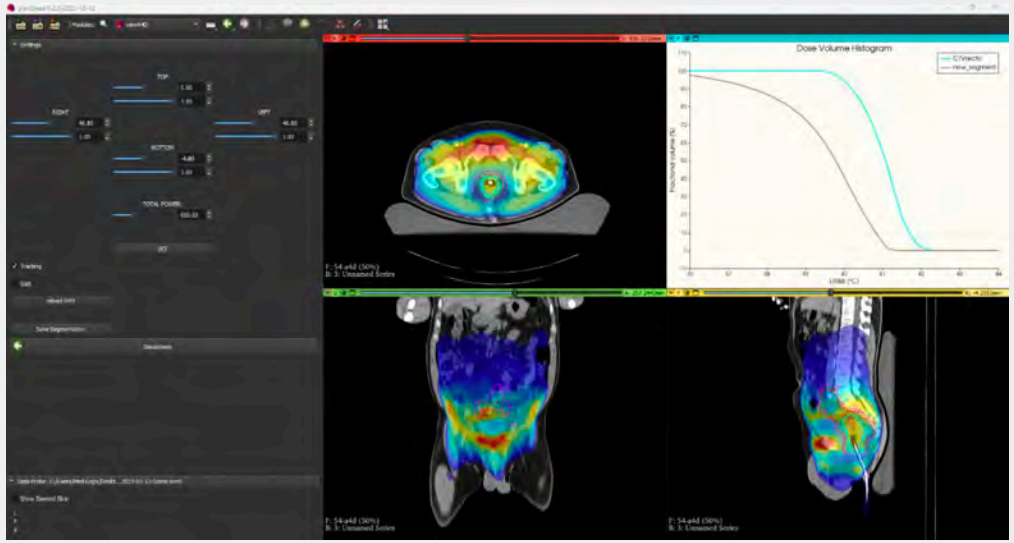
ALBA4D precision hyperthermia

REAL



PLAN2heat 3D adaptive simulation

ESTIMATED



TEMPERATURE COMPARISON

Hospital Universitario de Gran Canaria Doctor Negrín

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QA PROCEDURES
E FIELD MEASUREMENTS WITH GANTRY ROBOT

ROBOTIC GANTRY

igus

ALBA4D
precision hyperthermia

AUTOMATED & PRECISE
EFIELD MEASUREMENT

PHANTOM
(1.5gr/L salt)

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

HYPERBOOST
Boosting the effect of Radiotherapy

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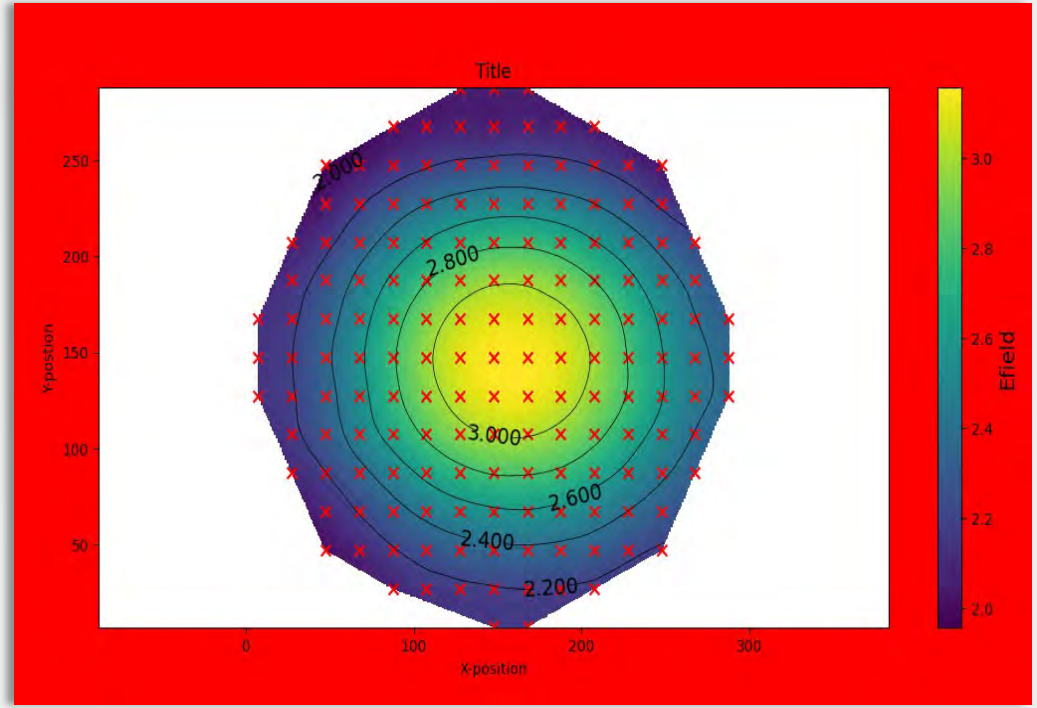
QA PROCEDURES
E FIELD MEASUREMENTS WITH GANTRY ROBOT

ONLINE E-FIELD GRAPH FOR VISUALISATION OF FOCUS



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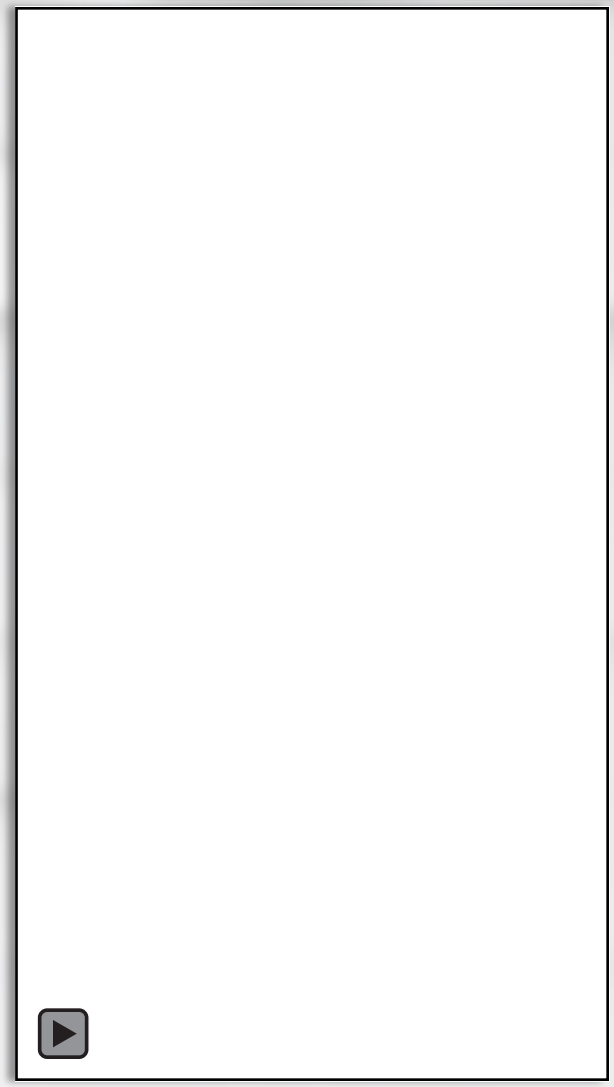
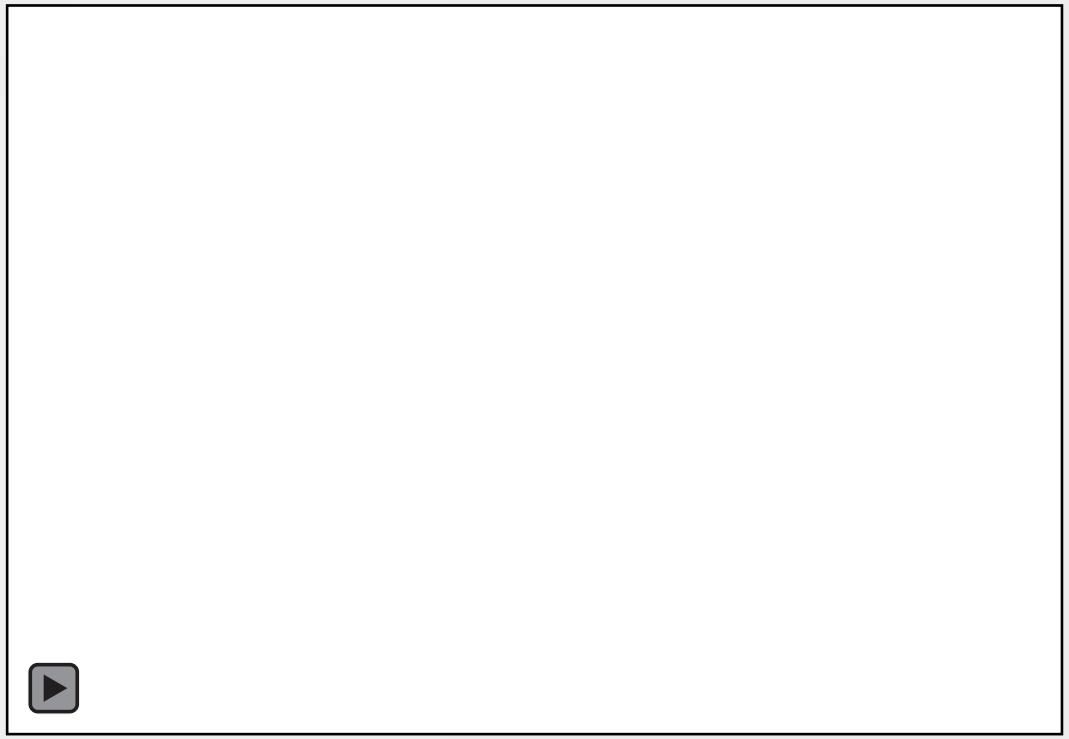
QA PROCEDURES
E FIELD MEASUREMENTS WITH GANTRY ROBOT

SIMULATED E-FIELD GRAPH FOR VISUALISATION OF FOCUS





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SUMMARY

1. NEED OF HT TREATMENT PLANNING SYSTEM
2. DEMOSTRATION OF PLAN2HEAT WORKFLOW
3. HYPERBOOST APPROACH TO THE CURRECT VERSION OF P2H
4. SIDE PROJECTS WHERE TPS – REAL DATA RELATIONSHIP IS DEMONSTRATED (ANTENNA VALIDATION, TEMPERATURE DATA VALIDATION, E-FIELD MEASUREMENTS FOR QA)

THANK YOU FOR YOUR ATTENTION

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CHALMERS
UNIVERSITY OF TECHNOLOGY

Hyperboost consortium meeting

ESR 9, Mattia De Lazzari

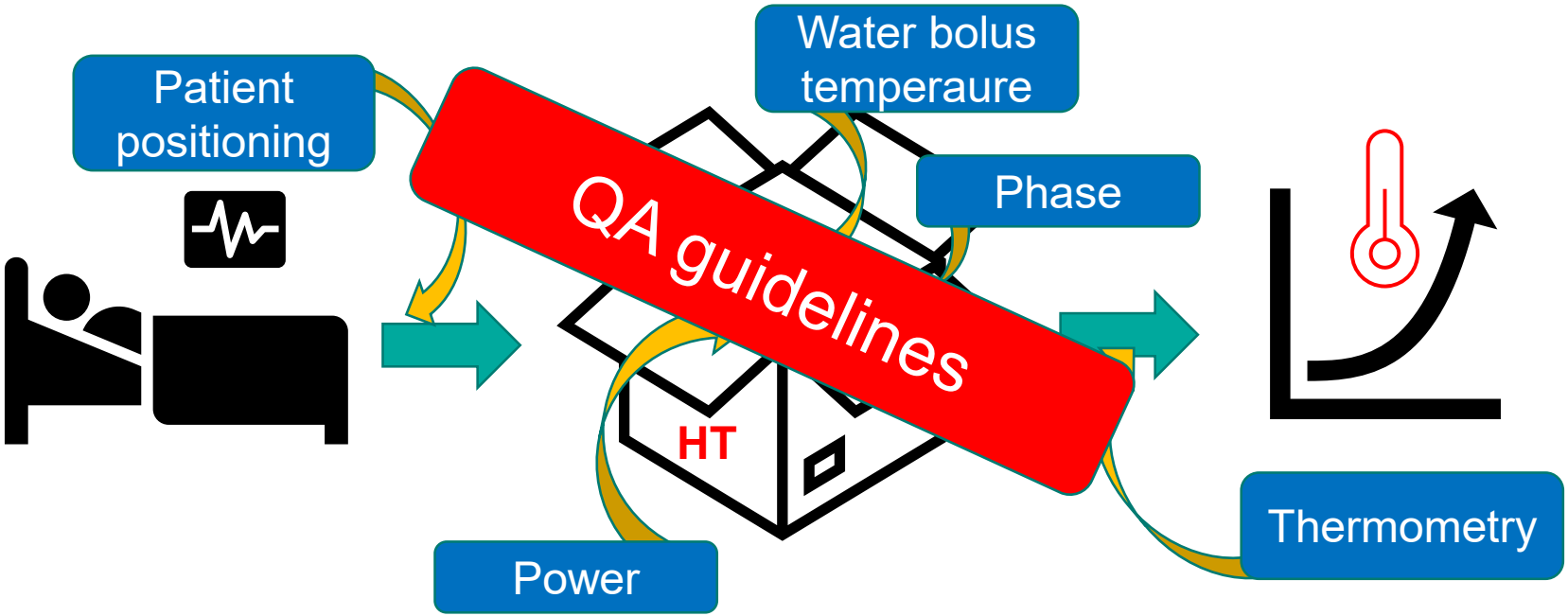
Quality Assurance (QA)

ISO 9000:2015 definition:
systematic actions providing adequate confidence that quality requirements will be fulfilled.

- Strong evidence from clinical trials:
  - A **high-quality heating** is **positively** correlated with treatment outcome
  - **Low heating quality** correlates with **poor** outcome

- Heating quality depends on many **uncertainties**

Quality Assurance (QA)



Quality Assurance (QA) protocols

- Allow for:
  - ✓**High-quality** and **uniform** treatments
  - ✓**Device-independent** clinical trials

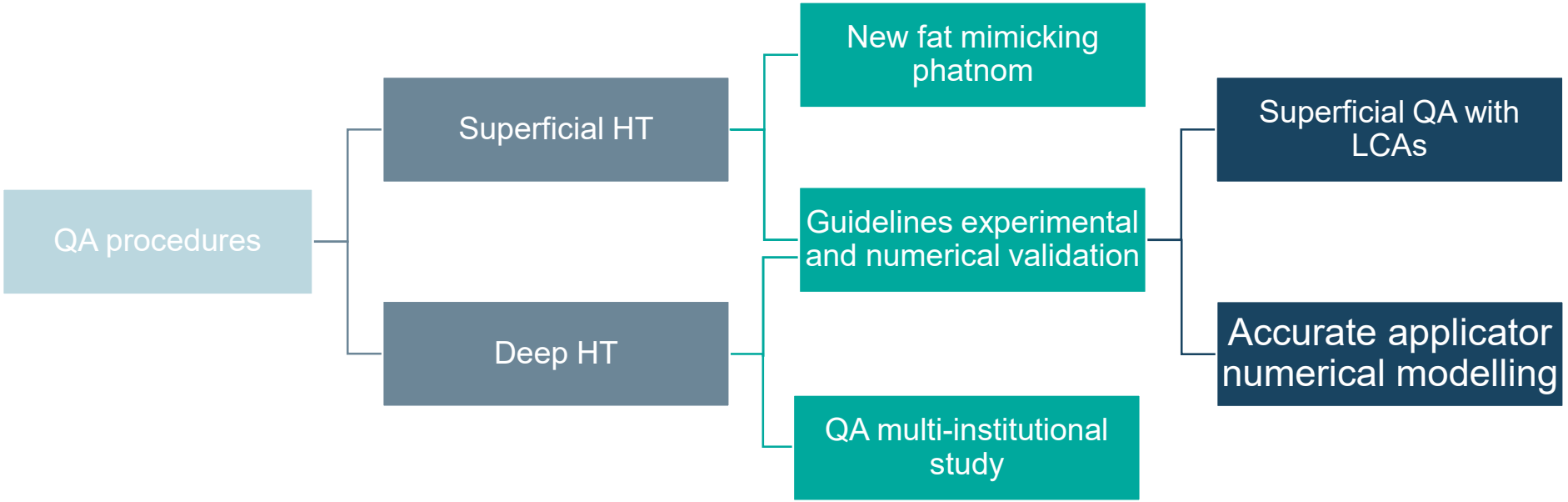
- How?
  - ✓Straightforward procedures to robustly demonstrate the technical performance of the devices

Available QA guidelines

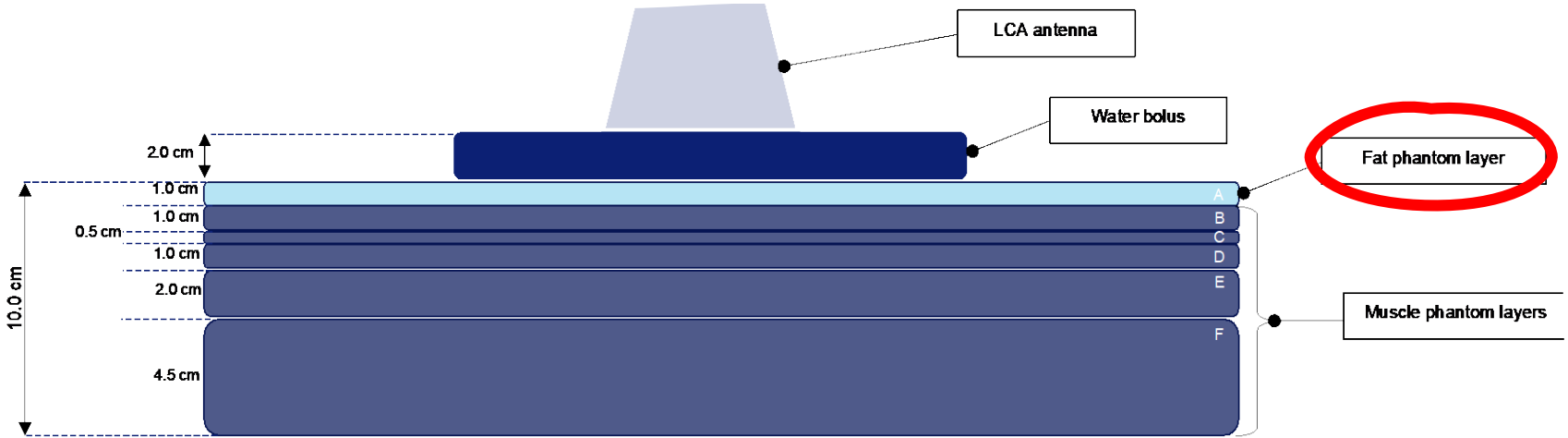
Superficial HT	Dobsicek Trefna et al., 2017, Quality assurance guidelines for superficial hyperthermia clinical trials: I. Clinical requirements II. Technical requirements for heating devices
Interstitial HT	Dobsicek Trefna et al., 2019, Quality assurance guidelines for interstitial hyperthermia
Deep HT	Bruggmoser et al., 2011, - Quality Assurance for Clinical Studies in Regional Deep Hyperthermia - Guideline for the clinical application, documentation and analysis of clinical studies for regional deep hyperthermia

Challenges

- QA guidelines implementation **hampered by**:
  - Lack of **detailed testing procedures**
  - Lack of **suitable phantom** materials
  - Limited **experimental evaluation**


QA procedures
Superficial HT
Deep HT
New fat mimicking phatnom
Guidelines experimental and numerical validation
QA multi-institutional study
Superficial QA with LCAs
Accurate applicator numerical modelling

Superficial HT QA

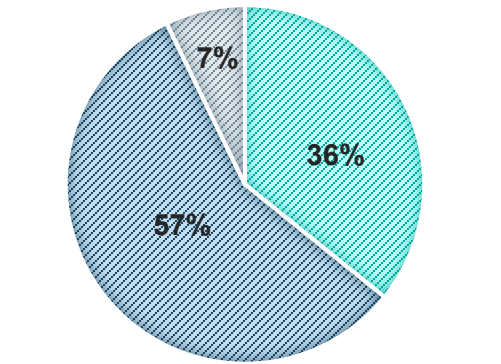


Fat phantom development

- **Need:** crucial role for superficial HT, especially for capacitive devices (8-27 MHz)
- **Desiderable features:**
  - ☑ Thermal stability
  - ☑ Mechanical stability
  - ☑ Simply to make with accessible ingredients
  - ☑ Reproducible

Fat phantom development

Dielectric properties



- Thermal properties
- Mechanical properties
- QA assessment

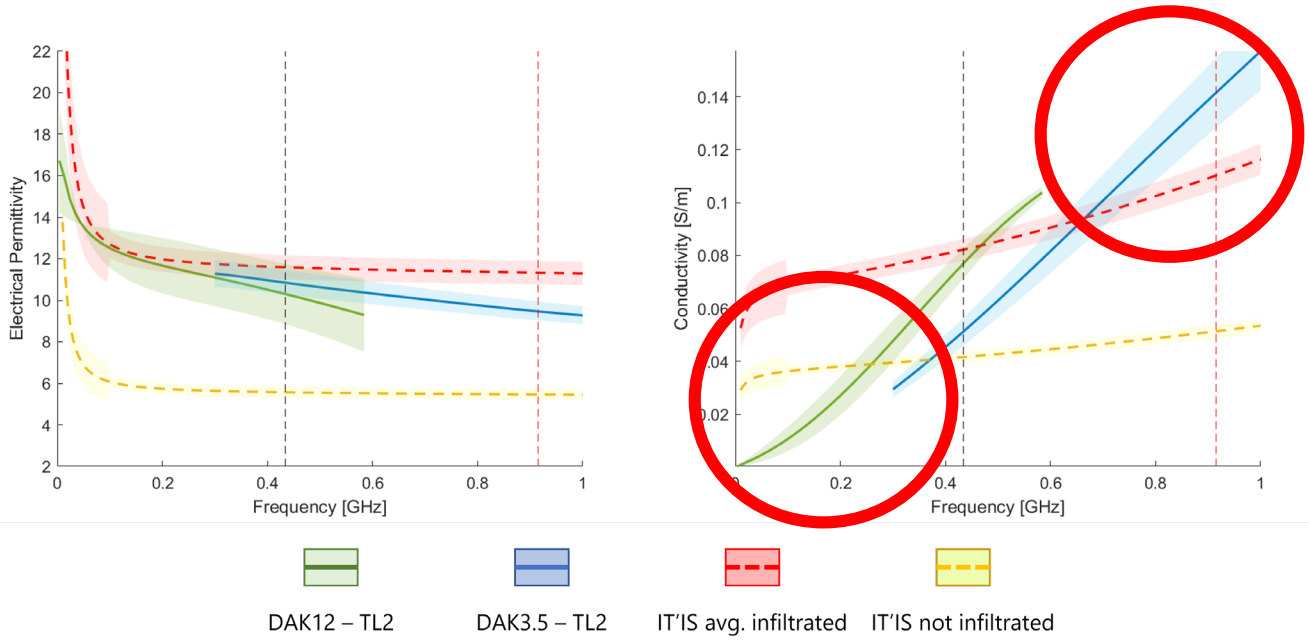
Fat phantom development

Property	Reference value for fat tissue[1]	Measured value at 22-24°C
k [W/m/°C]	0.21±0.02	0.246±0.000
Cv [J/kg/°C]	2.348±0.372	2.556±0.002

- Not visibile melting point up to 130°C
- High flexibility and easy to handle

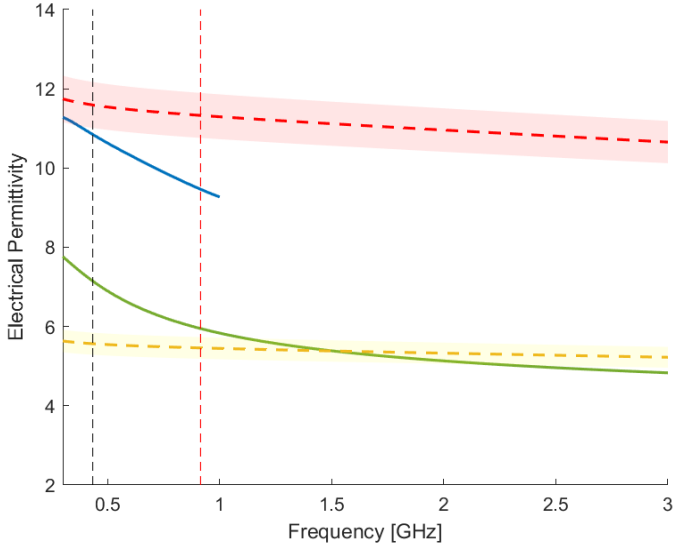
1 Hasgall PA, Di Gennaro F, Baumgartner C, Neufeld E, Lloyd B, Gosselin MC, Payne D, Klingenböck A, Kuster N, "IT'IS Database for thermal and electromagnetic parameters of biological tissues," Version 4.1, Feb 22, 2022, DOI: 10.13099/VIP21000-04-1. itis.swiss/database

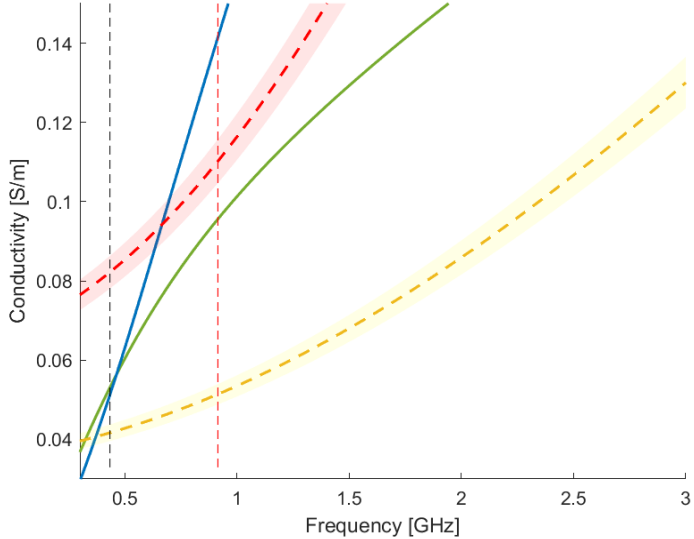
Fat phantom development



1 Hasgall PA, Di Gennaro F, Baumgartner C, Neufeld E, Lloyd B, Gosselin MC, Payne D, Klingenböck A, Kuster N, "IT'IS Database for thermal and electromagnetic parameters of biological tissues," Version 4.1, Feb 22, 2022, DOI: 10.13099/VIP21000-04-1. itis.swiss/database

Fat phantom development



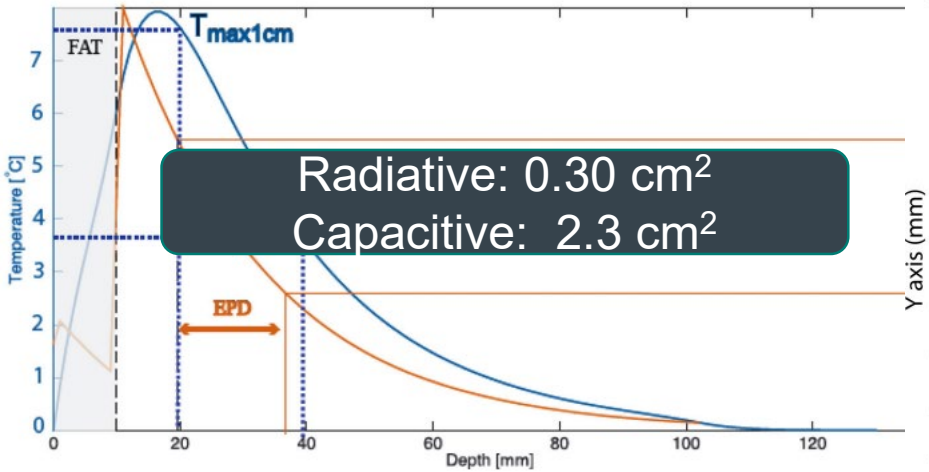


52% wt

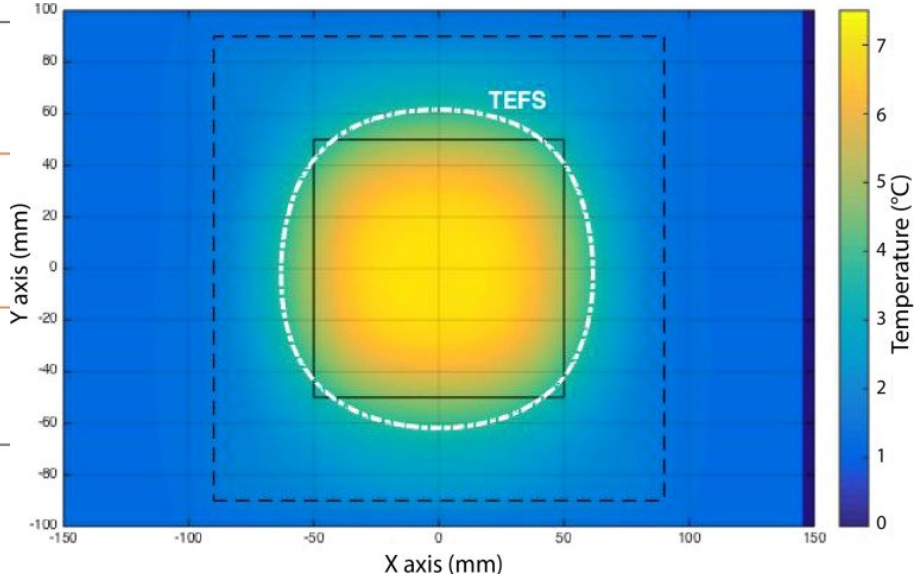
57% wt

Fat phantom development

Numerical evalutation of the low conductivity impact



Radiative: 0.30 cm^2
Capacitive: 2.3 cm^2



Radiative: 2 mm
Capacitive: 3 mm

LCA applicator QA verification

- **Need:** QA guidelines for superficial HT[1] with limited experimental feasibility verification

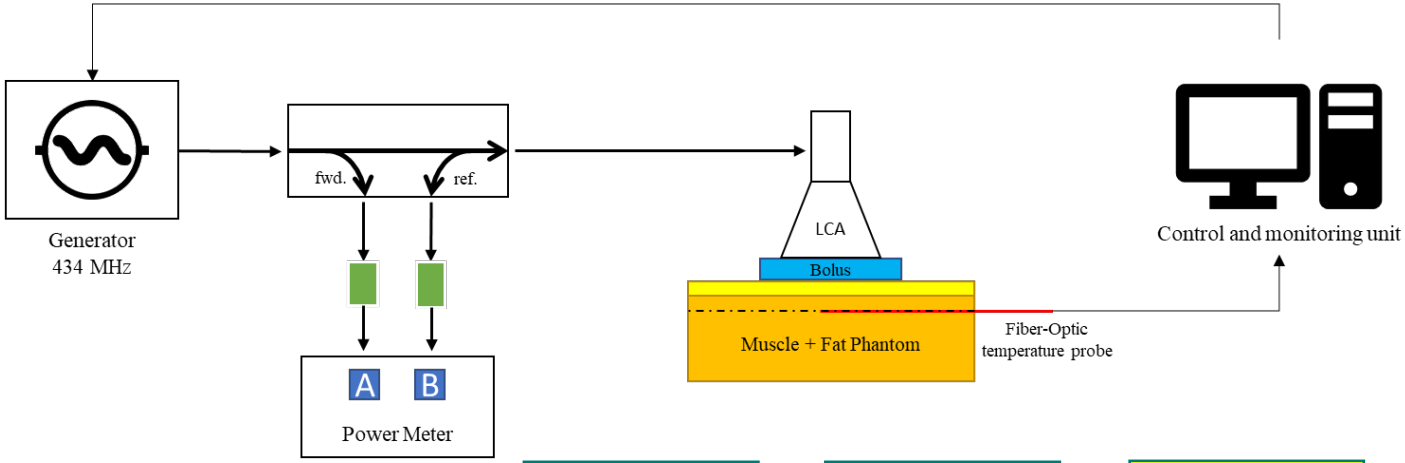
ESR 9 + 10

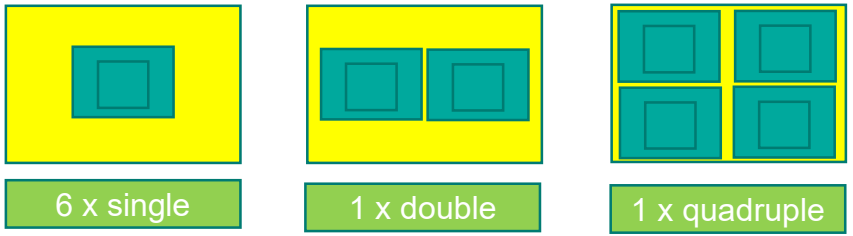
- **How:**
  - QA evaluation of the lucite cone applicator (LCA) in term of temperature according to the most recent QA guidelines
  - Comparison with numerical analysis in terms of QA indicators (ESR 10)

1

LCA applicator QA verification

Experimental setup





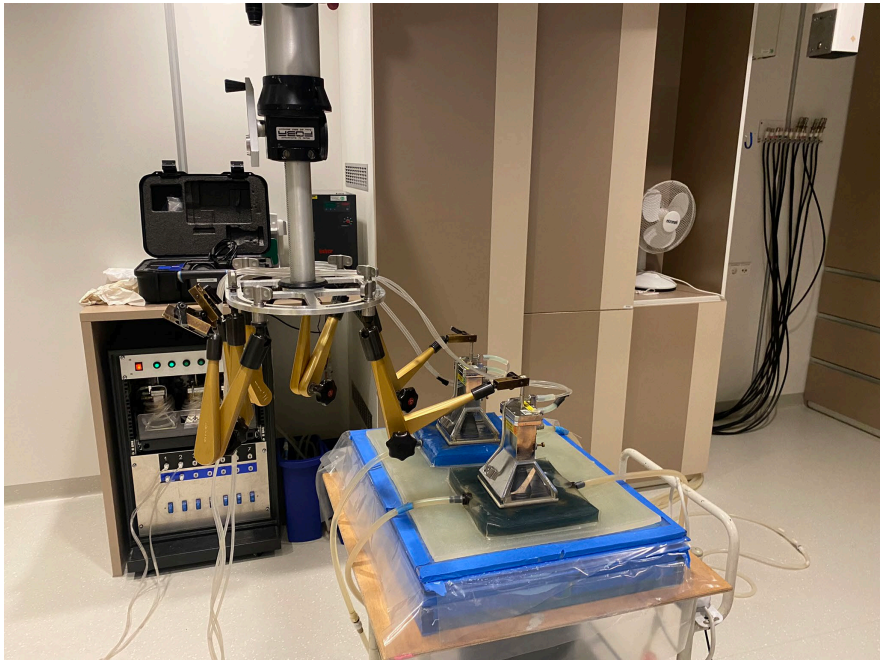
LCA applicator QA verification

Antenna calibration

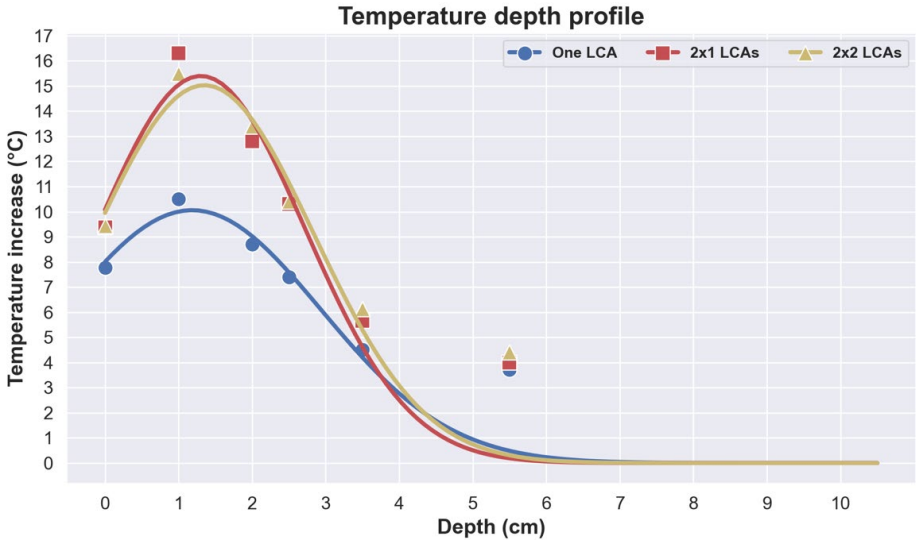
Heating

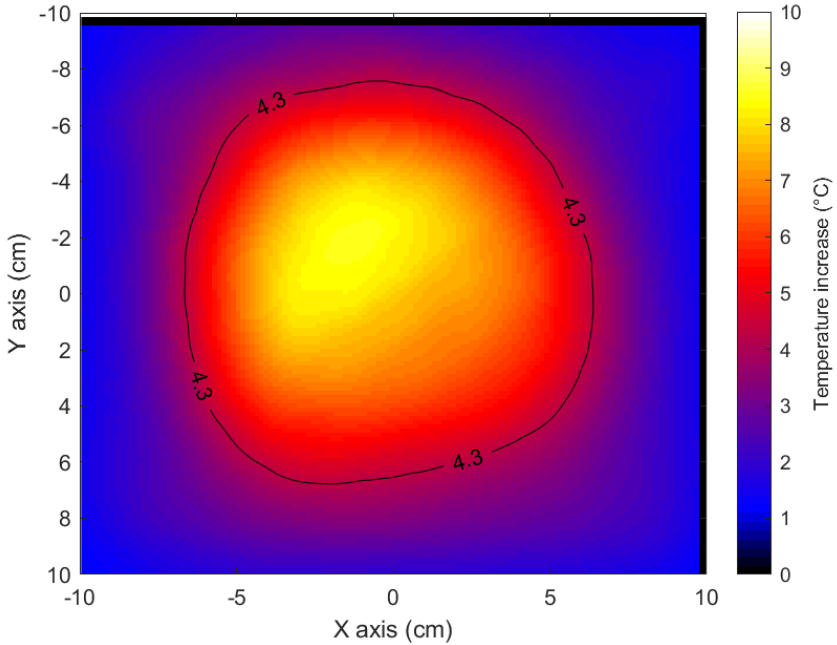
- 200 W for 6 min

Thermal images acquisition



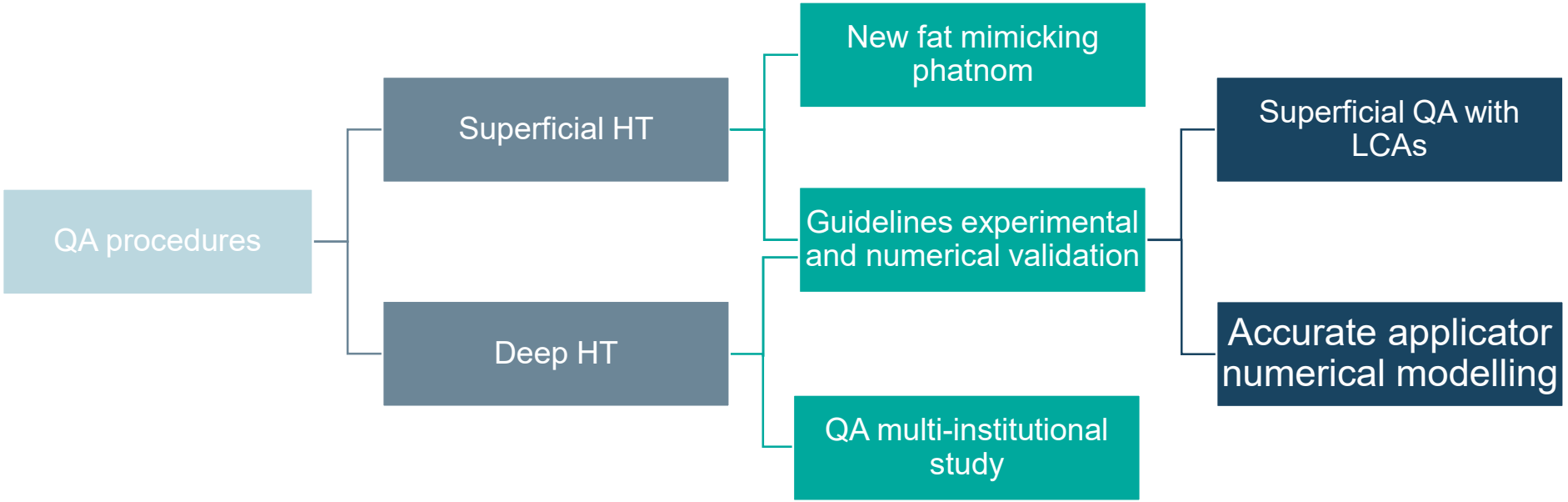
LCA applicator QA verification





LCA applicator QA verification

- Evaluation of:
  - Temperature increase (Target: 6°C/6 min @ 1 cm depth in muscle)
  - TEFS
  - TEPD
- **Results:**
  - LCA approved according to QA guidelines
  - Time consuming implementation
  - Extra data recording necessary


QA procedures
Superficial HT
Deep HT
New fat mimicking phatnom
Guidelines experimental and numerical validation
QA multi-institutional study
Superficial QA with LCAs
Accurate applicator numerical modelling

Accurate numerical modelling

- **Need:**
  - Currently, guidelines on computational modelling are missing
  - ESHO Benchmarks are available, but no real applicator is considered

- **Plan:**
  - Definition of settings for an accurate modelling
  - Application of them for:
    - Phantom design validation
    - Numerical validation of applicators

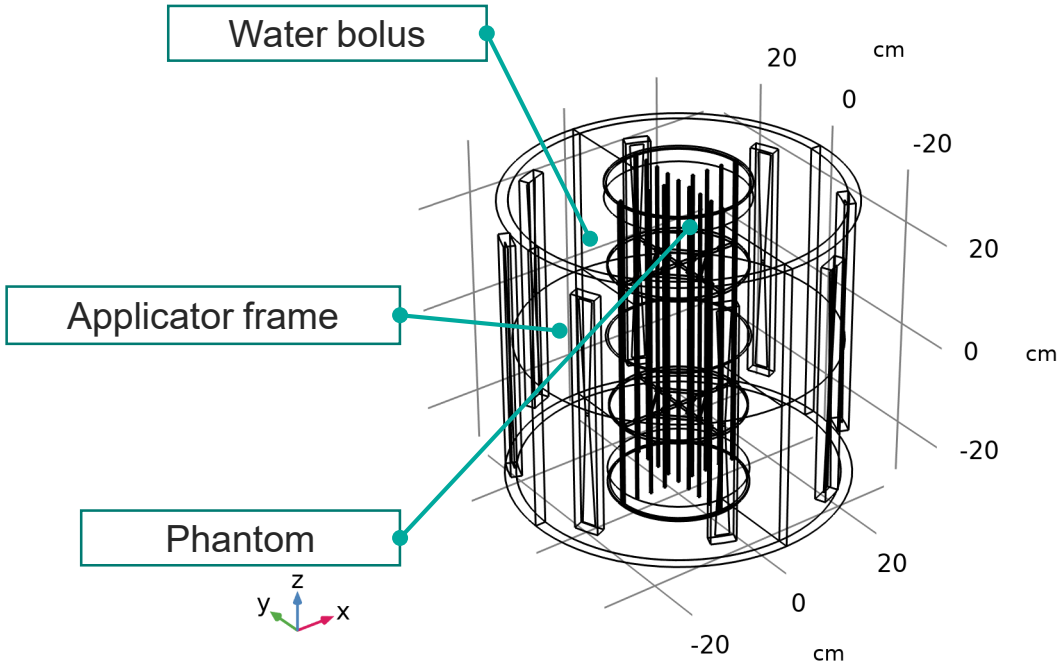
Accurate numerical modelling

Sigma 60 applicator

1000 W, 10 min heating

Perfax phantom

Comsol multiphysics

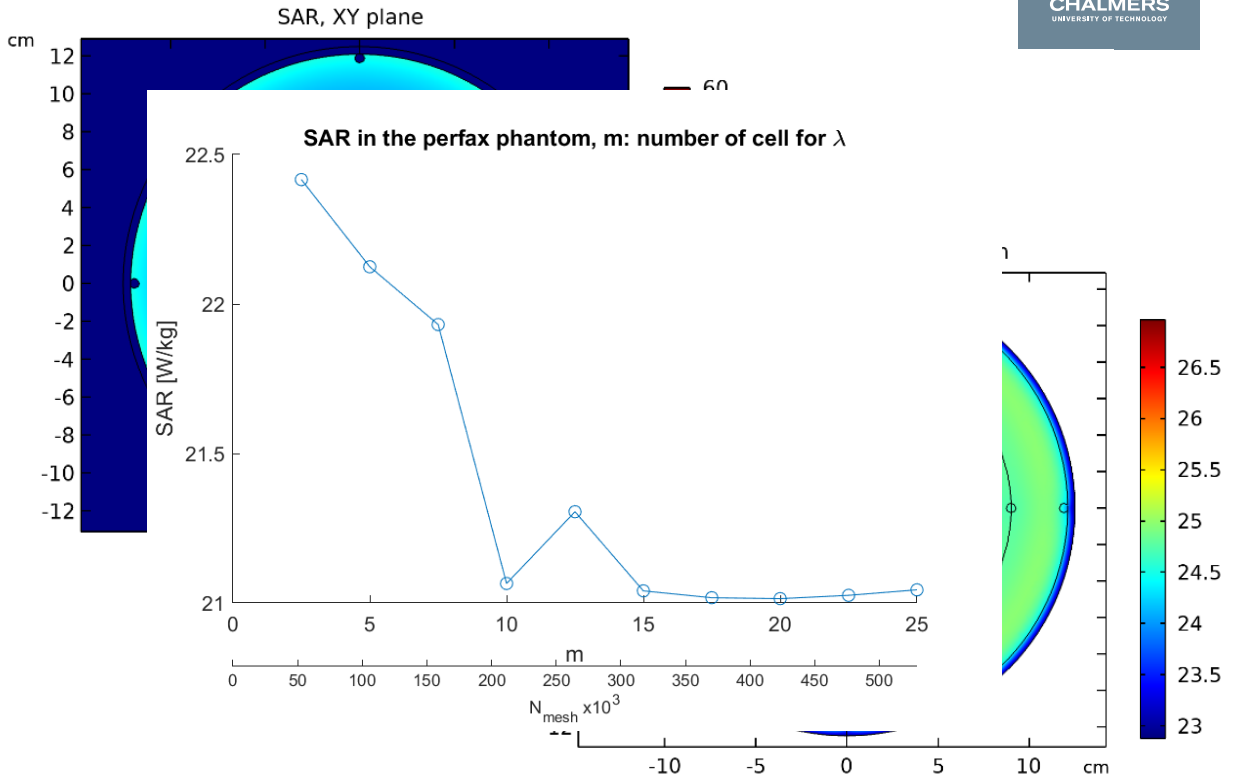


Accurate numerical modelling

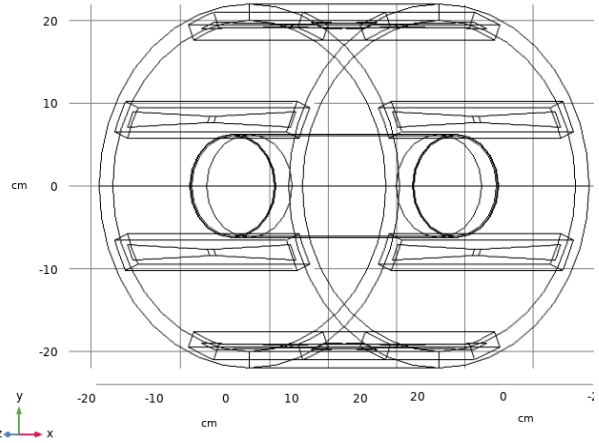
Geometrical elements modelling

EM/thermal simulation

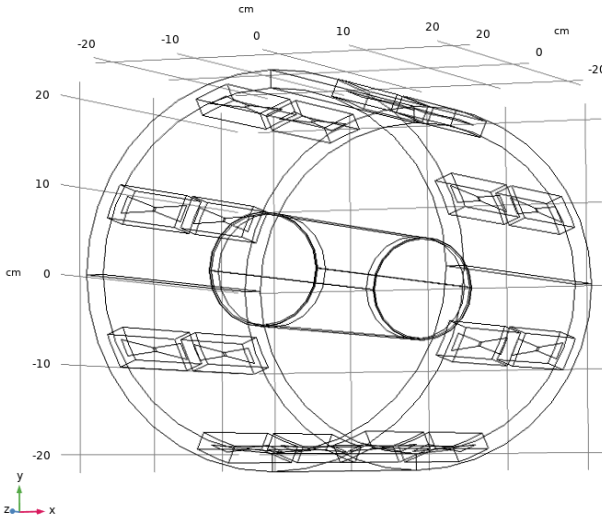
Optimal mesh settings definition



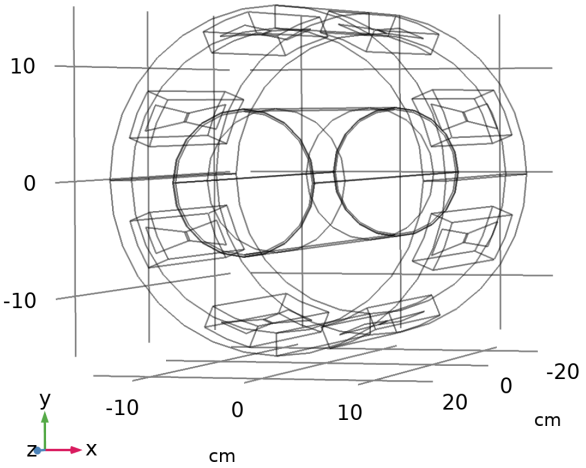
Accurate numerical modelling



Sigma 40



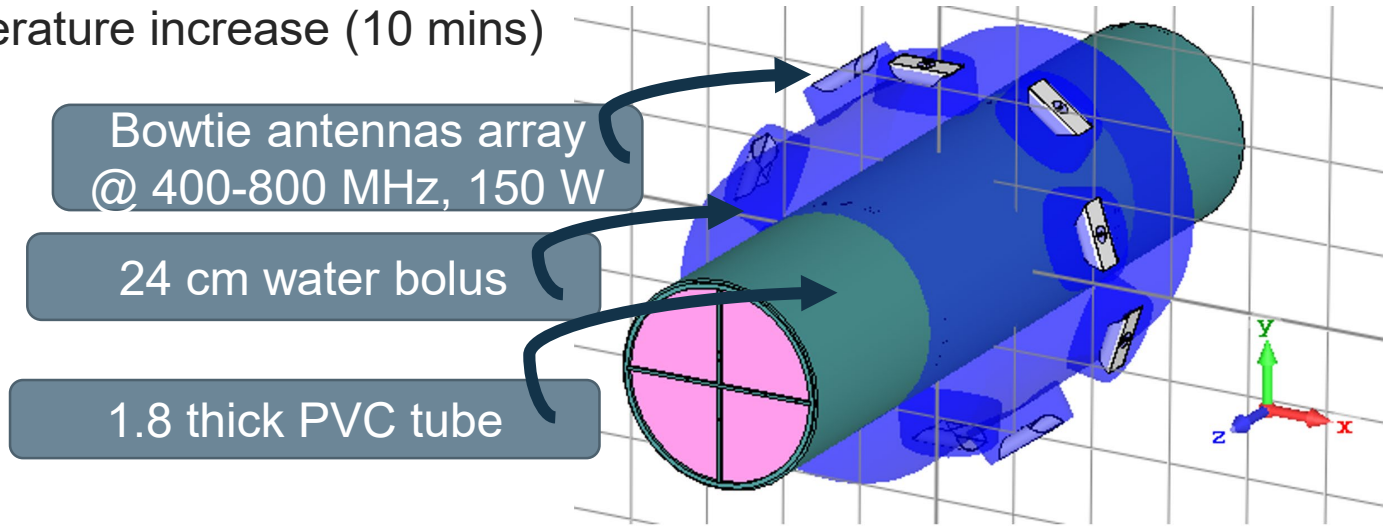
Sigma 40 MR



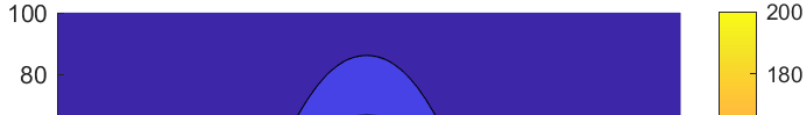
Sigma 30

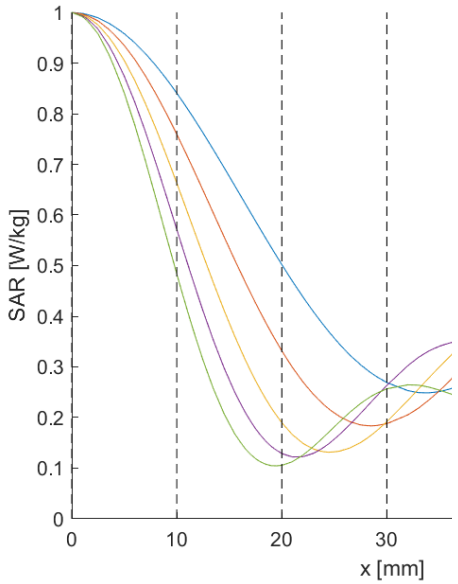
QA phantom design

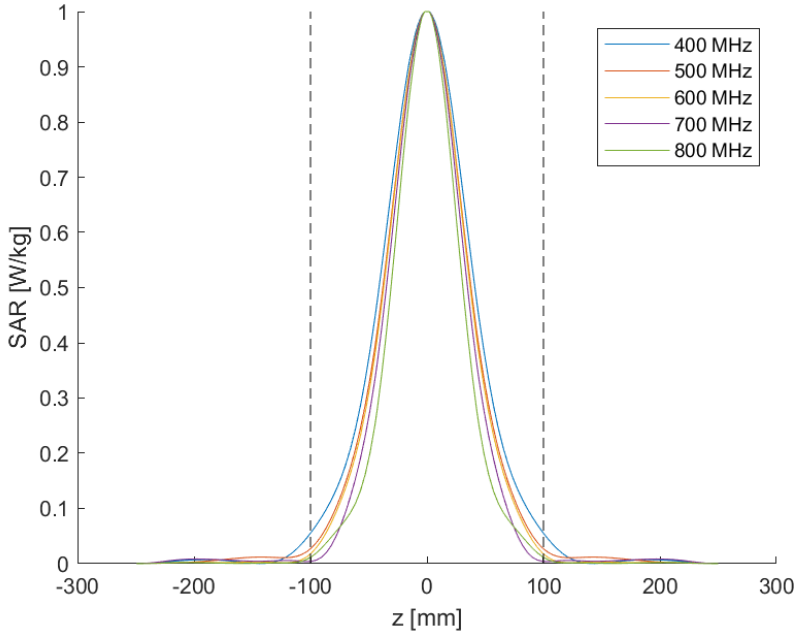
- **Need:** design of a QA phantom for H&N and limbs HT
- **How:** EM and thermal simulations (CST MW studio)
  - SAR
  - Temperature increase (10 mins)

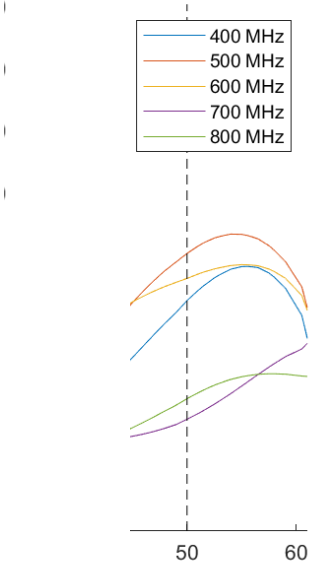


QA phanto


100
80
200
180

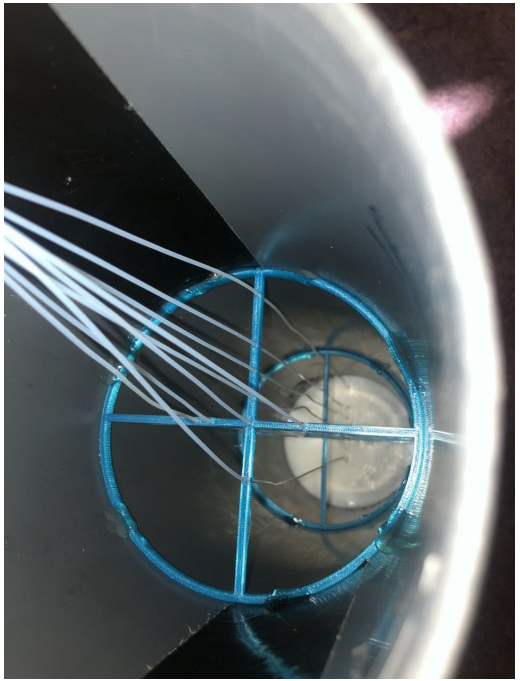

SAR [W/kg]
x [mm]
0
10
20
30
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1


SAR [W/kg]
z [mm]
400 MHz
500 MHz
600 MHz
700 MHz
800 MHz
-300
-200
-100
0
100
200
300


400 MHz
500 MHz
600 MHz
700 MHz
800 MHz
50
60

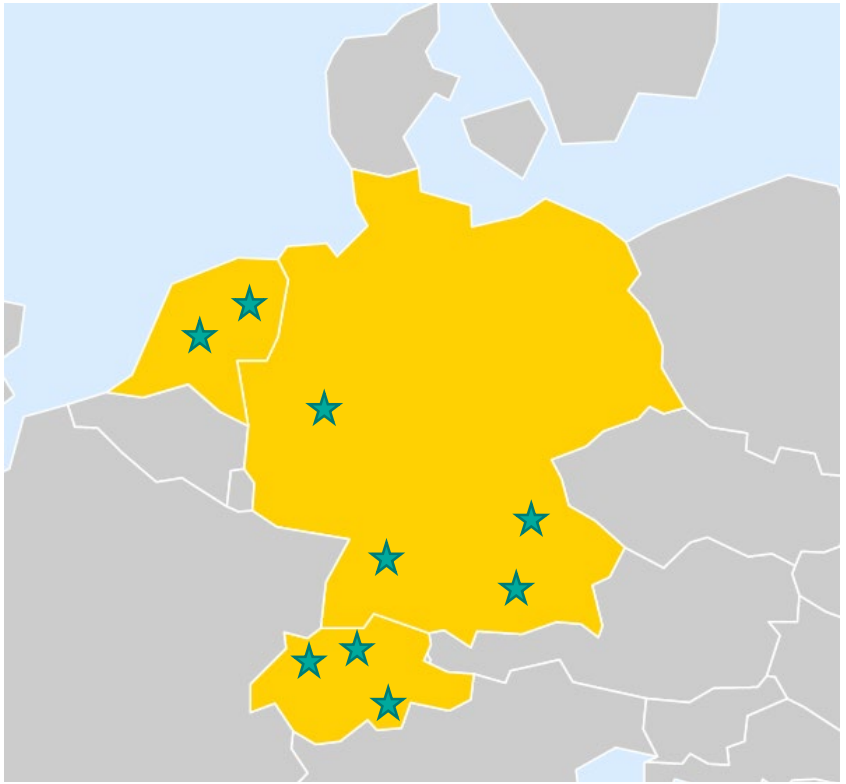
QA phantom design

- 1.2 mm catheters
- Agarose phantom



QA deep HT comparative study

- Comparative study for QA on deep HT devices
- ESR 9 + 10
- 9 centers involved
- Apply new QA protocols for deep HT devices
- Study thermal parameters used in clinical practice (ESR 10)



HT systems development in the perspective of the new EU MDR

- Collaboration with **industry** (Dr. Sennewald, Sensius)

- More than 30 applicable standards, risk analysis
- Final goal: written **guidance** available for HT system developers

Acknowledgements

Prof. Hana D. Trefna

Prof. Sergio Curto
Carolina C. Seabra

Prof. Dario Rodriguez

Martin Wadepohl

HYPERBOOST CONSORTIUM MEETING

ESR 10: Carolina Carrapiço Seabra

HYPERBOOST
Boosting the effect of Radiotherapy

Erasmus MC
University Medical Center Rotterdam
Cancer Institute

ESR 10 within HYPERBOST

WP5: Clinical implementation of the personalised radiotherapy + hyperthermia treatment planning platform

Quality must be both high, consistent and uniform

HOW ?

ESR 10 within HYPERBOST

Data reporting template for RT + HT combined treatment

PATIENT

APPLICATORS → QA, commissioning guidelines

(MR-) THERMOMETRY → standardised calculations, parameters

Modelling, Treatment Planning

CONTENTS

- ESHO - QA guidelines for superficial HT systems
- QA tests for the introduction of the new HT MR compatible BSD system
- QA guidelines and experiments for deep HT systems
- MR thermometry for tumour temperature prediction

CONTENTS

- ESHO - QA guidelines for superficial HT systems (ESRs 9 & 10)

ESHO - QA guidelines applied to LCA

Superficial HT →

Trefna et al., 2017,
Quality assurance guidelines for superficial hyperthermia clinical trials:
I. Clinical requirements
II. Technical requirements for heating devices

Why:

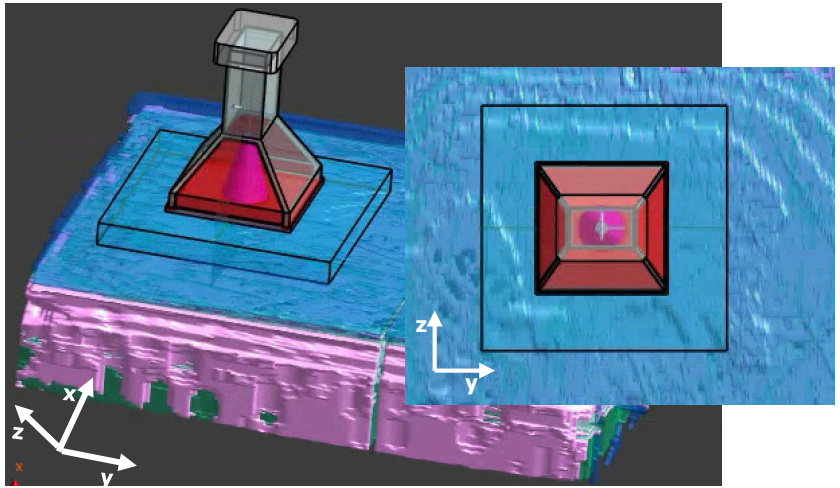
- QA guidelines for superficial HT with limited experimental feasibility verification

How:

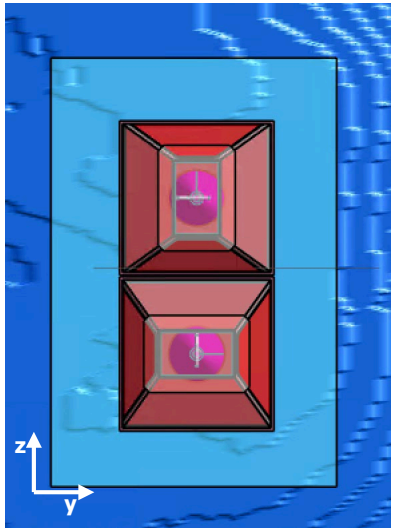
- QA evaluation of the lucite cone applicator (LCA) in terms of temperature according to the most recent QA guidelines.
- Comparison with numerical analysis in terms of QA indicators.
- Evaluation of the ease of the application of guidelines in daily practice.

ESHO - QA guidelines applied to LCA

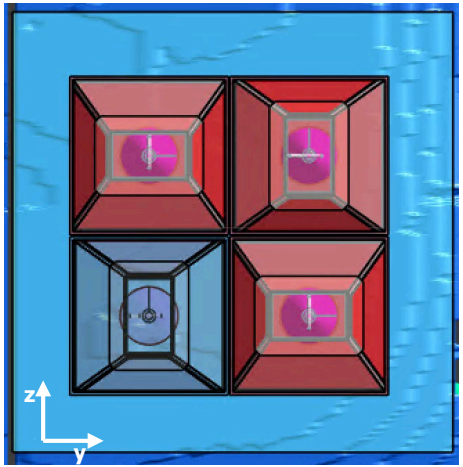
1 LCA setup



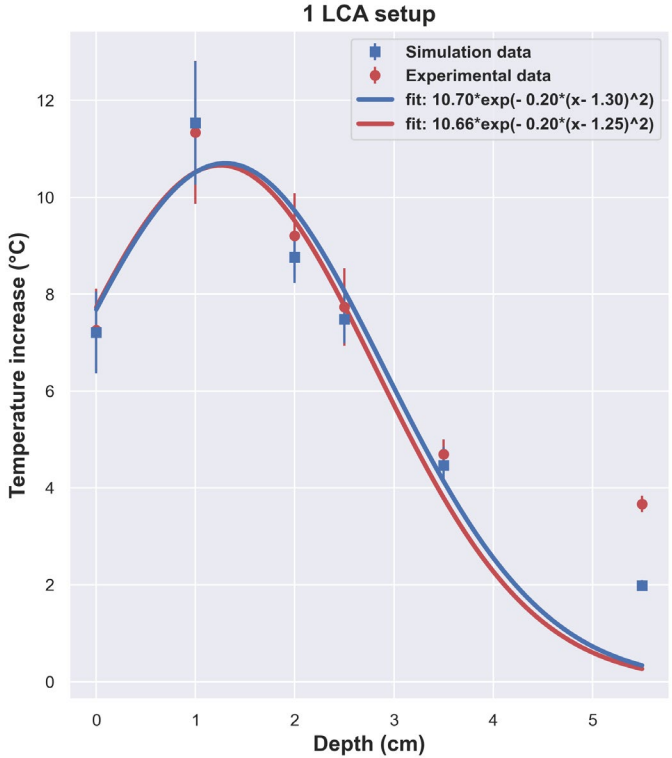
1x2 LCAs setup



2x2 LCAs setup

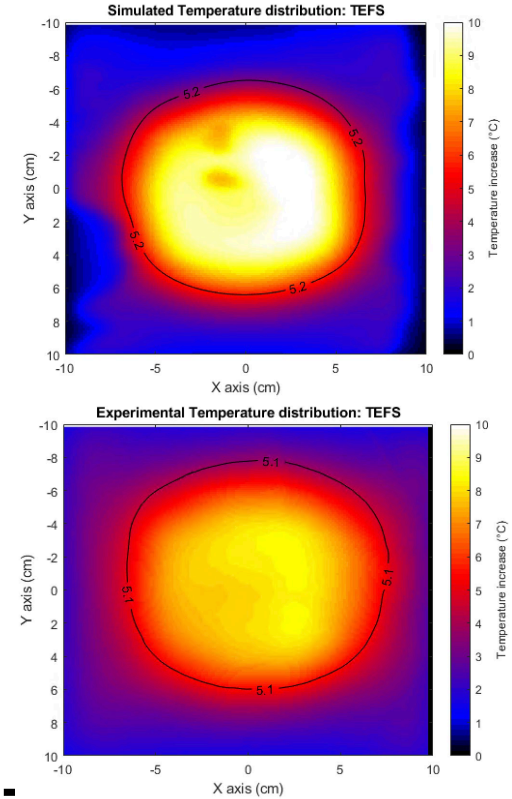


ESHO - QA guidelines applied to LCA



	One LCA
Simulation TEPD (cm)	3.00 ± 0.12
Experimental TEPD (cm)	3.11 ± 0.11

ESHO - QA guidelines applied to LCA



	One LCA
Simulation TEPD (cm)	3.00 ± 0.12
Experimental TEPD (cm)	3.11 ± 0.11
Simulation TEFS (cm^2)	113.3 ± 11.3
Experimental TEFS (cm^2)	120.6 ± 13.2

ESHO - QA guidelines applied to LCA

Evaluation of:

- Temperature increase (Target: 6°C/6 min @ 1 cm depth in muscle)
- TEFS
- TEPD

Results:

- LCA followed minimum requirements according to QA guidelines
- Time consuming implementation
- Extra data recording necessary
- Works mainly for one LCA setup

CONTENTS

MR compatible BSD system

Deep HT → Bruggmoser et al., 2011,
- Quality Assurance for Clinical Studies in Regional Deep Hyperthermia
- Guideline for the clinical application, documentation and analysis of clinical studies for regional deep hyperthermia

Why:

- No specific commissioning procedures nor requirements defined in the literature.
- Available QA do not make use of MR capabilities.

How:

- QA evaluation of the HT systems and its components.
- Validation of the MR thermometry in phantoms.
- MRT used for systems evaluation and end-to-end testing.

MR compatible BSD system

- The experimental set up consisted of a homogeneous cylindrical perfax and/or an anthropomorphic pelvic phantom.

MR compatible BSD system

Category	Parameter	Metric	Definition
1. Technical evaluation	- S11	Reflection from the antennas	-
	- Compatibility	SNR (double echo gradient recalled echo)	$SNR = \left(\frac{P_{signal}}{P_{noise}}\right)$
2. MRT accuracy	- Bias	Mean error	$ME = \frac{1}{n}\sum_{j=1}^{n}(T_{MRT} - T_{probe})$
	- Accuracy	Mean absolute error	$MAE = \frac{1}{n}\sum_{j=1}^{n}\lvert T_{MRT} - T_{probe}\rvert$
	- MRT precision	Spatial temperature precision	$SD^2 = \frac{1}{n}\sum_{j=1}^{n}(T_{MRT} - T_{probe})^2$
3. Heating ability	- Focusing	Temperature increase in a ROI in target	$\overline{T}_{ROI} = \frac{1}{card(j)}\sum_{j=1}^{n} T_j$
	- Precision	Spatial temperature precision	$SD^2_{ROI} = \frac{1}{n}\sum_{j=1}^{n}\overline{T}^2_{ROI}$
	- Steering	Relocation of the maximum heating point	-

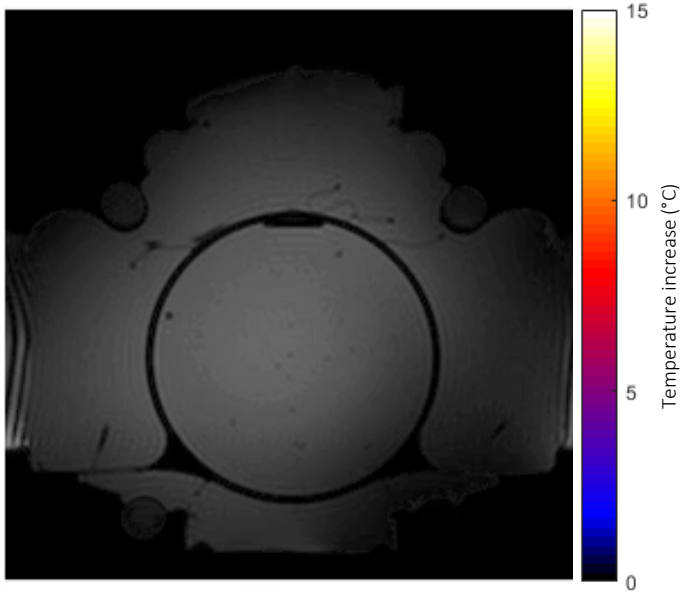
MR compatible BSD system

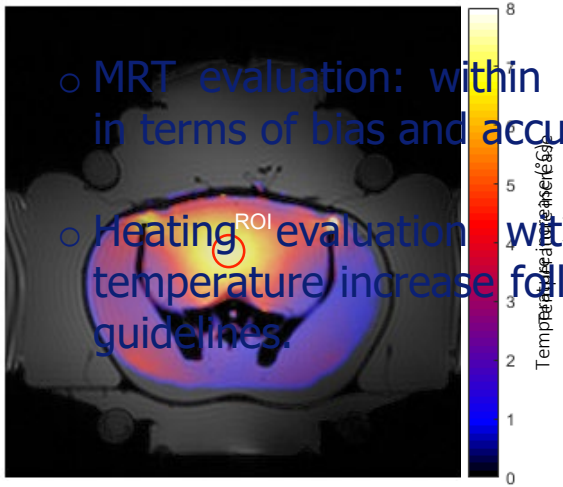
Category	Parameter	Metric	Definition	Results
1. Technical evaluation	- S11	Reflection from the antennas	-	@ 100MHz -11.4dB
	- Compatibility	SNR (double echo gradient recalled echo)	$SNR = \left(\frac{P_{signal}}{P_{noise}}\right)$	SNR = 171 (previuos systems ~50)
2. MRT accuracy	- Bias	Mean error	$ME = \frac{1}{n}\sum_{j=1}^{n}(T_{MRT} - T_{probe})$	0.29
	- Accuracy	Mean absolute error	$MAE = \frac{1}{n}\sum_{j=1}^{n}\lvert T_{MRT} - T_{probe}\rvert$	0.44
	- MRT precision	Spatial temperature precision	$SD^2 = \frac{1}{n}\sum_{j=1}^{n}(T_{MRT} - T_{probe})^2$	1.26
3. Heating ability	- Focusing	Temperature increase in a ROI in target	$\overline{T}_{ROI} = \frac{1}{card(j)}\sum_{j=1}^{n} T_j$	7.24ºC
	- Precision	Spatial temperature precision	$SD^2_{ROI} = \frac{1}{n}\sum_{j=1}^{n}\overline{T}^2_{ROI}$	1.01ºC
	- Steering	Relocation of the maximum heating point	-	deviation from TPS: ±0.5cm

<0.5/1°C

Feddersen et al. Cancers, 2021

MR compatible BSD system





- MRT evaluation: within minimum requirements in terms of bias and accuracy.
- Heating evaluation with MRT: in terms of temperature increase followed quality assurance guidelines.

CONTENTS

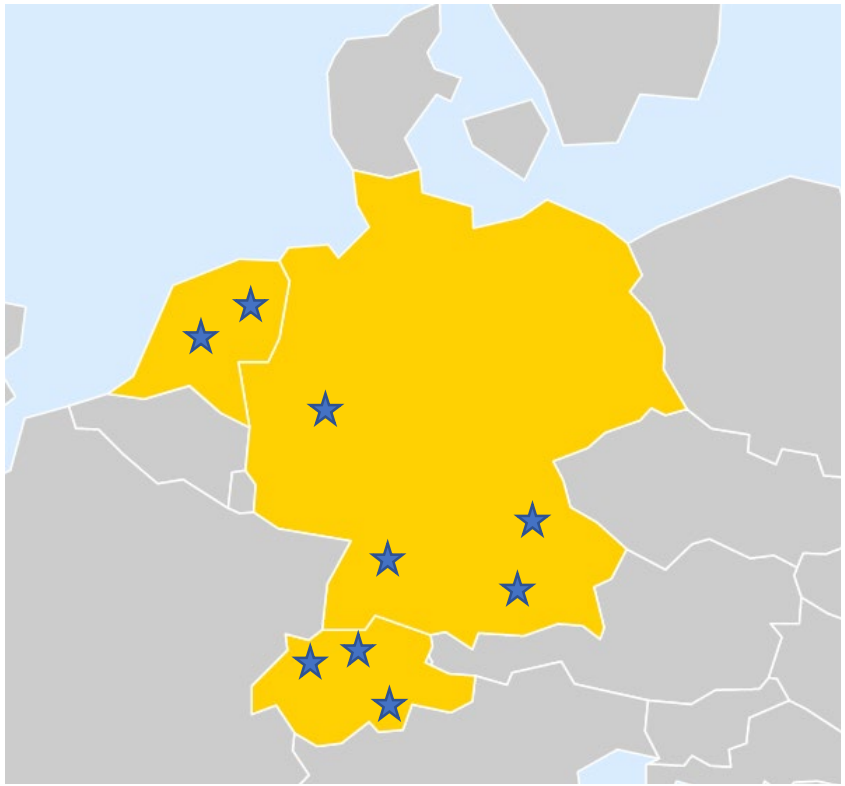
- QA measurements for deep HT systems (ESRs 9 & 10)

HYPERBOOST
Boosting the effect of Radiotherapy

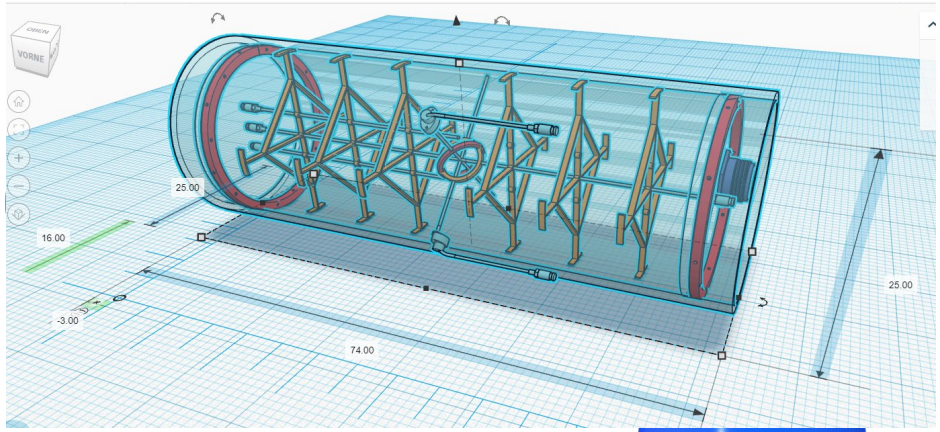
QA DEEP HT COMPARATIVE STUDY

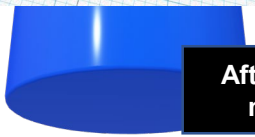
ESRs 9 + 10

- Comparative study for QA on deep HT devices.
- 9 centers involved.
- Apply new QA protocols for deep HT devices.
- Study temperature, thermal parameters used in clinical practice and how these are acquired and calculated.



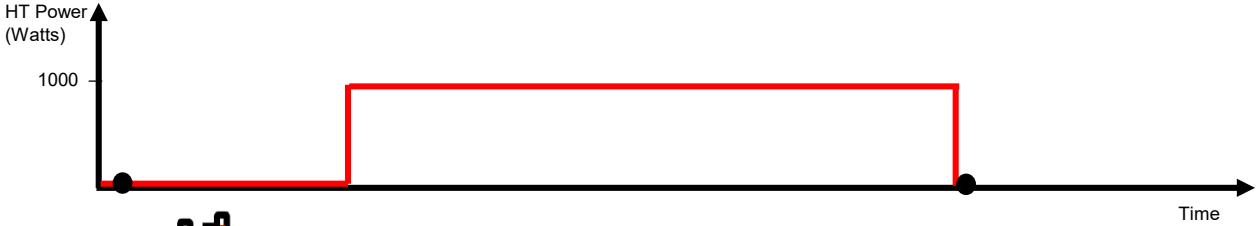
QA MEASUREMENTS FOR DEEP HT SYSTEMS





Baseline mapping

After heating mapping



i. 30 cm track with measurements every 1 cm (takes ≈3.5 min)

ii. 20 cm track with measurements every 0.5 cm (takes ≈ 6 min)

QA MEASUREMENTS FOR DEEP HT SYSTEMS

+ QA information

How is it obtained?
Are these data recorded and stored?

Category	Description		
HT system (and applicator)	e.g., 8 MHz radiofrequency capacitive system [62]		
Coupling method	e.g., water or mineral oil [33]; 5% NaCL [62]		
Temperature of cooling liquid	e.g., mean of 39 °C		
	Invasive	Superficial	
Thermometry system (uncertainty)	e.g., thermistor (±0.2 °C)	e.g., thermistor (±0.2 °C)	
Invasive thermometry placement	e.g., intraluminal	Not applicable	
Temperature acquisition	e.g., continuous and stationary in the bladder and rectum e.g., mapping with a step size of 1 cm and mean map length of 14 cm	e.g., skin surface of the buttocks and abdomen	
Temperature acquisition rate (min)	e.g., every 5 min or continuous	e.g., every 5 min or continuous	
Number of probes and sensors per probe	e.g., 2 probes in the rectum and bladder (each probe with 3–5 sensors)	e.g., 2 probes on the skin surface of the buttocks and 1 probe in the abdomen (each probe with 3–5 sensors)	
Total number of sensors	e.g., mean of 8 sensors e.g., mean of 14 sensors within mapping	e.g., mean of 8 sensors e.g., mean of 14 sensors within mapping	
Sampling rate	number of sensors per area/volume of target	e.g., number of sensors per area of target	
	Invasive	Superficial	Total
Temperature and thermal dose parameters	T90 Tmin Tmean Tmax CEM43 TRISE AUC	T90 Tmin Tmean Tmax	T90 Tmin Tmean Tmax CEM43

Carrapiço-Seabra, C. et al., Cancers, 2022

CONTENTS

- MR thermometry for tumour temperature prediction

HYPERBOOST
Boosting the effect of Radiotherapy

MRT TUMOUR FOR TEMPERATURE PREDICTION

MR Thermometry → VilasBoas-Ribeiro et al., 2021, MR thermometry accuracy and prospective imaging-based patient selection in mr-guided hyperthermia treatment for locally advanced cervical cancer

Why:

- No direct target temperature information from probe measurements.

How:

- Calculation of 3D MR temperature maps.
- Evaluation of target MR temperature and correlation with probe data.

MRT TUMOUR FOR TEMPERATURE PREDICTION

MR Thermometry → VilasBoas-Ribeiro et al., 2021, MR thermometry accuracy and prospective imaging-based patient selection in mr-guided hyperthermia treatment for locally advanced cervical cancer

Why:

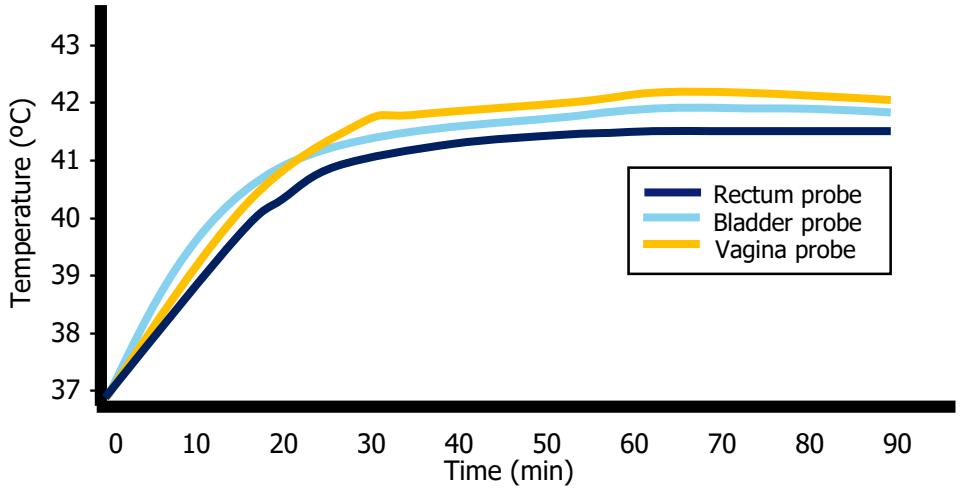
- No direct target temperature information from probe measurements.

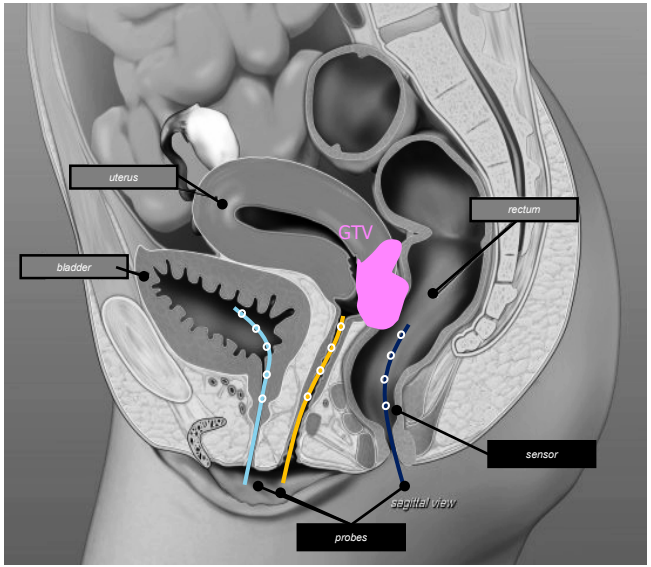
How:

- Patients with treated with RT+HT for cervical cancer with the BSD-2000-3D MR-compatible system integrated into a 1.5 T GE Signa Excite scanner (General Electric Healthcare).

MRT TUMOUR FOR TEMPERATURE PREDICTION

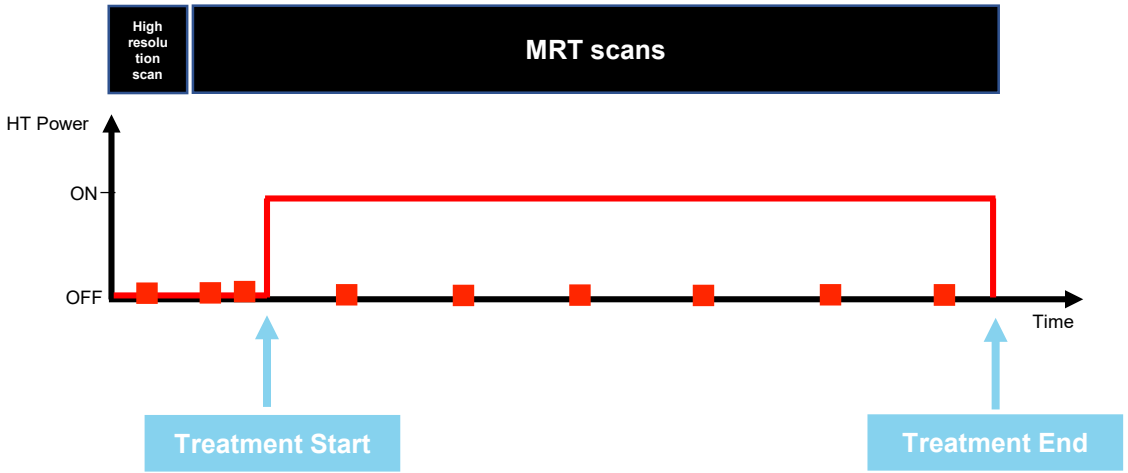
Thermometry Data

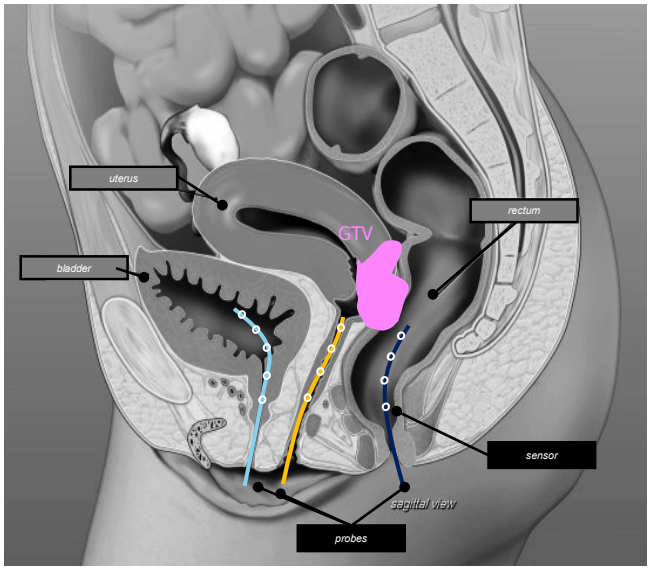




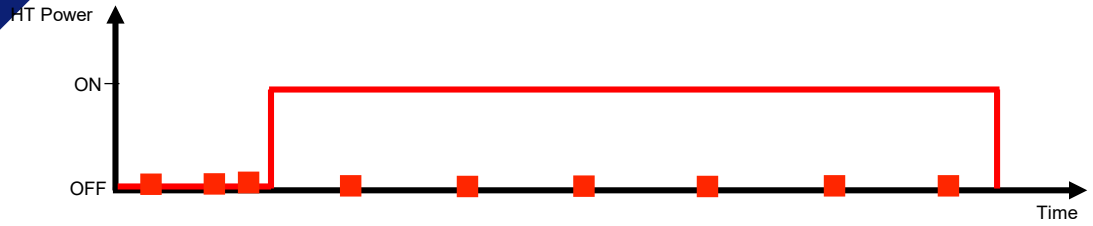
MRT TUMOUR FOR TEMPERATURE PREDICTION

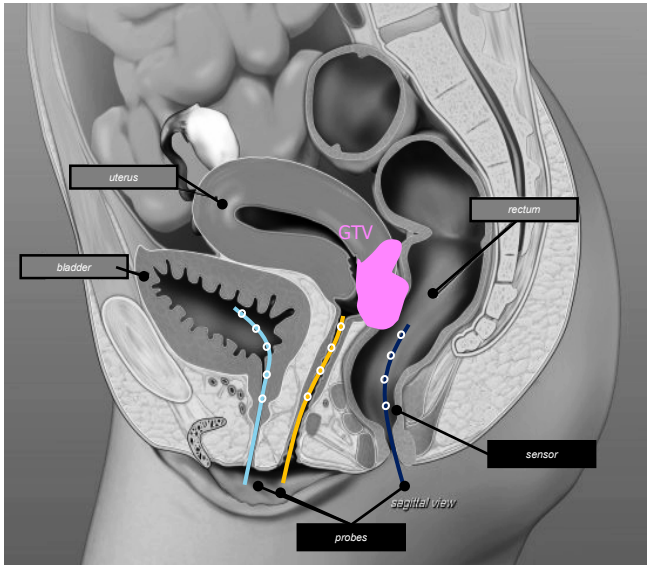
MR Thermometry Data



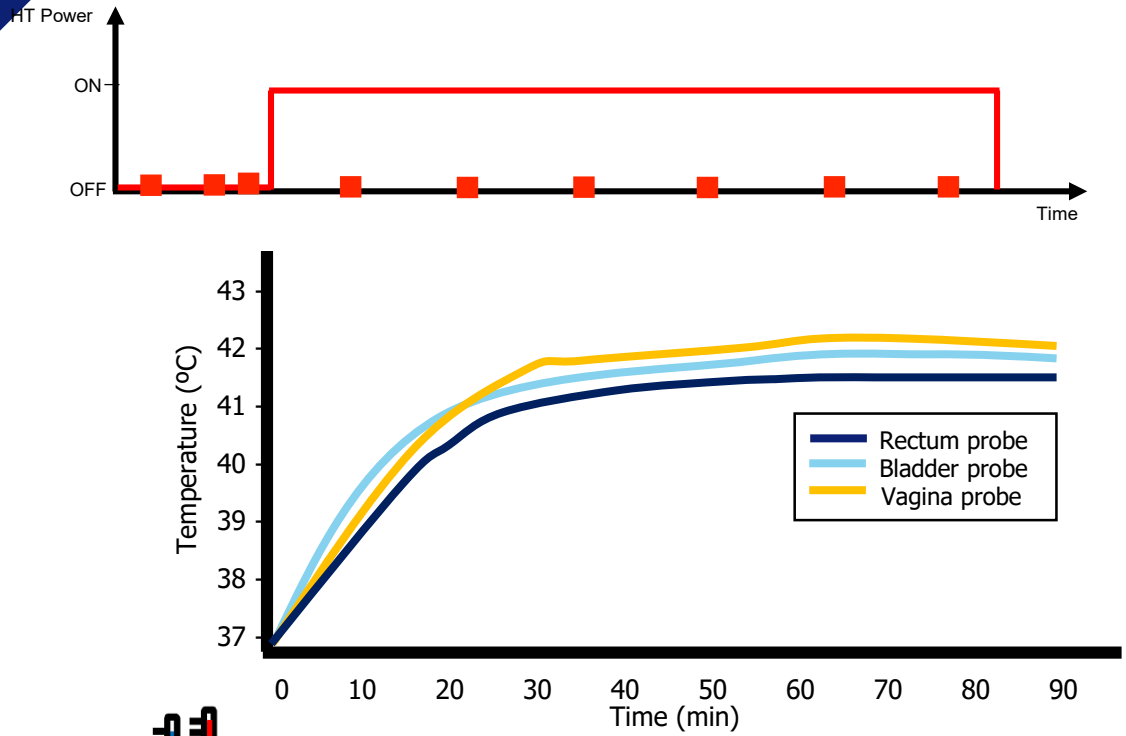


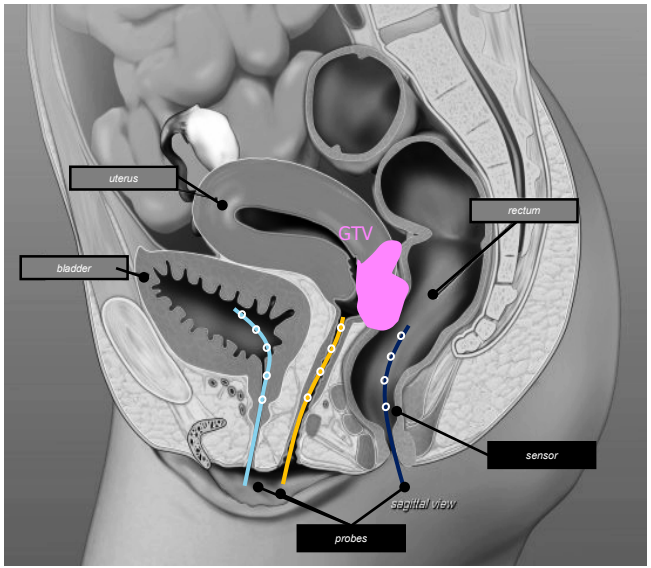
MRT TUMOUR FOR TEMPERATURE PREDICTION



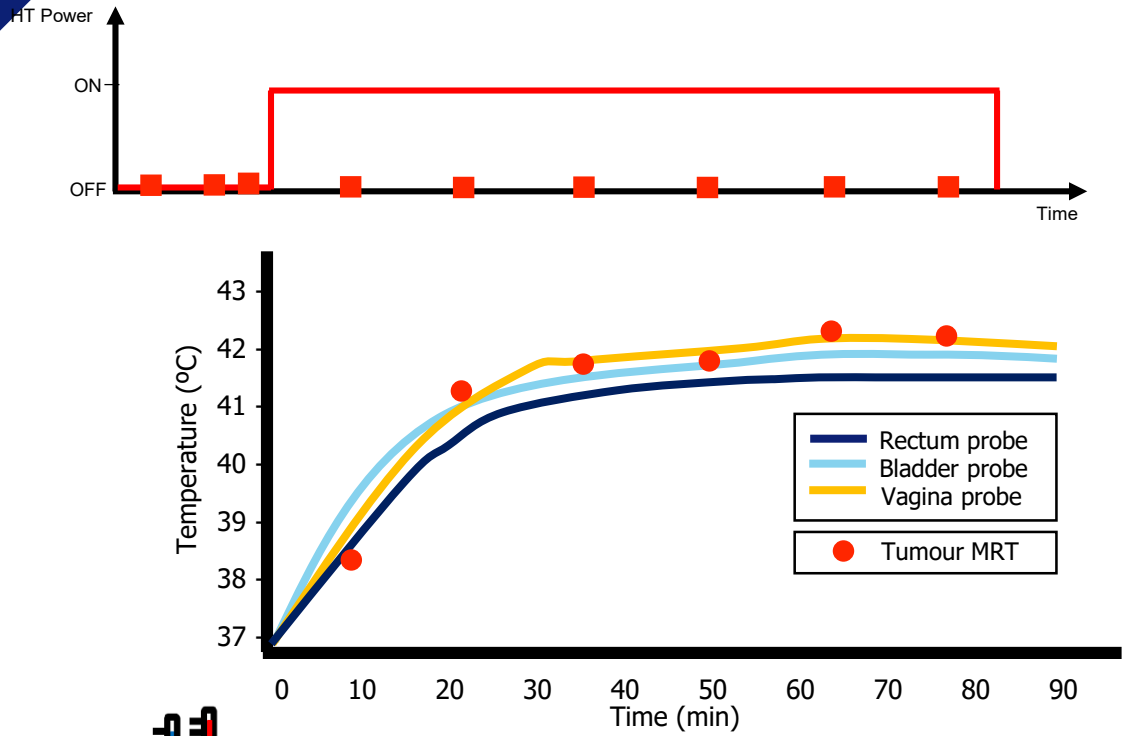


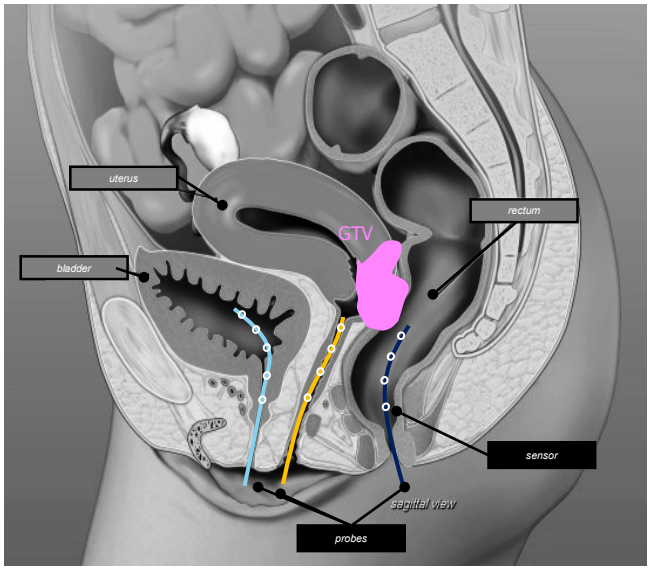
MRT TUMOUR FOR TEMPERATURE PREDICTION



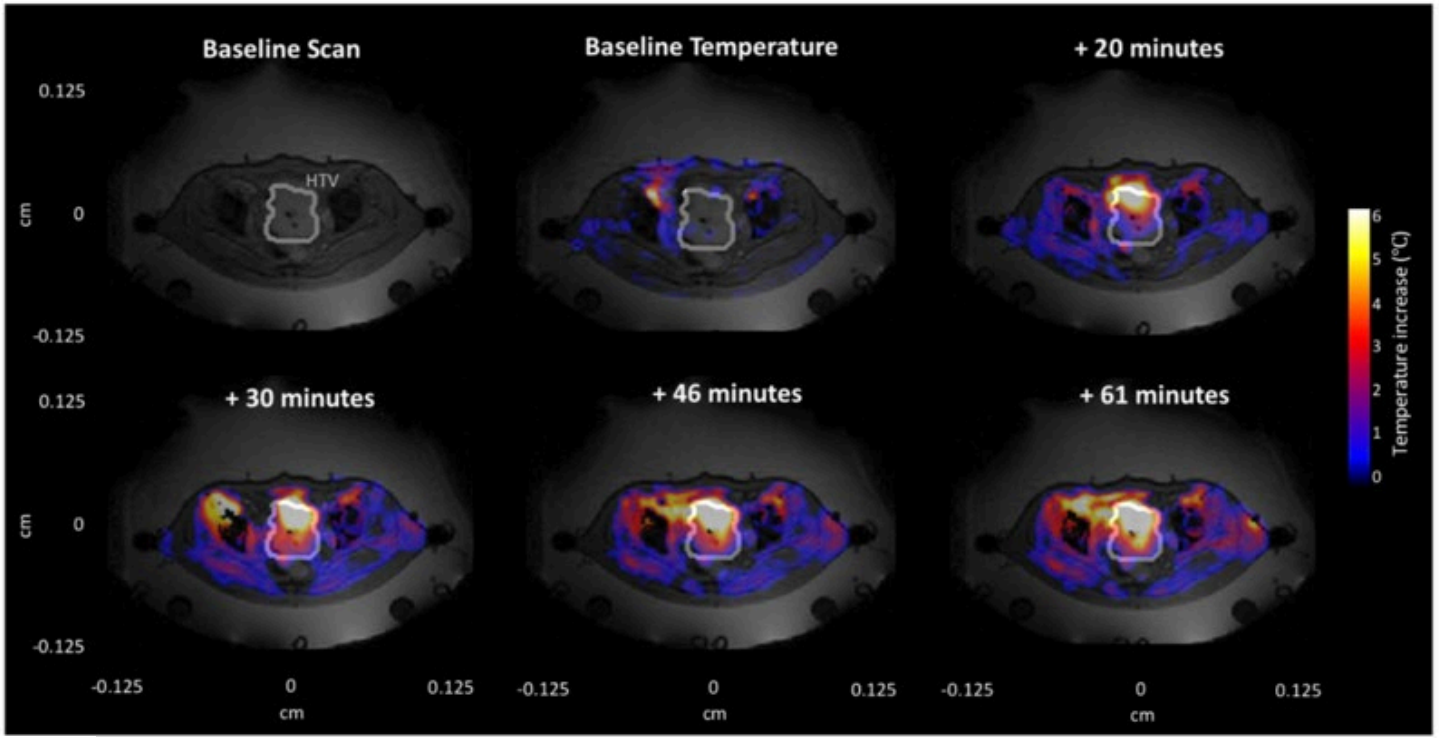


MRT TUMOUR FOR TEMPERATURE PREDICTION



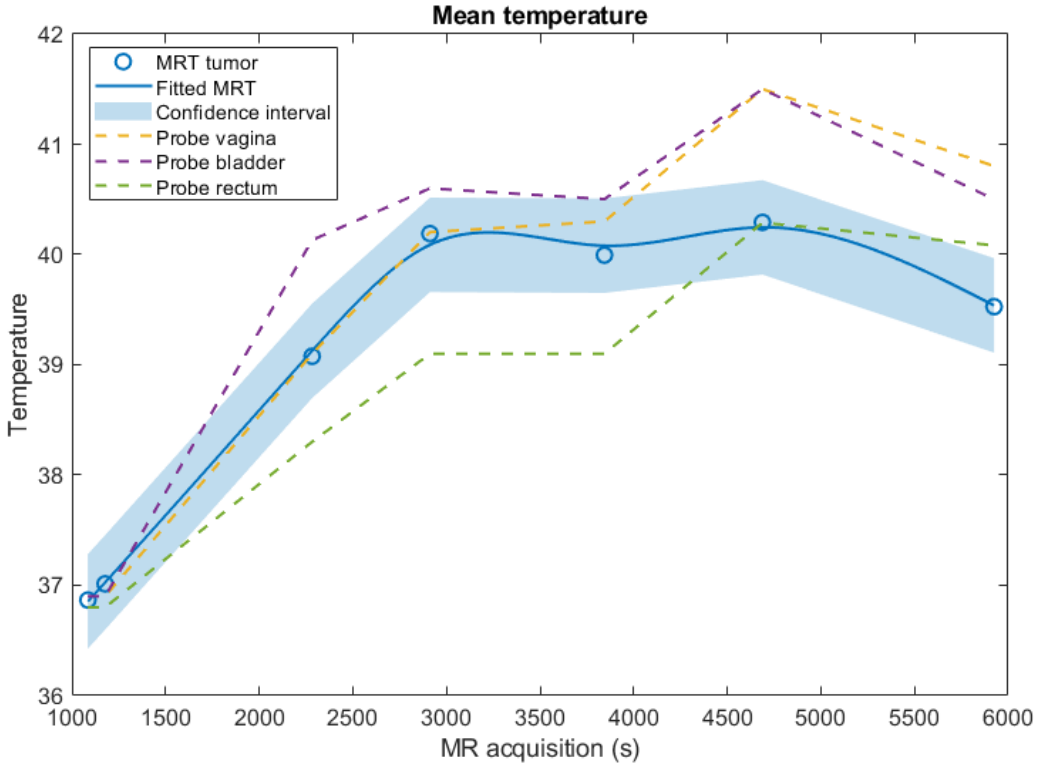


MRT TUMOUR FOR TEMPERATURE PREDICTION



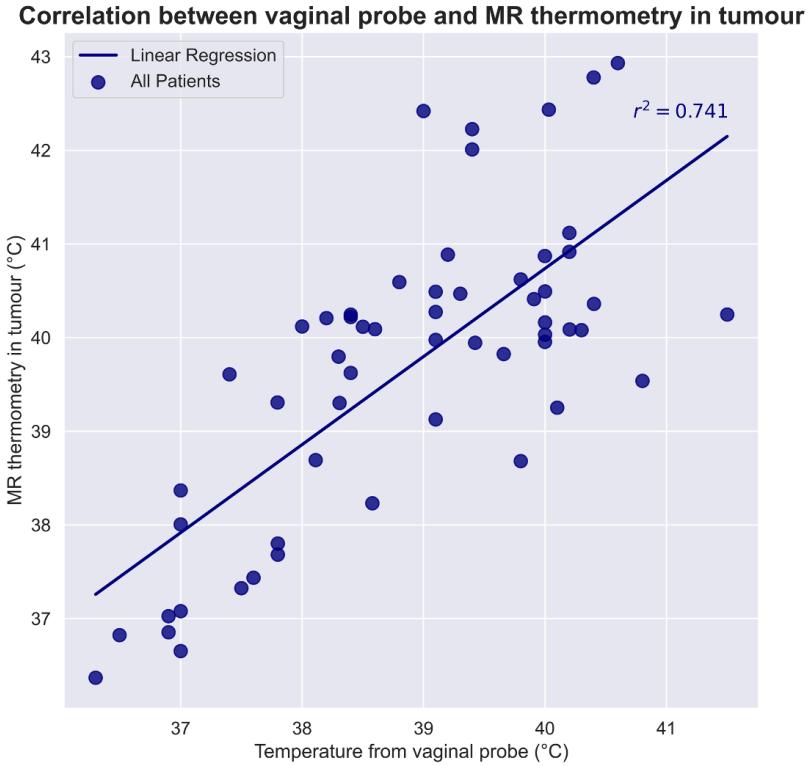
MRT TUMOUR FOR TEMPERATURE PREDICTION

Metric	MRT	Vagina probe
max	40.3	41.5
mean	38.9	39.4
median	39.5	40.2
std	1.5	1.8
range	3.4	4.6
Within Probe T		



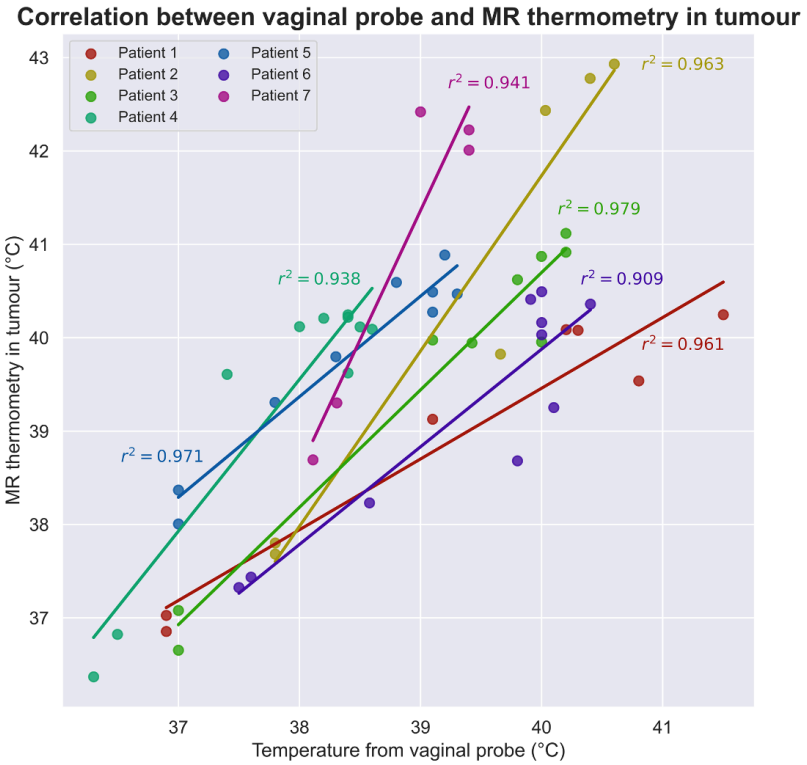
MRT TUMOUR FOR TEMPERATURE PREDICTION

- Target T50 was 39.6ºC.
- Vaginal probe was 39.4ºC.



MRT TUMOUR FOR TEMPERATURE PREDICTION

- Differences in patient condition and characteristics such as treatment tolerance and tumour physiology (e.g., perfusion and size) and patients' thermoregulation.



CONCLUSIONS

- QA procedures have been performed on different systems (superficial and deep) allowing for regular quality verifications and fair comparisons between different institutes systems.
- Thermometry procedures are essential and should also be performed in a uniform manner.
- MR-thermometry may provide new insights on how the tumour is being heated and what regions should be better targeted.

Acknowledgments

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ESR 9

Mattia De Lazzari

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Erasmus MC
University Medical Center Rotterdam
Cancer Institute

Hyperboost training week , Erlangen 2023

Rupali Khatun, ESR 11

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Hyperthermia

- Quality-controlled hyperthermia
  - one of the well-accepted cancer treatment modalities
  - works in combination with radio- and chemotherapy
- Tumour tissue is heated
  - To temperatures of 39 to 43°C
  - for 60 minutes
  - Temperature monitoring can be performed non-invasively
    - using Magnetic Resonance Imaging (MRI)

Shortcomings of MRI guided systems

- Noisy
- Small space
  - Can be claustrophobic
  - Not everyone can fit

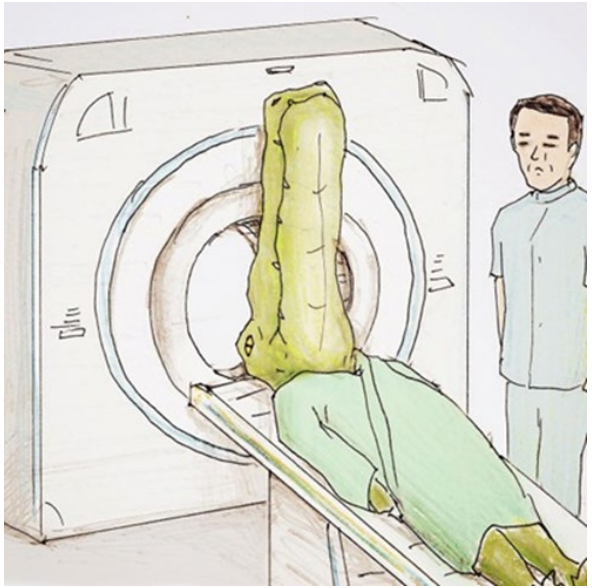
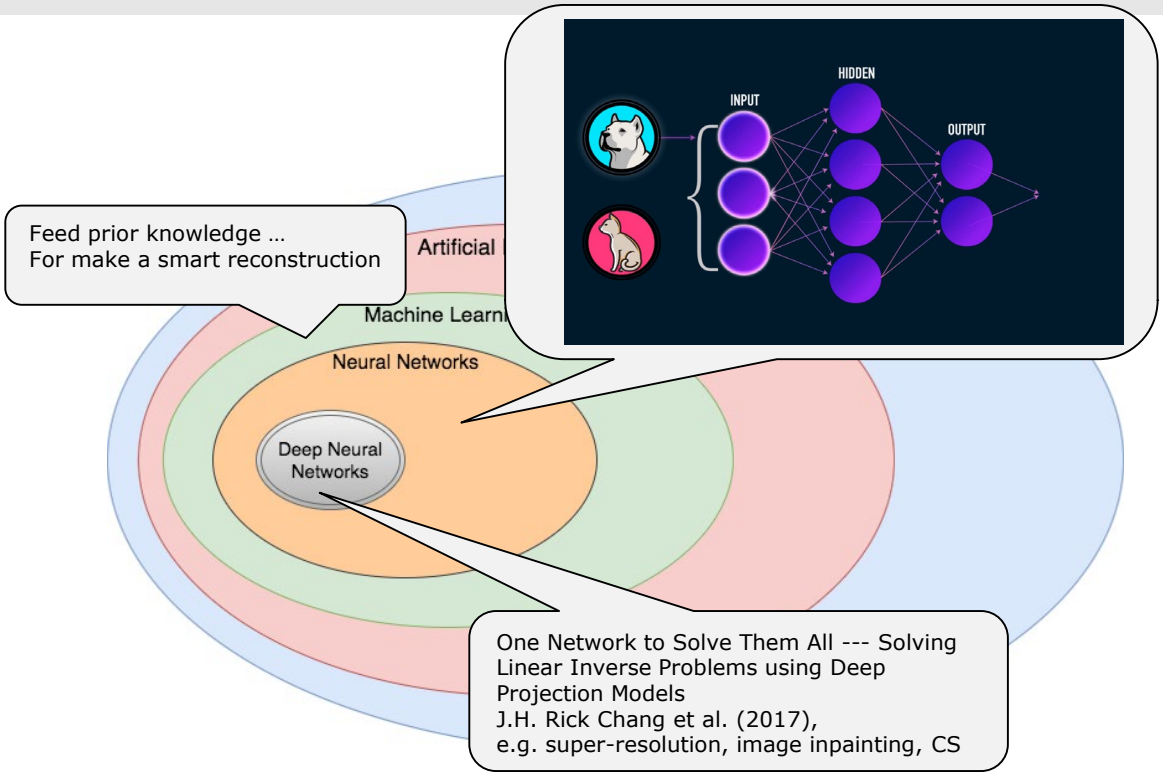


Illustration by @k5fuwa

Shortcomings of MRI guided systems

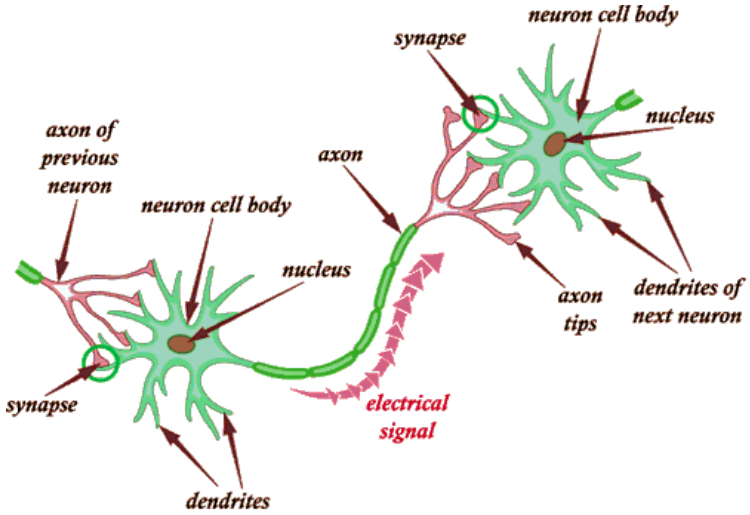
- MRI is an inherently slow process
  - Scan time for high-resolution imaging is long
    - compromises with the temporal resolution
    - can also lead to an increase motion artefact due to the movements of the patient
- Speed of the image acquisition can be increased by discarding parts of the data
  - undersampling
  - leads to loss of resolution
  - can also produce artefacts, due to the invalidation of the Nyquist criterion
- Aim of this work
  - reconstruct highly undersampled MR acquisitions
  - with better resolution and less artefacts using deep learning

Solution: Intelligent reconstruction

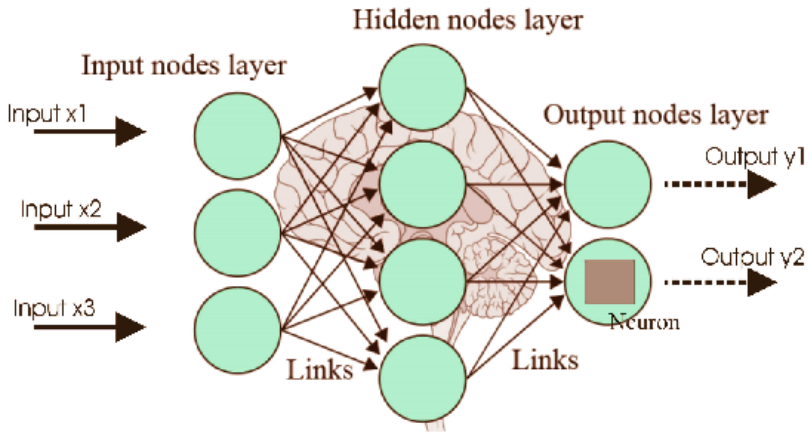


Artificial Neural Network

... make algorithms smart like humans



Neuron in our brain.



Neural Network develop using A.I.

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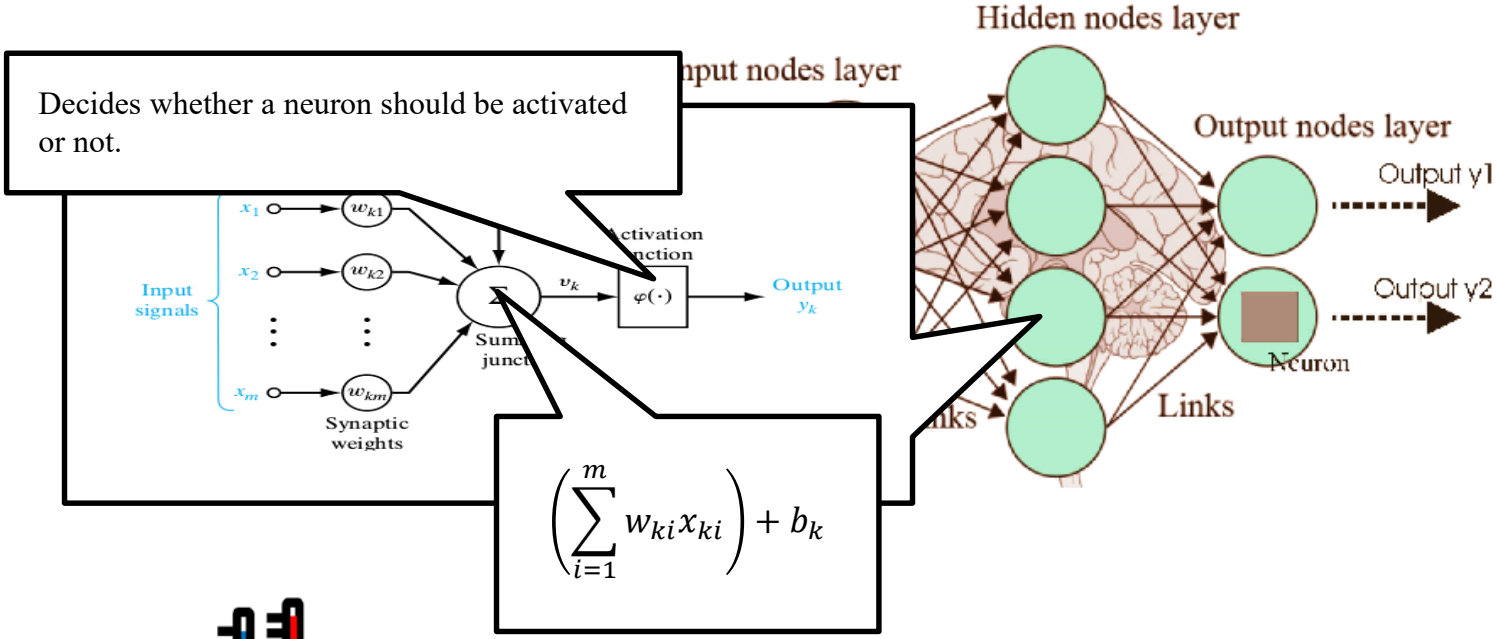
Artificial Neural Network

... make algorithms smart like humans

Decides whether a neuron should be activated or not.



$$\left(\sum_{i=1}^{m} w_{ki}x_{ki}\right) + b_k$$

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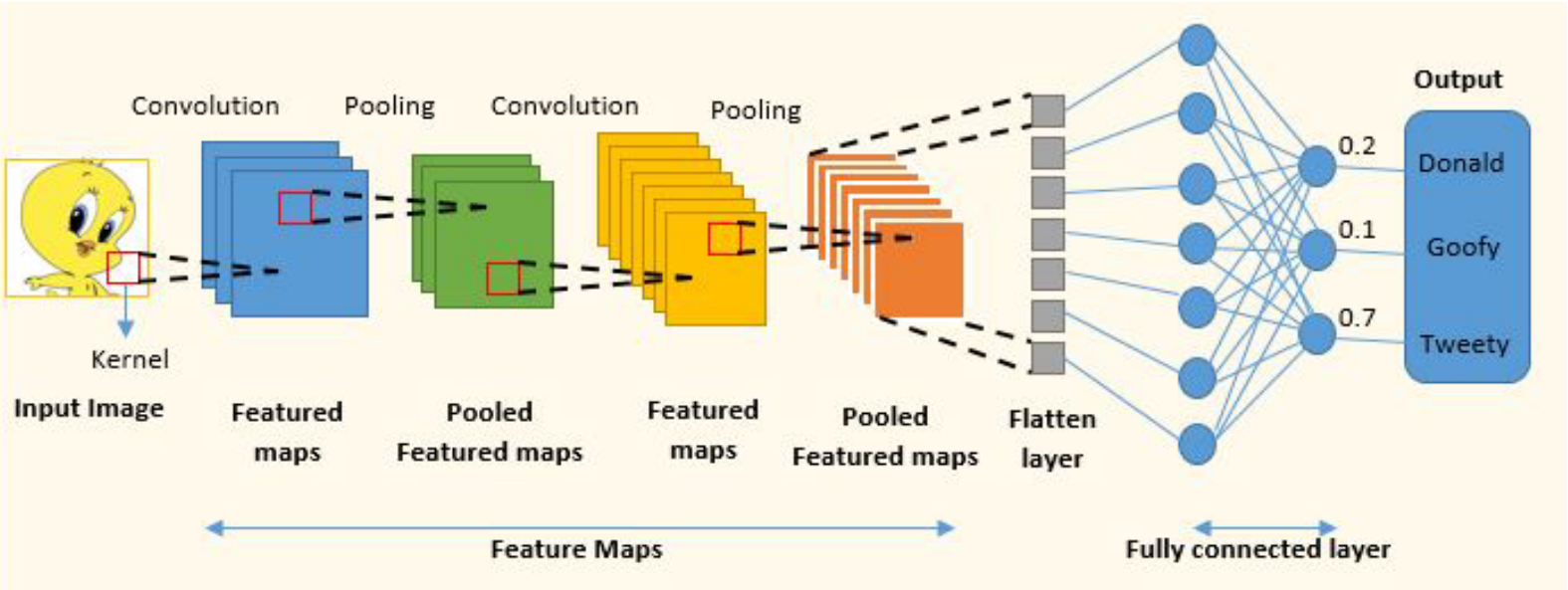
Convolutional neural network:



Improvements of highly undersampled MR hyperthermia using complex-valued convolutional networks

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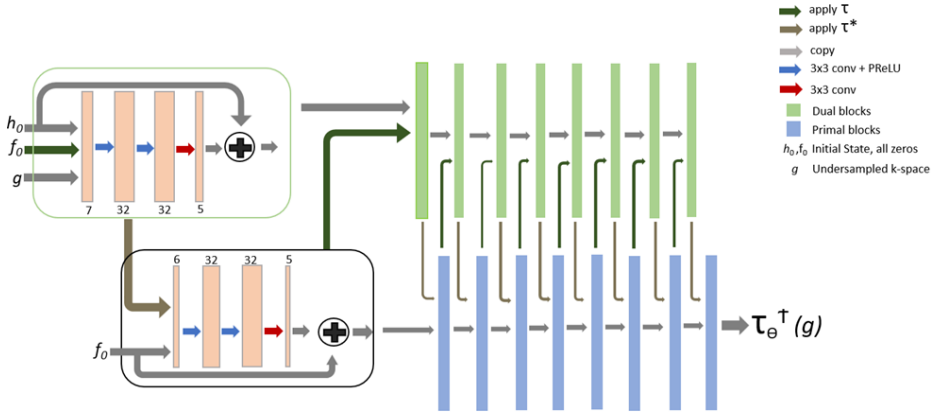
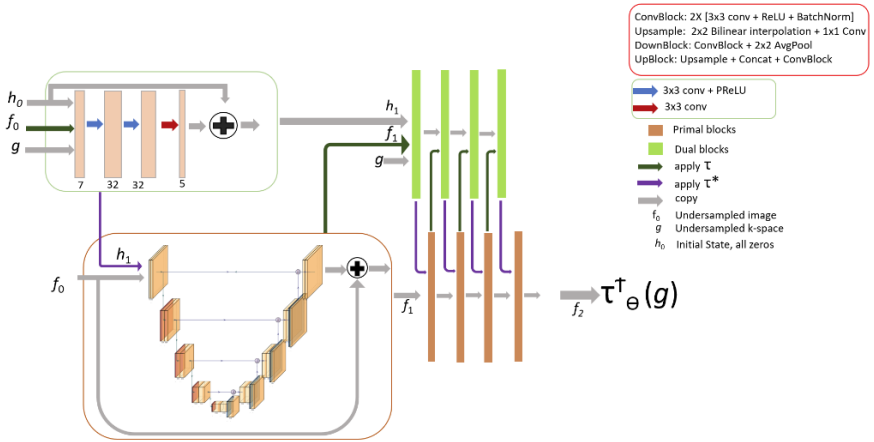
Network Architectures

Fourier-PDNet



Fourier-PDUNet



Complex-valued CNN

$$\begin{bmatrix} \Re(w \star x) \\ \Im(w \star x) \end{bmatrix} = \begin{bmatrix} w_r & -w_i \\ w_i & w_r \end{bmatrix} \star \begin{bmatrix} x_r \\ x_i \end{bmatrix}$$

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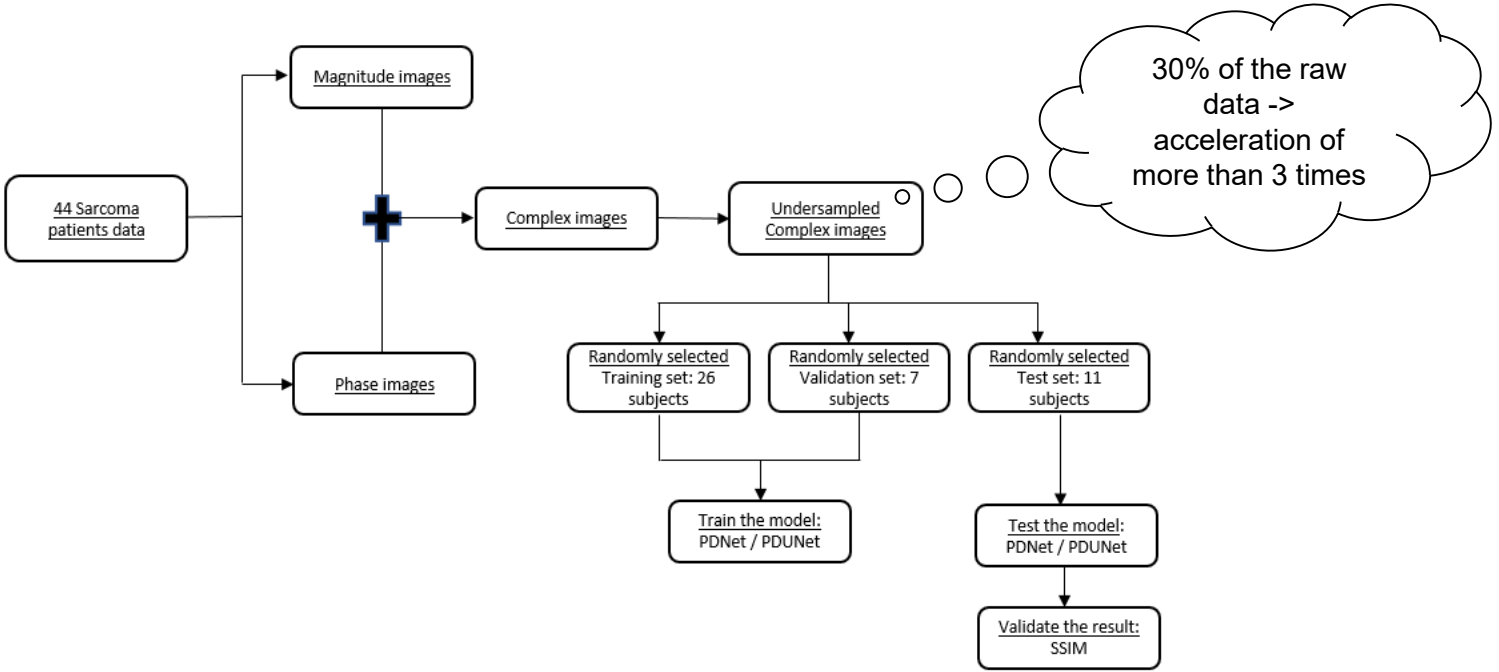
Methods: Experiment flow



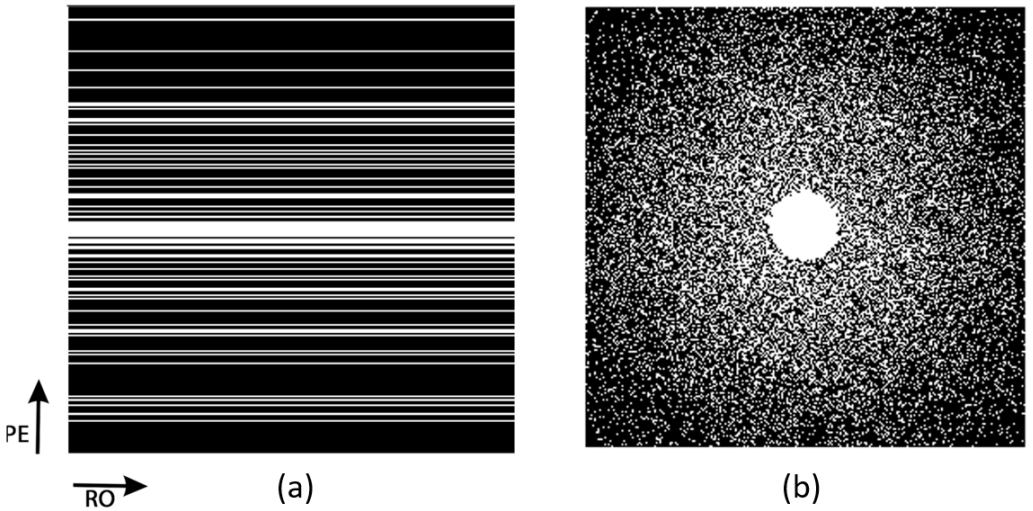
Methods & Data Collection : Focus on Sarcoma

Total Patients	Training set	Validation Set	Test set
44	26	7	11

Type of cancer	Number of Patients
Liposarcoma	15
Pleomorphic sarcoma	10
Synovial Sarcoma	7
Leiomyo sarcoma	5
Soft tissue sarcoma	3
Rhabdomyo sarcoma	2
Spindle cell sarcoma	2
Myxofibro sarcoma	1
Pleomorphic LeiomyoSarcoma	1
Ewing sarcoma	1
Fibro sarcoma	1

Undersampling Methods:

- Variable density random sampling
  - 1DVarden
  - 2DVarden
- Percentages – 25%, 20%, 10%



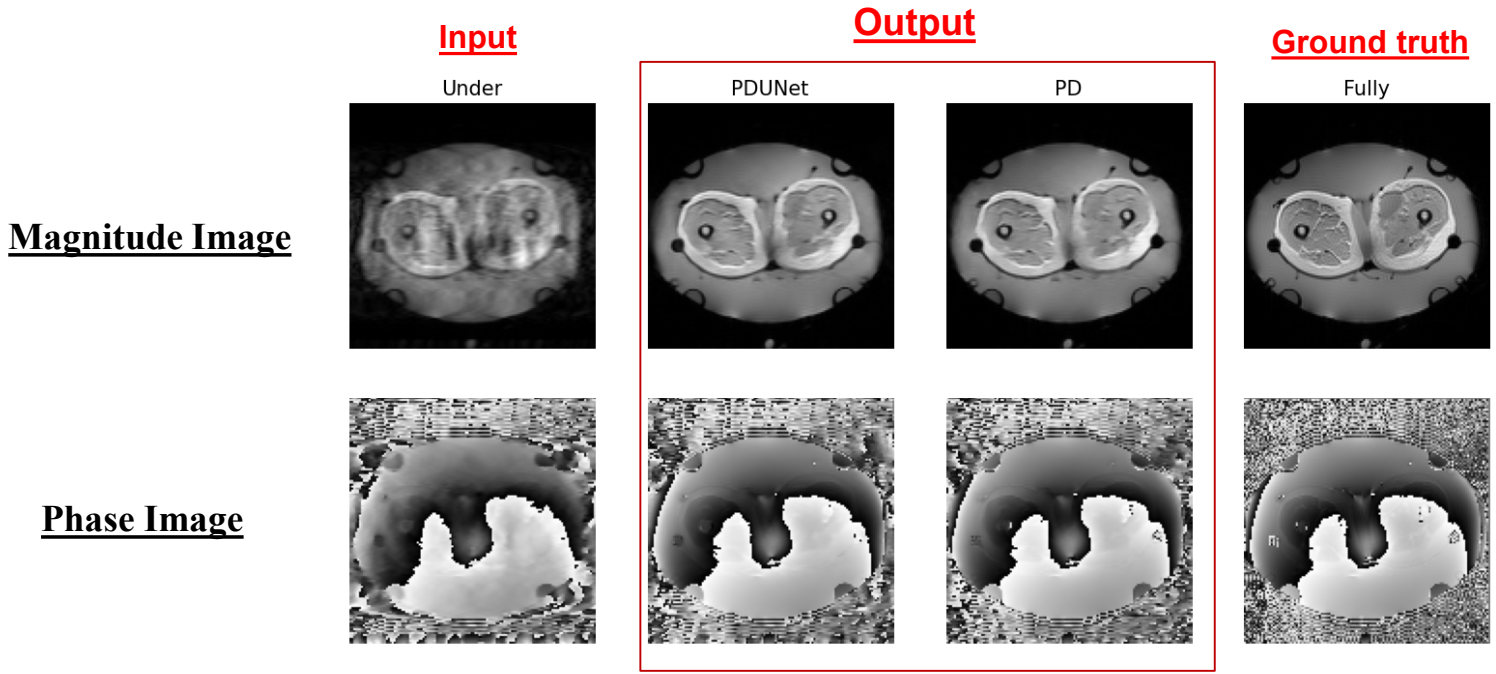
Training Environment:

Hardware:
Faculty of Computer Science, Otto von Guericke University Magdeburg, Germany

- 40 cores of intel xeon cpu- 20cores(5/ training)
- RAM – 768 gb
- 8 NVDIA – GeForce 2080ti Gpus (11 gb) - 4

- **Training Parameter**
  - Epoch – 100/ training
    - 10 hours/ Epoch

Results :



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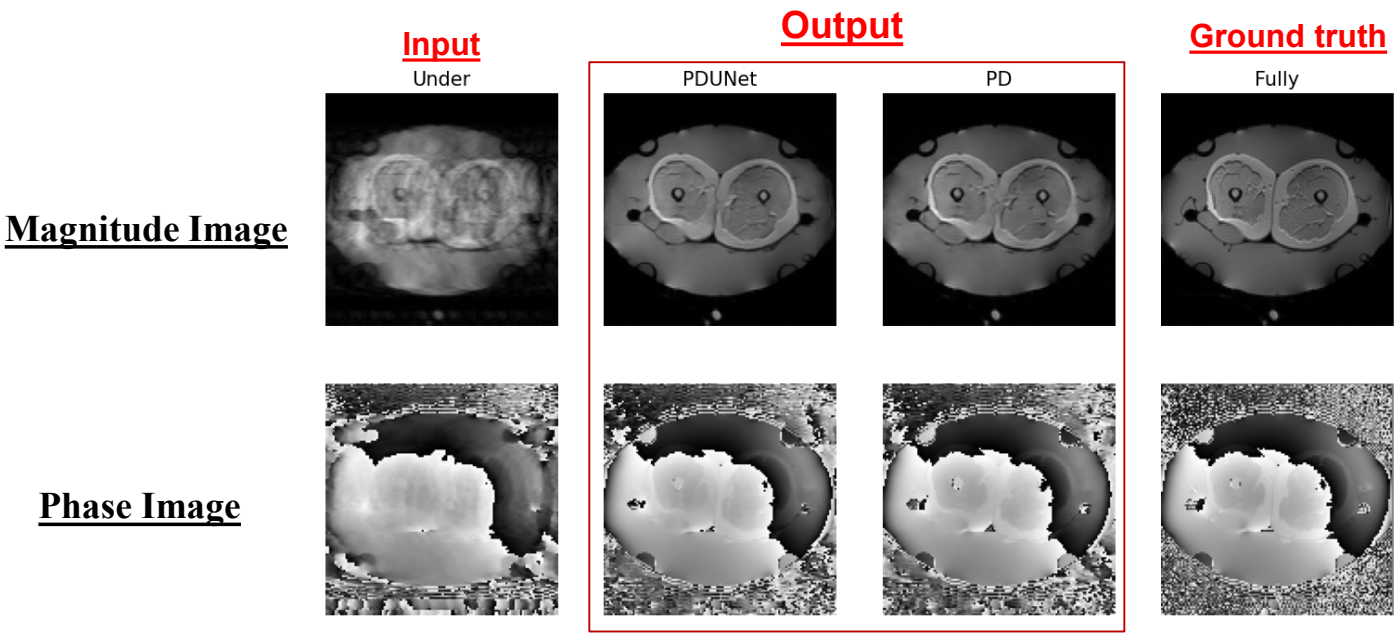
Results :


Input
Under
Output
PDUNet
PD
Ground truth
Fully
Magnitude Image
Phase Image

Results :

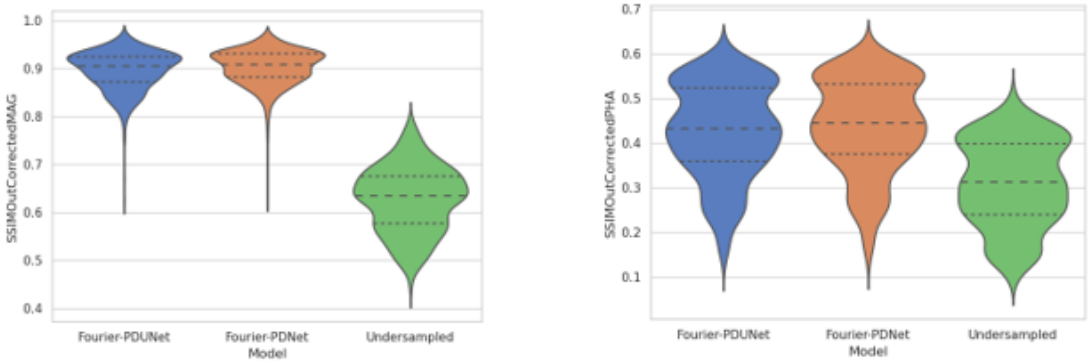


Figure 1: (a) SSIM value of magnitude images of different models. (b) SSIM value of phase images based on the indicated models used.

Table 1: Mean Value of RMSE of Reconstructed of Temperature Map from different models

Undesample	Fourier-PDUNet	Fourier-PDNet
1.508±0.059	1.079±0.039	1.079±0.036

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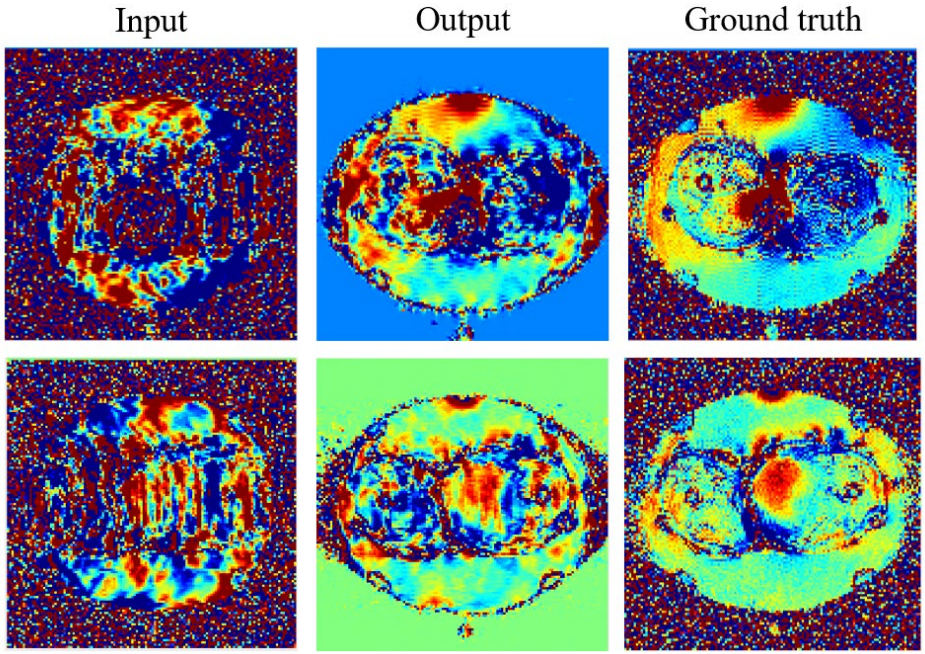
Results :



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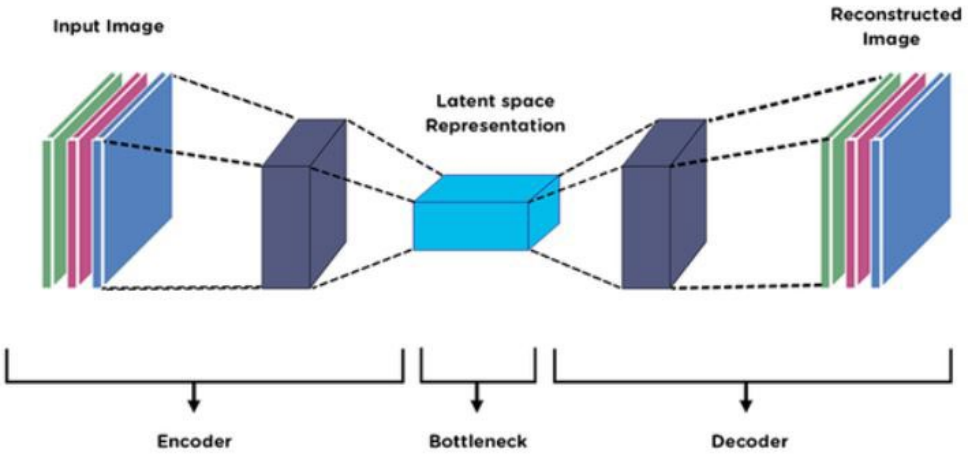
Future work:

Auto encoder (AE):

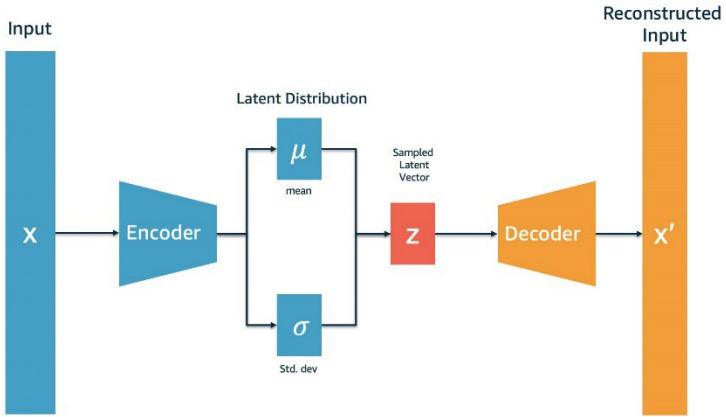
- Autoencoders are designed to reproduce their input, especially for images.



Future work:

Variational auto encoder (VAE):

- Key idea: make both the encoder and the decoder probabilistic.



Finding Biomarker

- By exploring Latent space.

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Conclusions:

Conclusions:

- The results show that deep learning-based methods were able to alleviate the undersampling problem and managed to bring the temperature difference close to the ground-truth. Still, a 1 °C temperature difference can be seen in the deep learning results. This can be attributed to the performance difference of the models between the magnitude and phase images.

- Deep learning has the potentiality to improve hyperthermia treatment and can be helpful to delivered better treatment.

Automatic segmentation and Understanding of Temperature distribution

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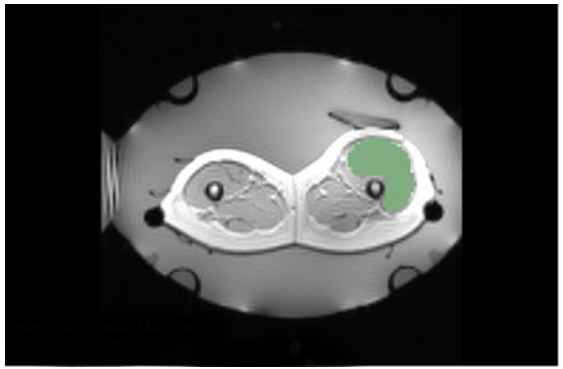
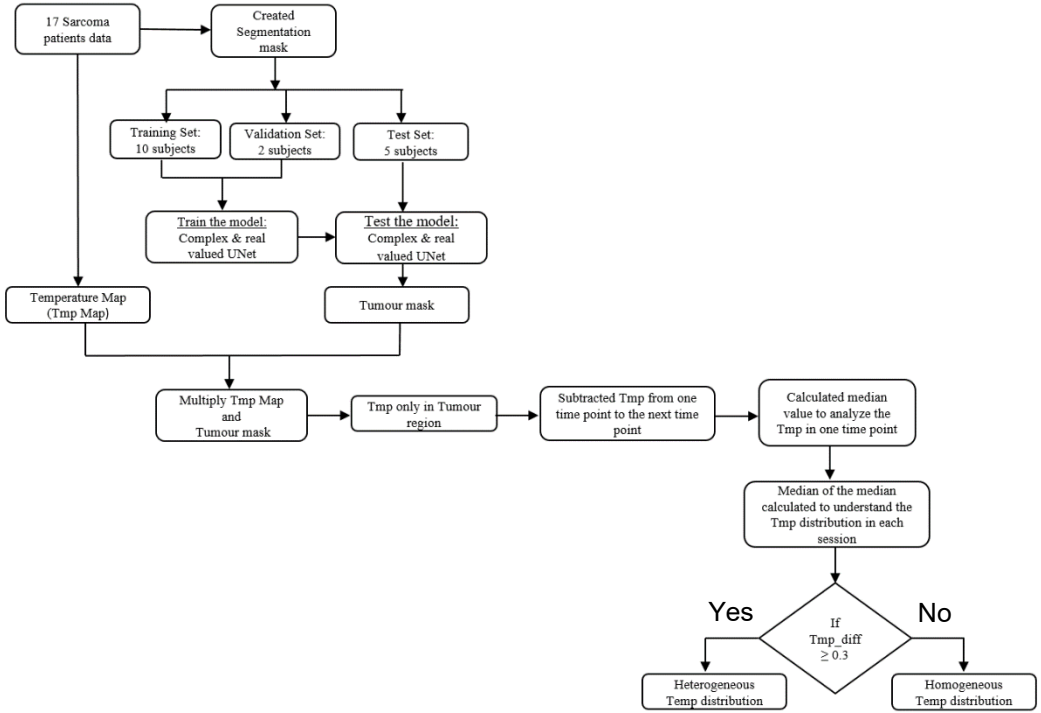
segmentation :

Segregate tumour and non-tumour tissues

- Semantic image segmentation is the process of linking each pixel in an image to a class label .
- 3D slicer



Methods: Experiment flow



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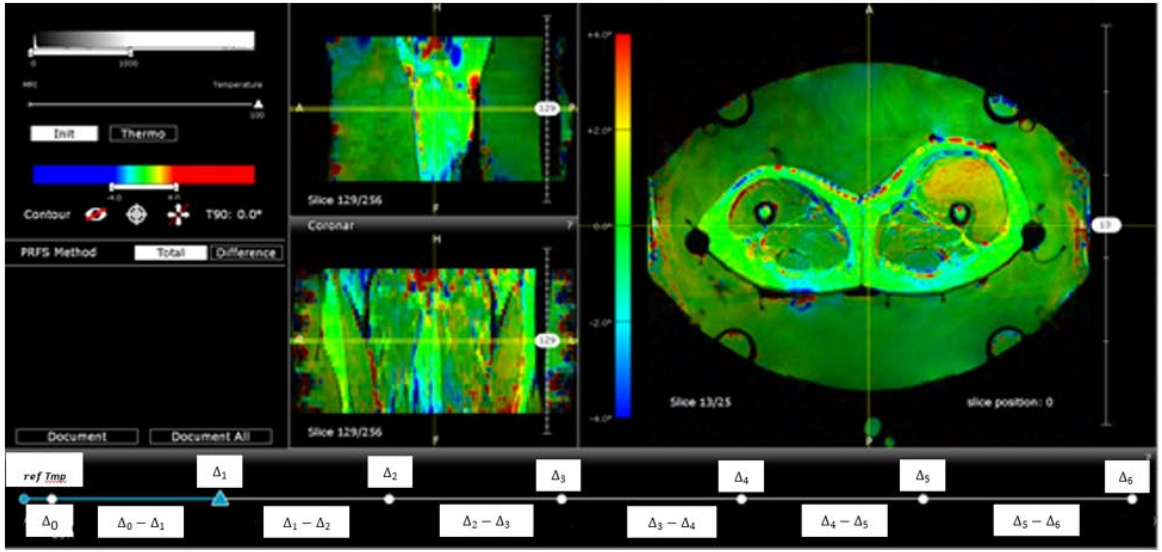
Methods:



Ref Tmp = First time point considered as reference temperature.

$$\Delta_{Tmp} = \Delta t_n - \Delta t_{n-1}$$

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Results:

	subID	sessio	TP	masked_mean	masked_median	masked_std	SessionWiseMedian	Median_masked_median	
18	4	20200511	1	1.926517612	2.077818687	0.970637314	20200511	0.418915058	
19	4	20200511	2	2.19016167	2.144845096	1.146147345			
20	4	20200511	3	0.460514873	0.603237683	1.146600671			heterogeneous
21	4	20200511	4	0.210930657	0.234592432	0.448405904			
22	4	20200511	5	-0.089833293	-0.100539614	0.482048983			
23	4	20200511	6	-0.104329754	-0.067026409	0.596591221			
24	4	20200508	1	0.396634504	0.43567166	0.814540912			
25	4	20200605	1	2.160855117	2.1783583	0.790707992	20200605	0.645129189	heterogeneous
26	4	20200605	2	0.862202884	0.955126332	0.7642917			
27	4	20200605	3	0.311329583	0.335132046	0.49070967			
28	4	20200605	4	-0.361423114	-0.351888649	0.37274918			
29	4	20200518	1	2.342269785	2.446463937	0.773657777	20200518	0.016756602	homogeneous
30	4	20200518	2	1.834382994	1.843226254	0.483911647			
31	4	20200518	3	-1.616199802	-1.558364015	0.949655322			
32	4	20200518	4	-0.057231522	0.016756602	0.975567317			
33	4	20200518	5	-0.440773541	-0.385401853	0.603897908			
34	4	20200602	1	0.733295752	0.821073513	0.588155123	20200602	0.100539614	homogeneous
35	4	20200602	2	1.577448347	1.59187722	0.491260541			
36	4	20200602	3	0.175890959	0.301618842	0.856294744			
37	4	20200602	4	-0.159007298	-0.150809421	0.326262812			
38	4	20200602	5	0.119405403	0.100539614	0.331445181			
39	4	20200602	6	-0.444265962	-0.43567166	0.358011522			
40	4	20200602	7	-0.388832459	-0.318375444	0.507067612			
41	4	20200528	1	2.02310514	2.044305482	0.745725687	20200528	0.134052818	homogeneous
42	4	20200528	2	1.940900361	1.96052247	0.905649002			
43	4	20200528	3	0.553161849	0.603237683	0.681642733			
44	4	20200528	4	-0.935953887	-0.854586718	0.488691715			
45	4	20200528	5	0.135829433	0.134052818	0.326266418			
46	4	20200528	6	-0.255016883	-0.21783583	0.78747574			
47	4	20200528	7	-0.047351398	-0.050269807	0.428516511			
48	4	20200525	1	0.689682562	0.770803706	0.883199963	20200525	0.335132046	heterogeneous
49	4	20200525	2	0.190750164	0.368645251	1.330122844			
50	4	20200525	3	1.088393751	1.022152741	1.219043989			
51	4	20200525	4	0.356027916	0.234592432	1.292846227			
52	4	20200525	5	-0.575527943	-0.402158455	1.130300901			
53	4	20200525	6	0.34973623	0.301618842	0.548142499			

If TmpDiff is <= 0.3
Homogeneous
Else
Heterogenous

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Results:

	subID	sessio	TP	masked_mean	masked_median	masked_std	SessionWiseMedian	Median_masked_median	
142	8	20190222	1	0.727826802	0.737290502	0.549523144	20190222	0.234592432	homogeneous
143	8	20190222	2	-0.05658707	-0.050269807	0.376334341			
144	8	20190222	3	0.596237472	0.552967876	0.402076688			
145	8	20190222	4	-0.1657367	-0.117296216	0.560094311			
146	8	20190222	5	0.235860763	0.21783583	0.397527005			
147	8	20190222	6	0.255202809	0.251349035	0.519240877			
148	8	20190222	7	0.299643172	0.318375444	0.410808303			
149	8	20190222	8	-0.058172484	-0.067026409	0.456591795			
150	8	20190228	1	0.864550103	0.904856525	0.638403999	20190228	0.552967876	heterogeneous
151	8	20190228	2	0.429848903	0.418915058	0.473425776			
152	8	20190228	3	0.622884099	0.619994285	0.390506278			
153	8	20190228	4	0.142312508	0.134052818	0.369335792			
154	8	20190228	5	0.563427274	0.569724479	0.36698303			
155	8	20190228	6	0.564915312	0.552967876	0.444270751			
156	8	20190228	7	-0.157343849	-0.134052818	0.512556464			

	subID	sessio	TP	masked_mean	masked_median	masked_std	SessionWiseMedian	Median_masked_median	
175	1	20201210	1	0.646732495	0.636750888	0.168344835	20201210	0.552967876	heterogeneous
176	1	20201210	2	0.540355203	0.552967876	0.285388296			
177	1	20201210	3	-1.45568666	-1.457824401	0.263215885			
178	1	20201210	4	-1.484496834	-1.474581003	0.721993498			
179	1	20201210	5	-1.583605805	-1.575120617	0.616504012			
180	1	20201210	6	2.078312011	2.044305482	0.506492523			
181	1	20201210	7	0.233490673	0.21783583	0.275636435			
182	1	20201210	8	8.549435562	8.478840769	2.925150181			
183	1	20201210	9	-6.871950029	5.797784399	17.98004324			
184	1	20210113	1	0.913249346	0.770803706	1.832589594	20210113	0.502698069	heterogeneous
185	1	20210113	2	1.493951287	1.558364015	2.77858144			
186	1	20210113	3	0.092843774	-3.10862E-15	1.080964061			
187	1	20210113	4	-0.1045763	-0.016756602	2.800499964			
188	1	20210113	5	1.031068299	0.971882934	2.993868863			
189	1	20210113	6	0.542890682	0.502698069	2.105293155			
190	1	20210113	7	0.096386764	0.268105637	2.045153391			

Challenges and Conclusions:

- Challenges
  - Presence of artefacts.
  - No proper trial about Temperature distribution.
- Better understanding of temperature distribution during hyperthermia for cancer treatment will enable us to deliver better treatment.
- Future work
  - Improving the networks' performance for segmentation.
  - Evaluating patient data from other clinics.
  - Evaluating other DL-models.
  - Comparing the output with probe data.

- ***Acknowledgement:*** This work has been supported by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 955625, Hyperboost.

HYPERBOOST
Boosting the effect of Radiotherapy

Universitätsklinikum
Erlangen

Thank You for Your Attention!

Translational Strahlenbiologie
Prof. Udo Gaipl

Strahlenklinik
Prof. Rainer Fietkau

rupali.khatun@uk-erlangen.de
benjamin.frey@uk-erlangen.de
udo.gaipl@uk-erlangen.de
www.strahlenklinik.uk-erlangen.de
@translatradbio

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Universitätsklinikum Erlangen

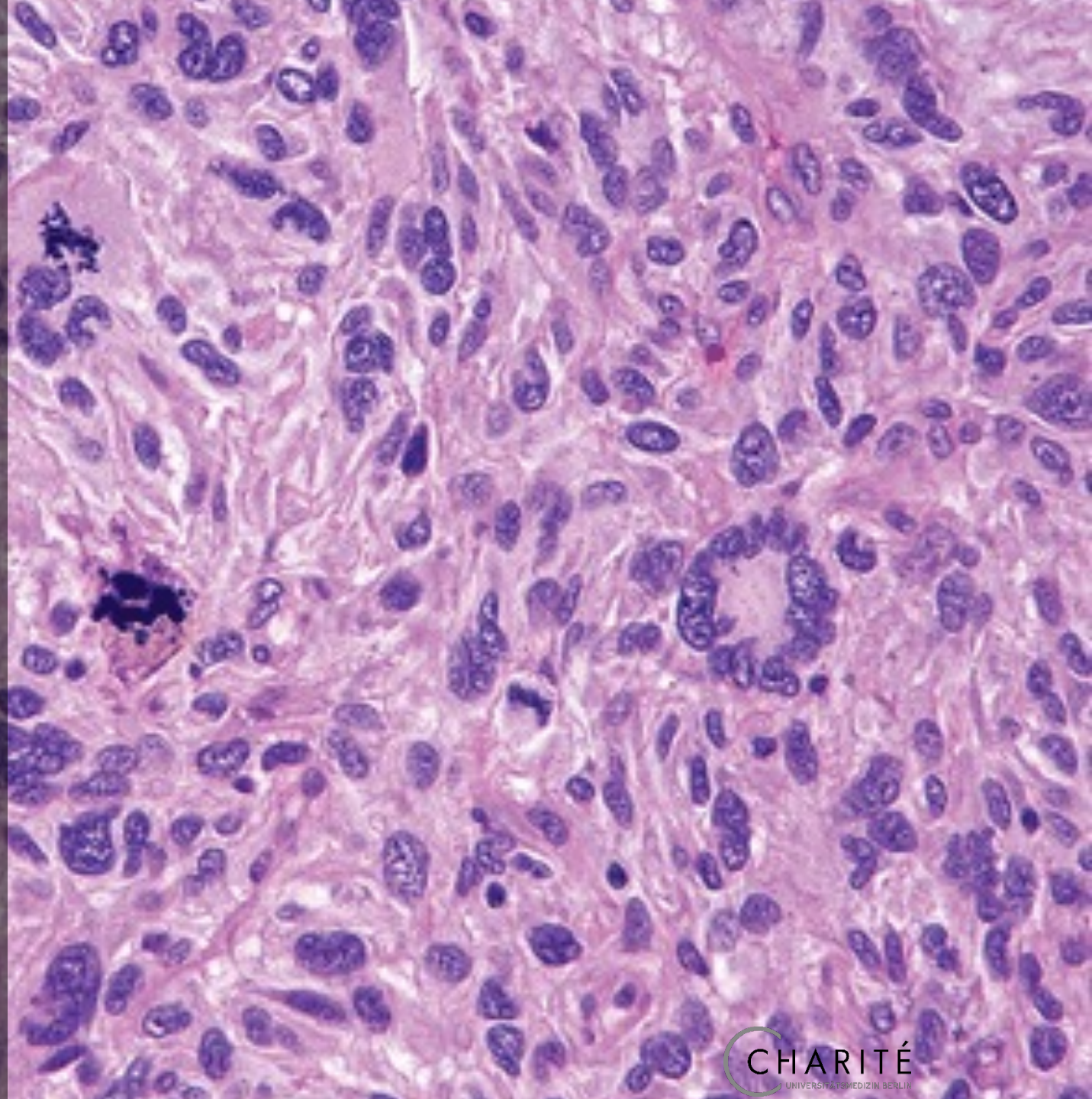
Hyperthermia in the treatment of high-risk soft tissue sarcomas & Biophysical effects of RF-EMFs on cancer cell lines

Paraskevi Danai Veltsista – ESR13

14.03.2023

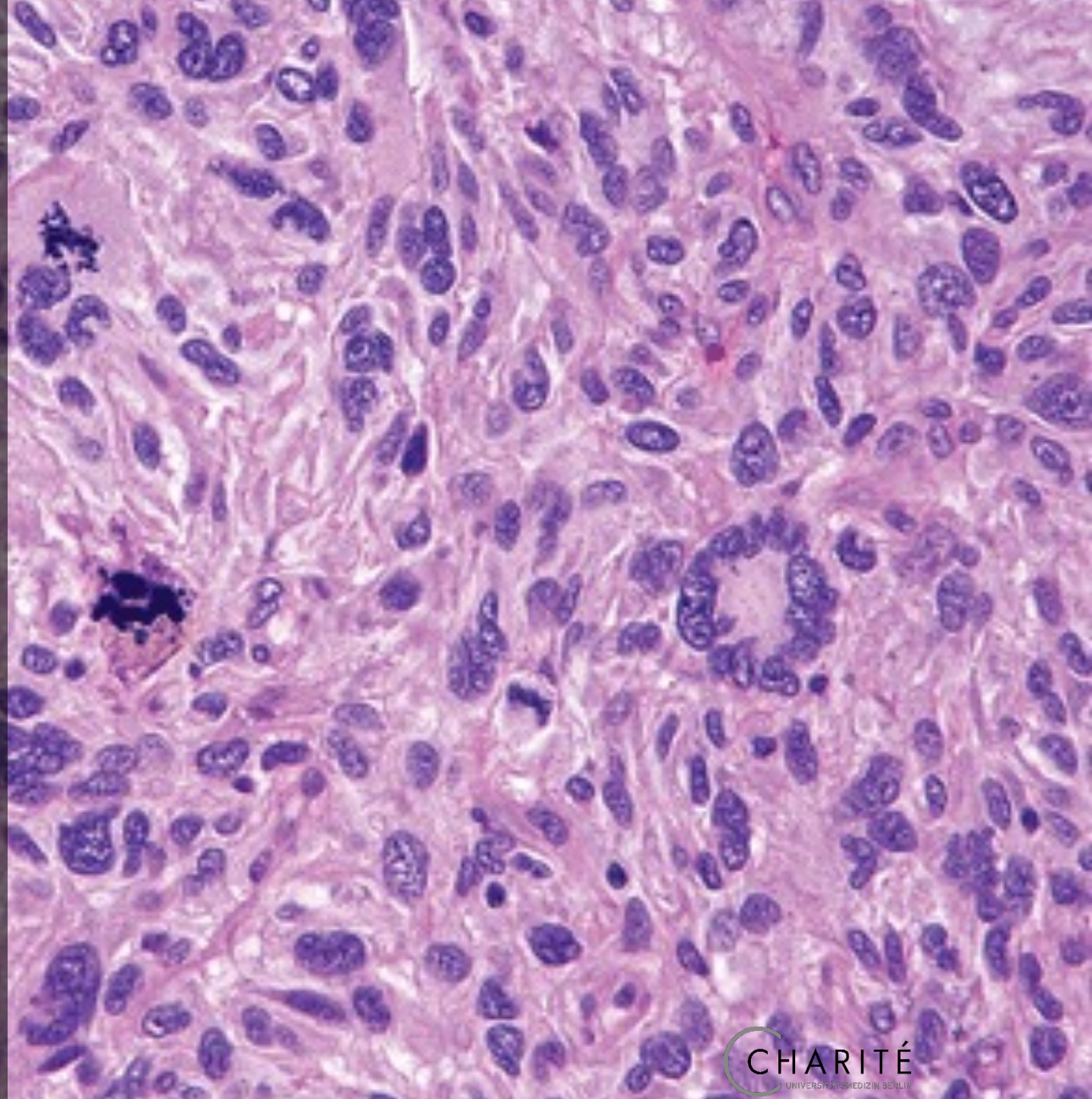
This project (Hyperboost; www.Hyperboost-h2020.eu) has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 955625

Hyperthermia in the treatment of high-risk soft tissue sarcomas

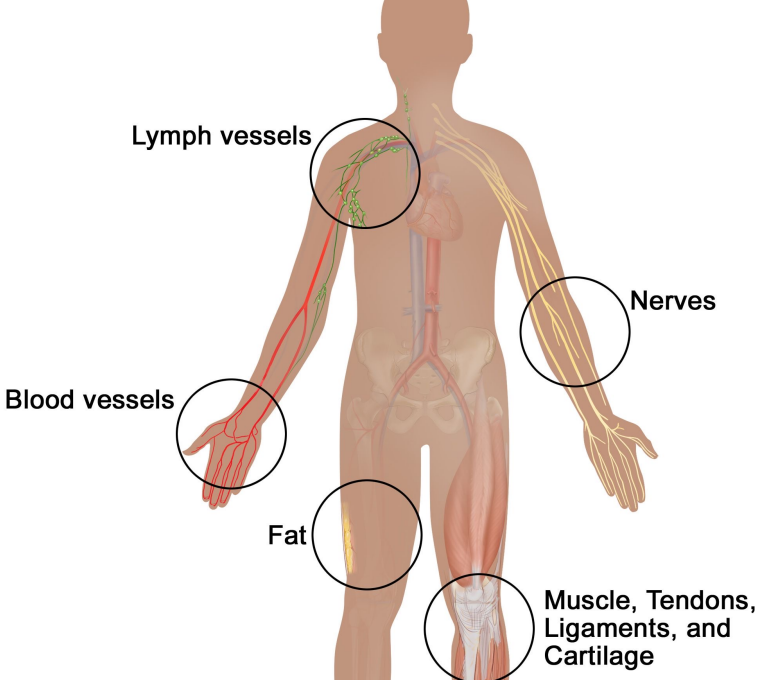


Goal of the project

- What data we have so far
- What remains unanswered
- Questionnaire to high-volume clinics
- Establishment and implementation of a concordant therapeutic protocol in the clinical setting

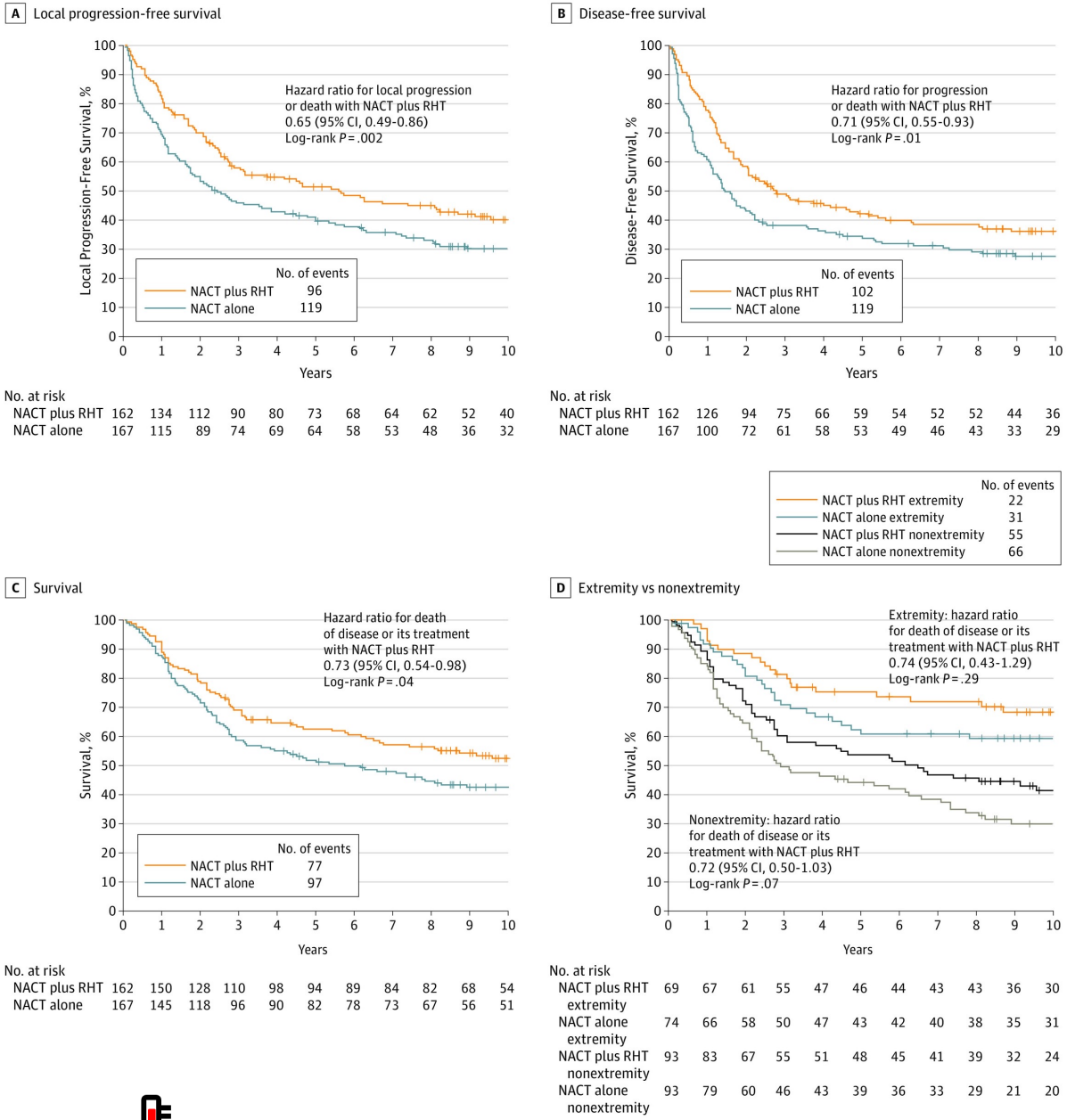


Soft-tissue Sarcomas (STS)



- Rare type of cancer (<1%)
- Diagnosis through physical examination, imaging and biopsy
- Treatment schemes involve combination of surgery, RT, CT and HT
- Prognosis depends on the size, location ,stage and the age of the patient

Issels, Rolf D., et al. "Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: the EORTC 62961-ESHO 95 randomized clinical trial." *JAMA oncology* 4.4 (2018): 483-492.



Largest, randomized phase III trial for high-risk STS -> Issels et al. assessed the safety and the efficacy of RHT combined with NA+A CT (EIA)

2010

2018

Median follow-up of more than 11 years, exhibited a 5-year OS of 62.7% vs 51.3% and a 10-year OS of 52.6% vs 42.7%, respectively.

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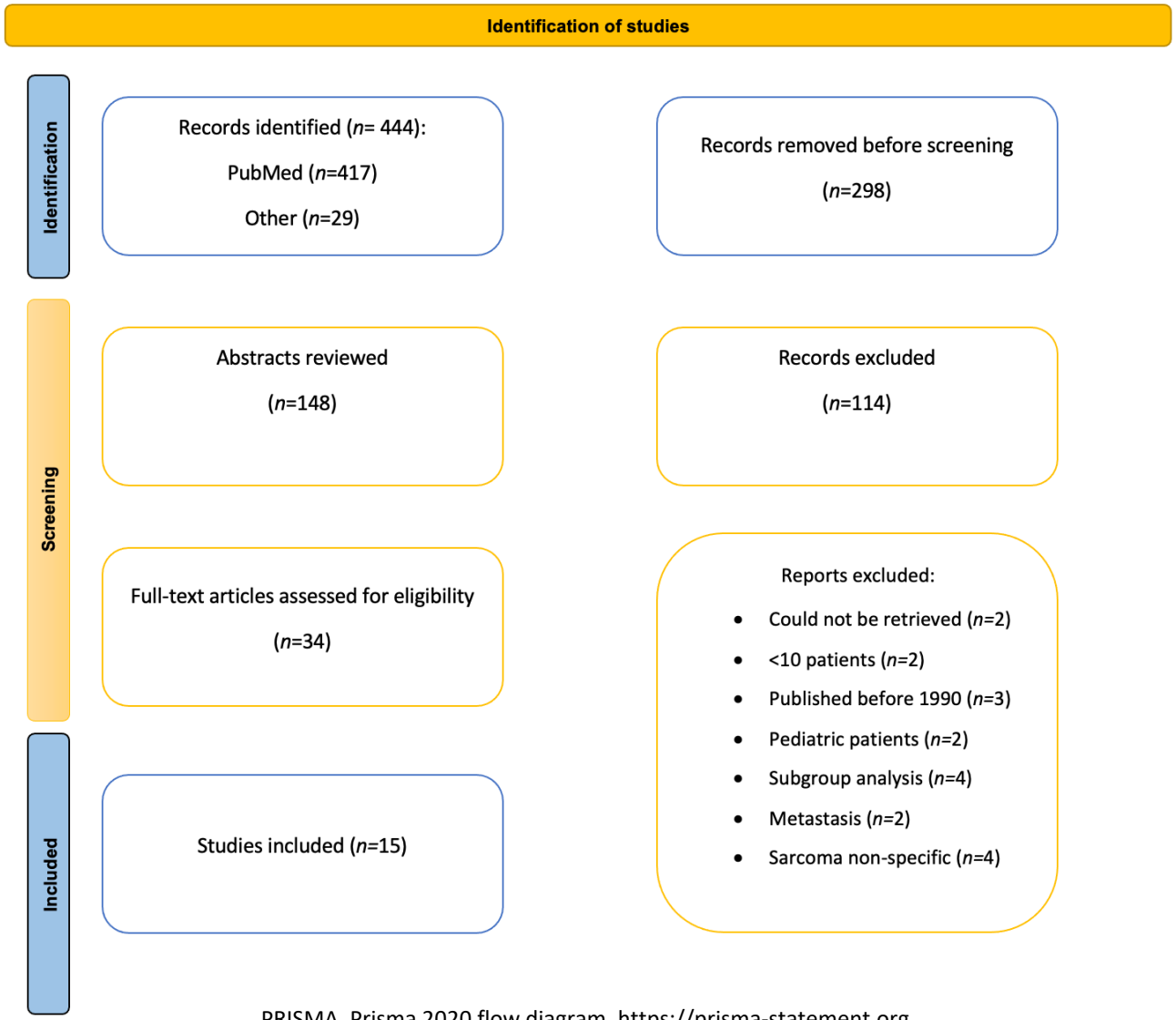
- 1990 to 07.2022
- Written in English
- Patients ＜18 years of age or/and patients with metastatic disease and review articles were excluded
- PubMed, personal electronic archive (+ sources referred to therein)→ supplementary sources of publications

Search terms
(Sarcoma) AND ((Hyperthermia) OR (hyperthermic) OR (Thermotherapy) OR (Thermal therapy) OR (thermometry))
(sarcoma) AND (”hyperthermia”[All Fields])
(sarcoma) AND (thermotherapy)
(sarcoma) AND (hyperthermic therapy)
(sarcoma) AND ((radiation) AND (hyperthermia))



PRISMA. Prisma 2020 flow diagram. https://prisma-statement.org

9 Prospective & 6 Retrospective

Schemes

- 3 CT
  (Conc. RT if indicated)
  EIA
- 12 RT
  (Conc. CT if indicated)
  5/12 Ifosfamide
  (+ Dx)

Information retrieved

- Thermometry
  Invasive - intratumoral, MR-based, Superficial
- Toxicity
  CTC, WHO, RTOG, CTCAE v.3.0
- Efficacy
  LFFS, DMFS, EFS, OS, LPFS, DFS etc.

General conclusions

Outcomes are affected by:

- The frequency of the RHT, the stage of the STS (primary lesions - less challenging than recurrences - higher LC),
- The response to the therapy, the localization of the STS (improved LC for extremity sarcomas)

-CT can improve survival when combined with RHT in a neoadjuvant manner

- NA CRT is equally beneficial with or without RHT
- Enhanced LC when RHT is incorporated, cannot always be translated into survival

Questions	Solution	Goal
• Timing & frequency of HT to avoid thermotolerance • Optimal therapeutic scheme combined to HT • Can tumors that are ineligible for RHT, be treated with SHT? • RHT contraindications (maximal length/closest possible localization magnitude of cardiac insufficiency) • How thermometry should be managed	Questionnaire to high-volume STS centers with access to RHT	Addressing these questions will lead to establishing and implementing a concordant therapeutic protocol in the clinical setting

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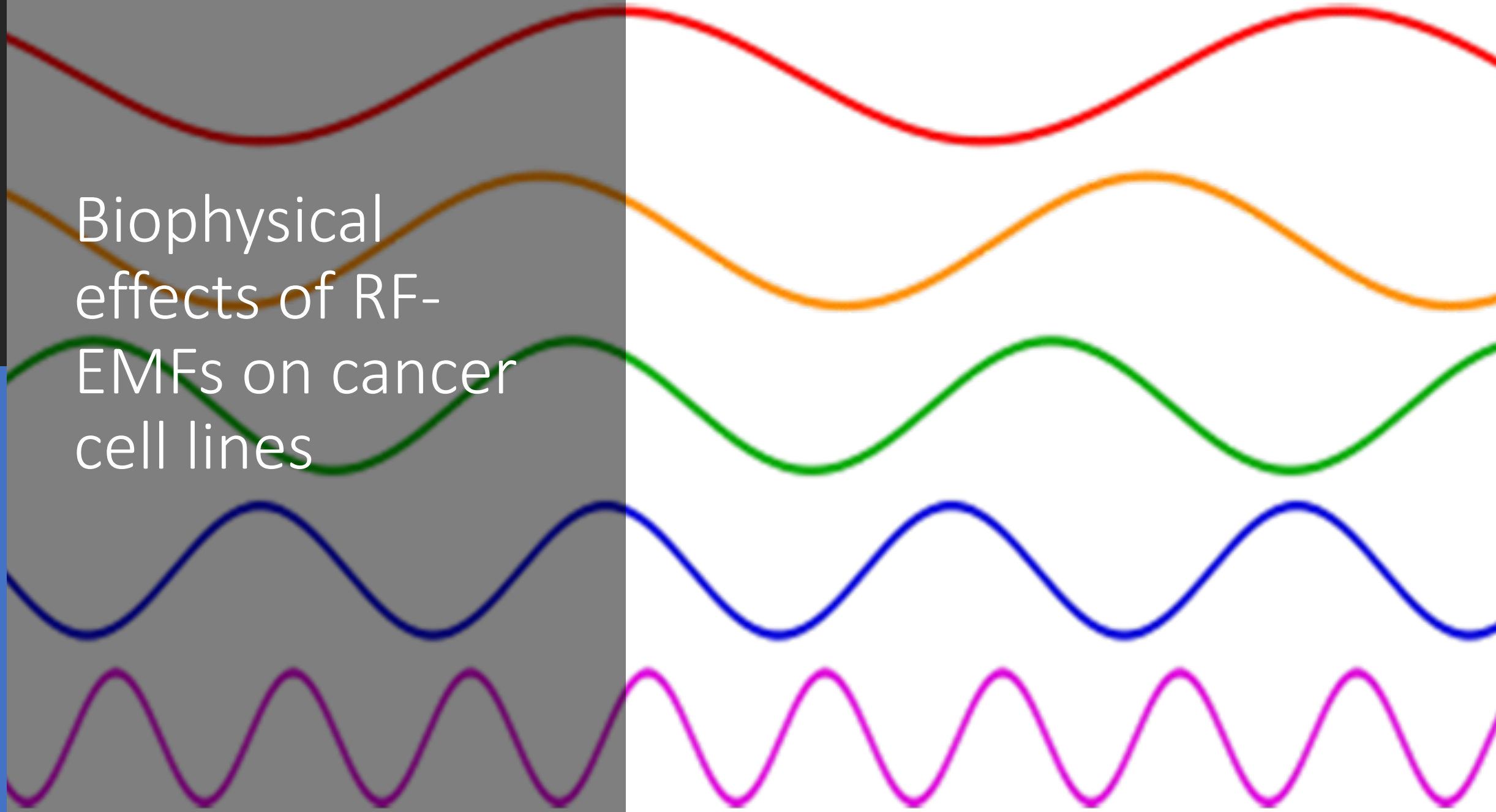
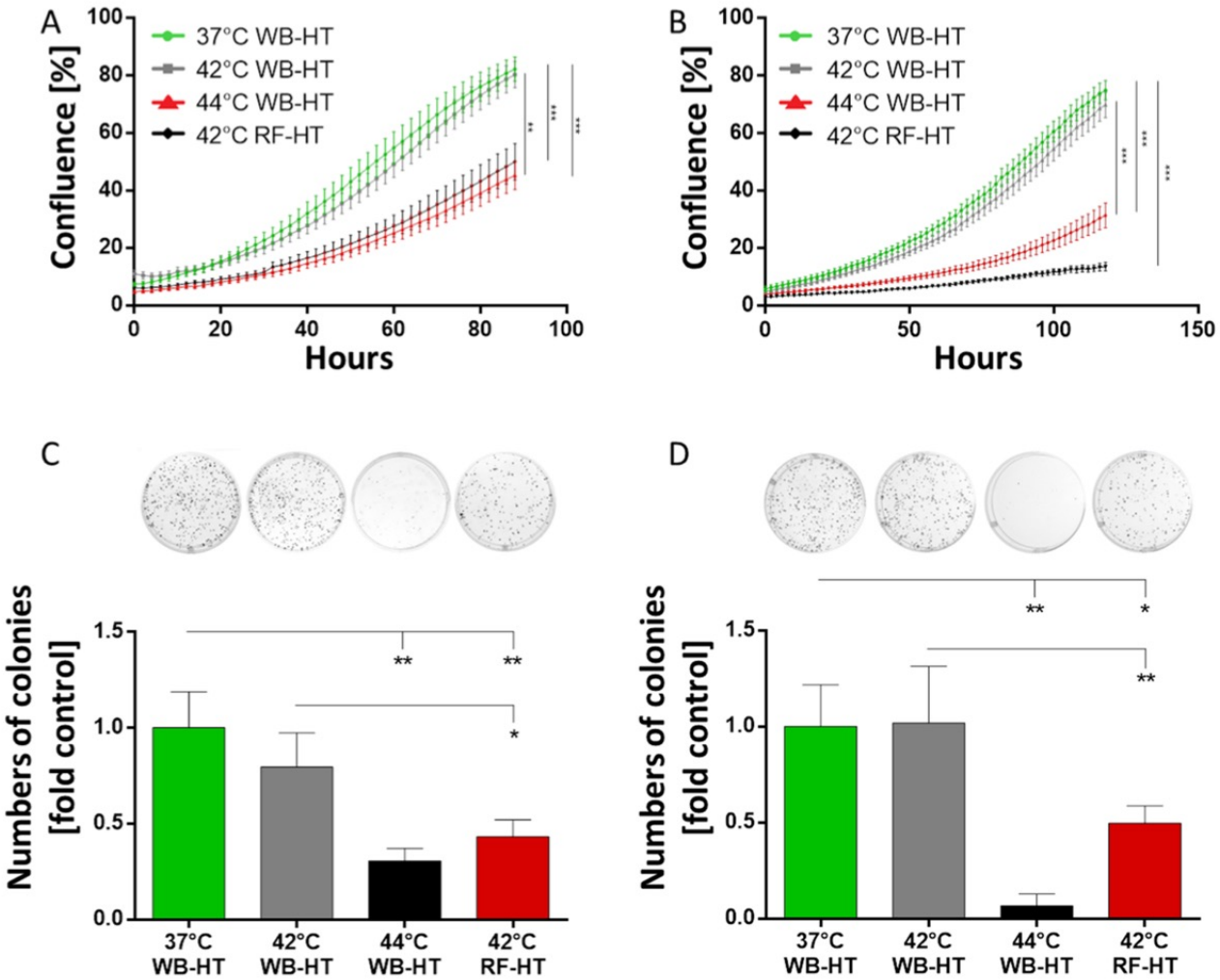
Biophysical effects of RF-EMFs on cancer cell lines



Previous data



Wust, Peter, et al. "Non-thermal effects of radiofrequency electromagnetic fields." *Scientific Reports* 10.1 (2020): 1-8.

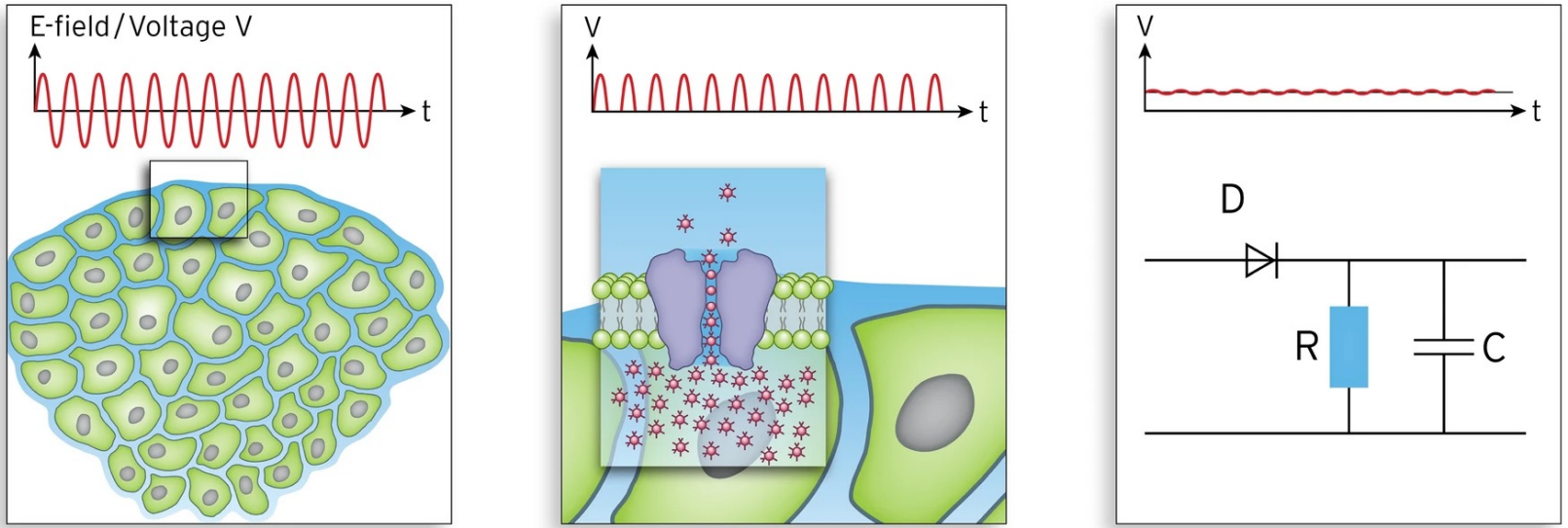
HT29 & SW480

- Proliferation and clonogenicity were assessed
- Experimental population (13.56MHz + 42°C) and control populations (37-42-44°C WB)
- Non-temperature induced effects

Previous data

Half-wave rectification
Ion channel D

Smoothing ion channel
with R and membrane with C

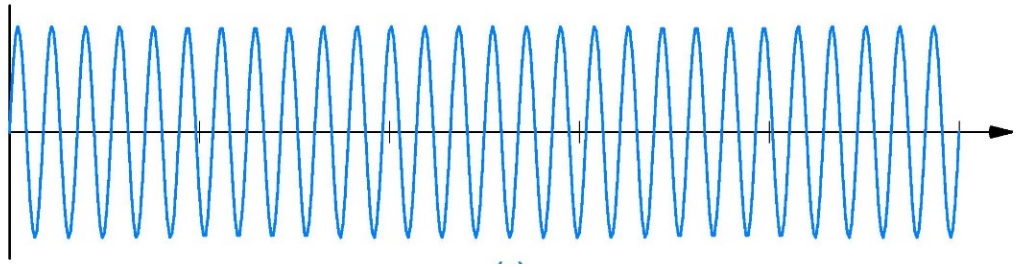


Electric field:

- Changes the voltage equilibrium across the membrane, when applied
- Affects the efflux of ions
- Ca^{2+} is a key-factor in the mode of action

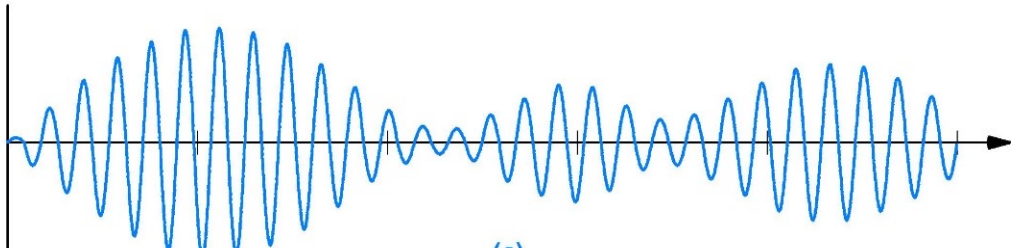
Wust, Peter, et al. "Non-thermal effects of radiofrequency electromagnetic fields." *Scientific Reports* 10.1 (2020): 1-8.

Radiofrequency Hyperthermia (RF-HT):



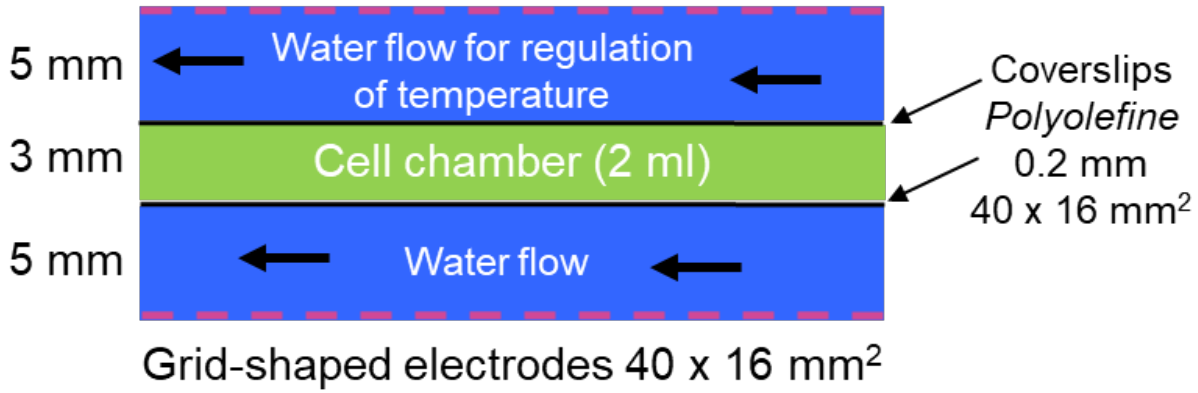
Lab-EHY, 13.56MHz

Amplitude Modulated RF Hyperthermia (AMRF-HT):

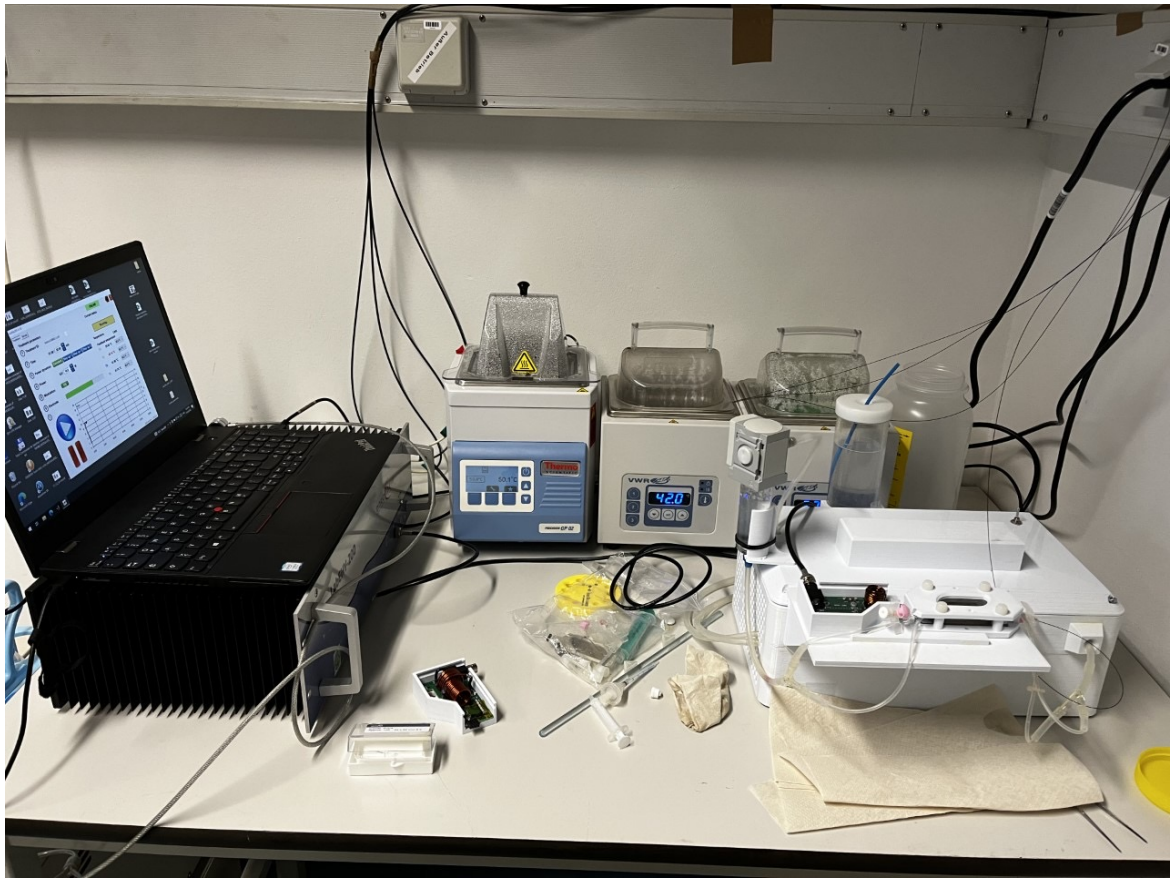


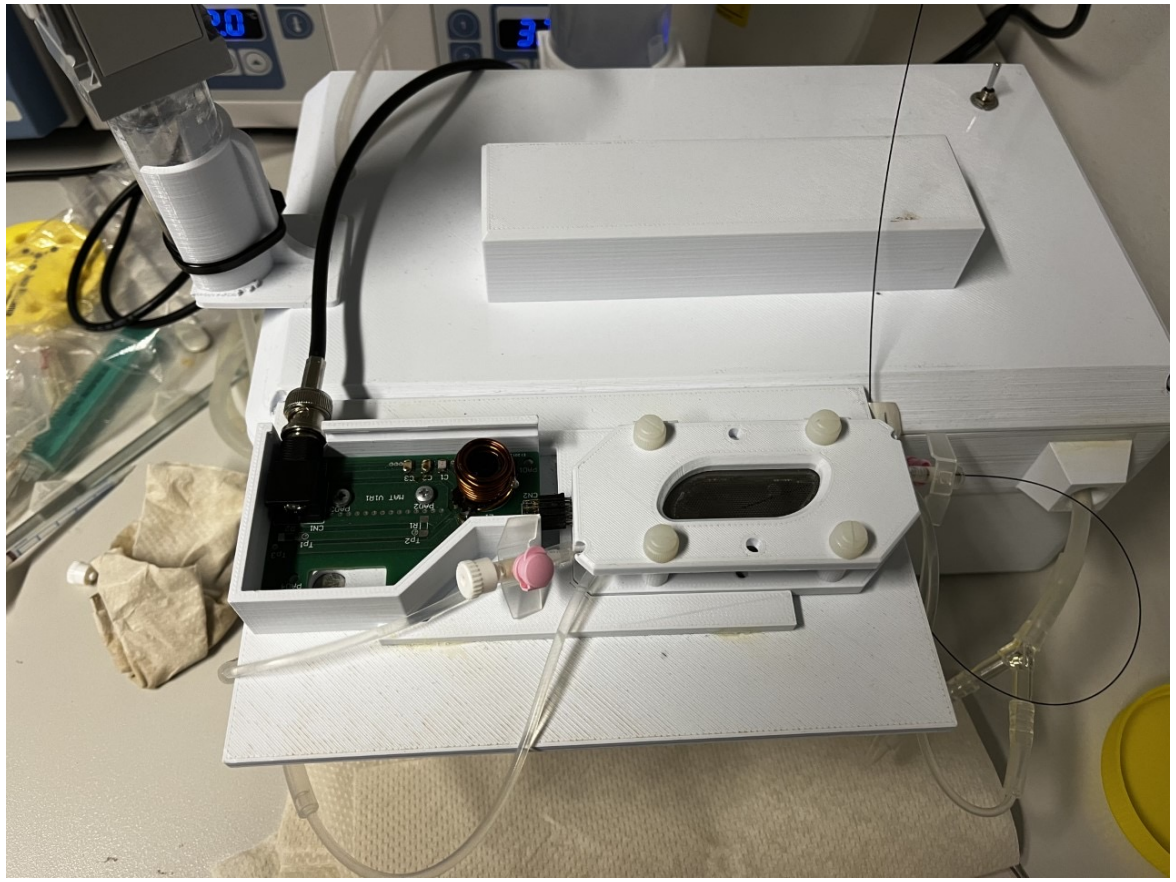
Lab-EHY, 13.56MHz, 100 Hz Mod., Mod. Index 50%

Model of multilayer applicator

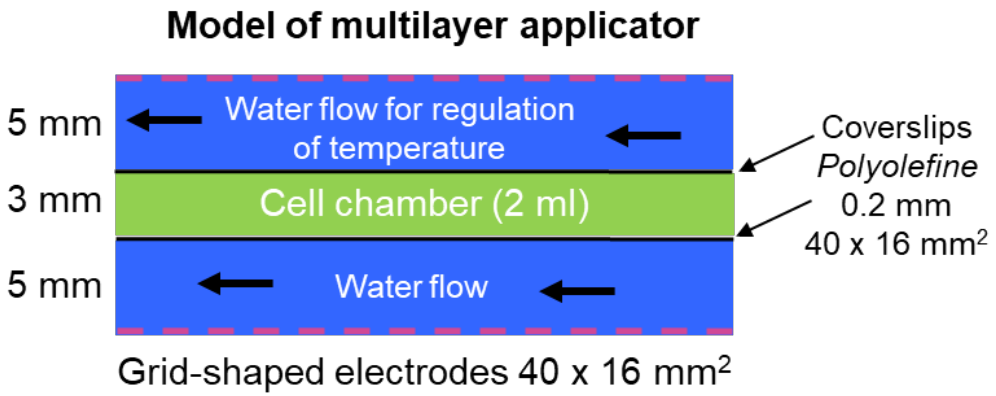


Setting layout



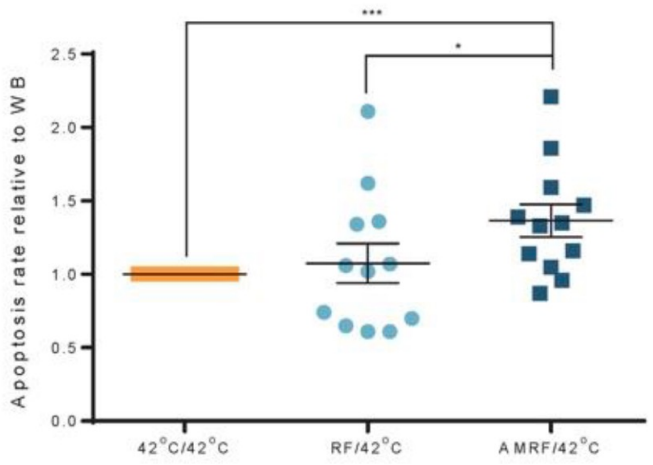


Data so far

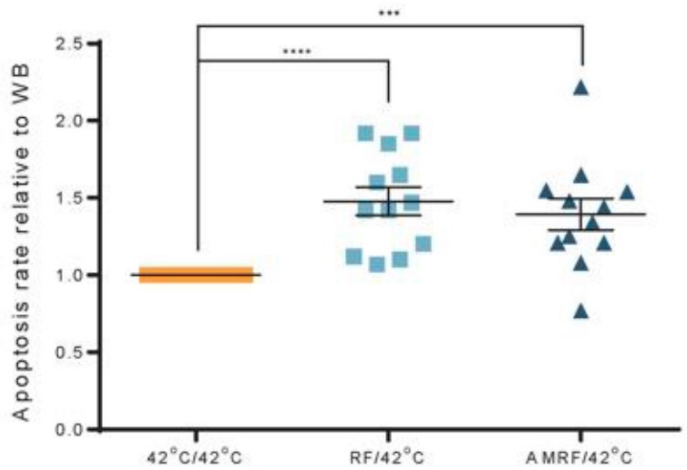


10W, up to 42°C for 65min

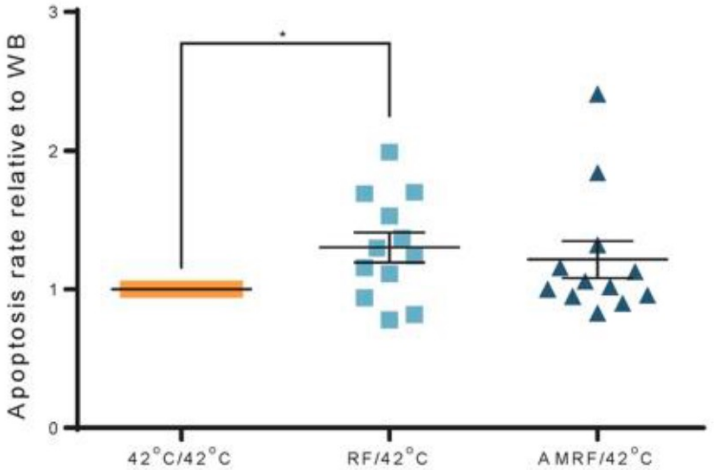
FACS (1h after the treatment)



HT29



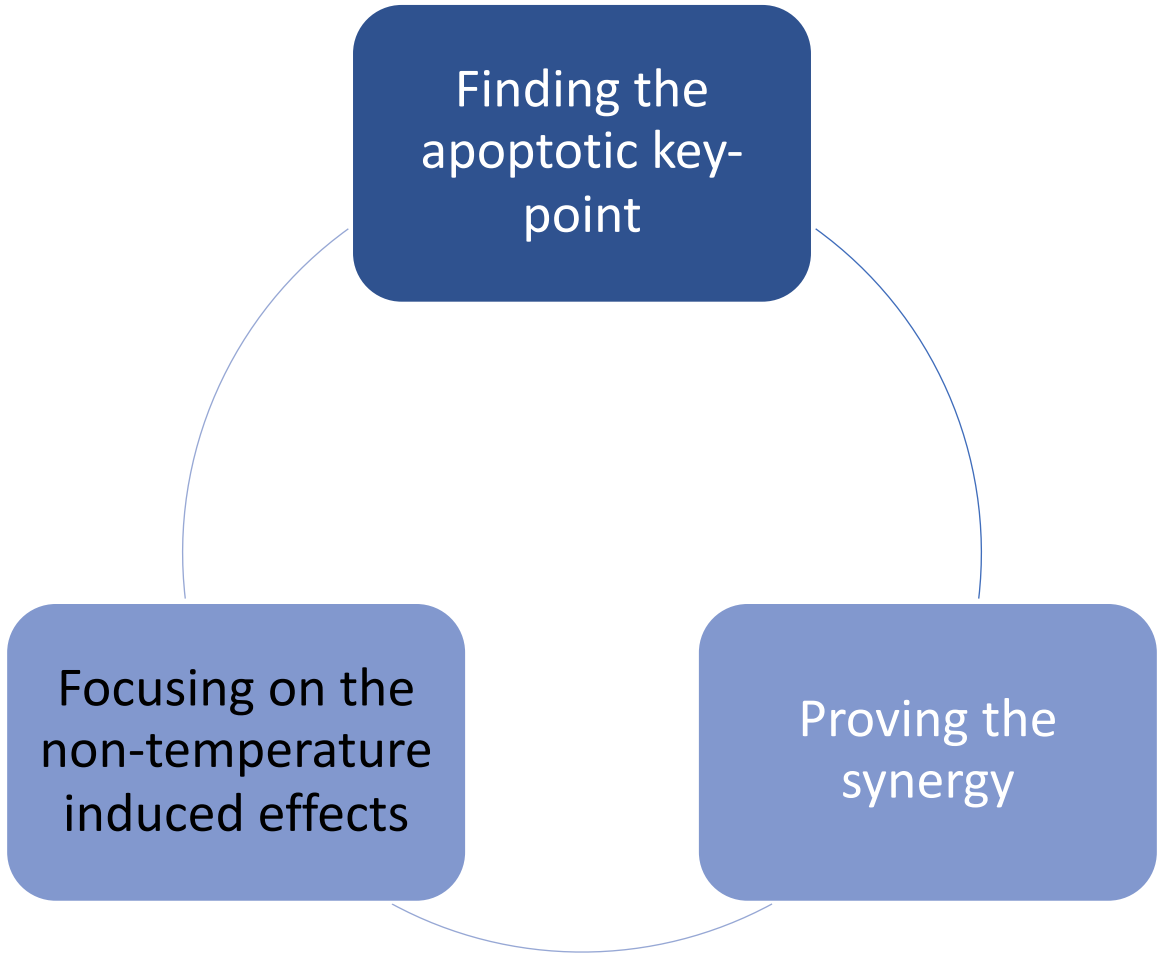
SW480



LoVo

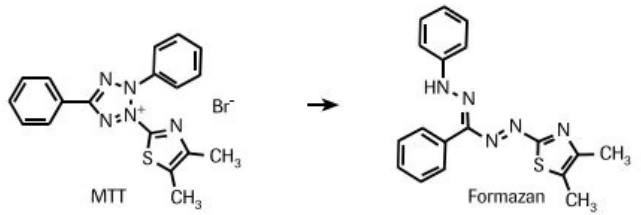
Wust, Peter, et al. "Radiofrequency electromagnetic fields cause non-temperature-induced physical and biological effects in cancer cells." *Cancers* 14.21 (2022): 5349.

Initial Plan

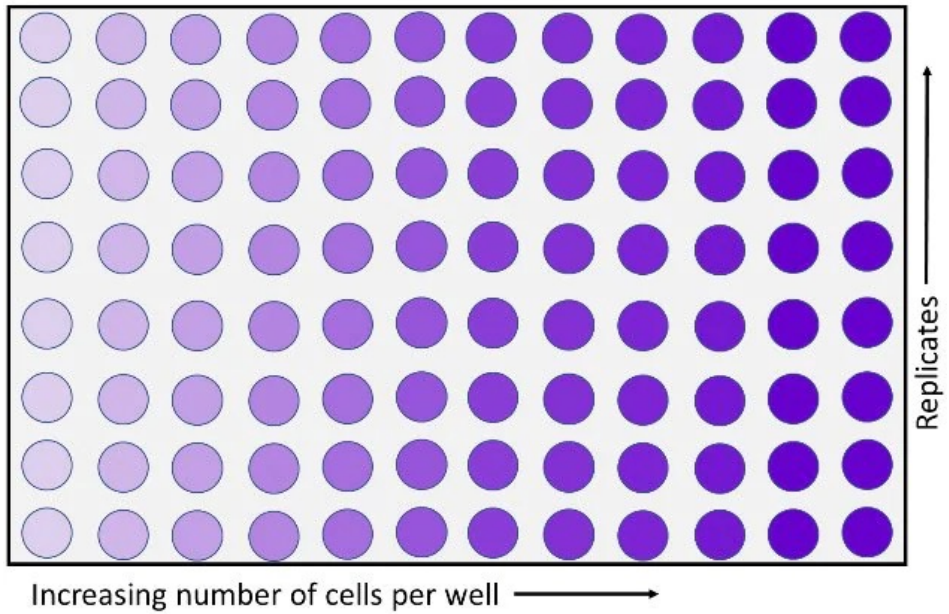


Approach - MTT

A



B



- RF
- RF + RT
- AMRF
- AMRF + RT

Treatment

MTT

- 24 hours
- 48 hours

30.000 cells/well

RT = 8Gy

Treatment duration = 65 min

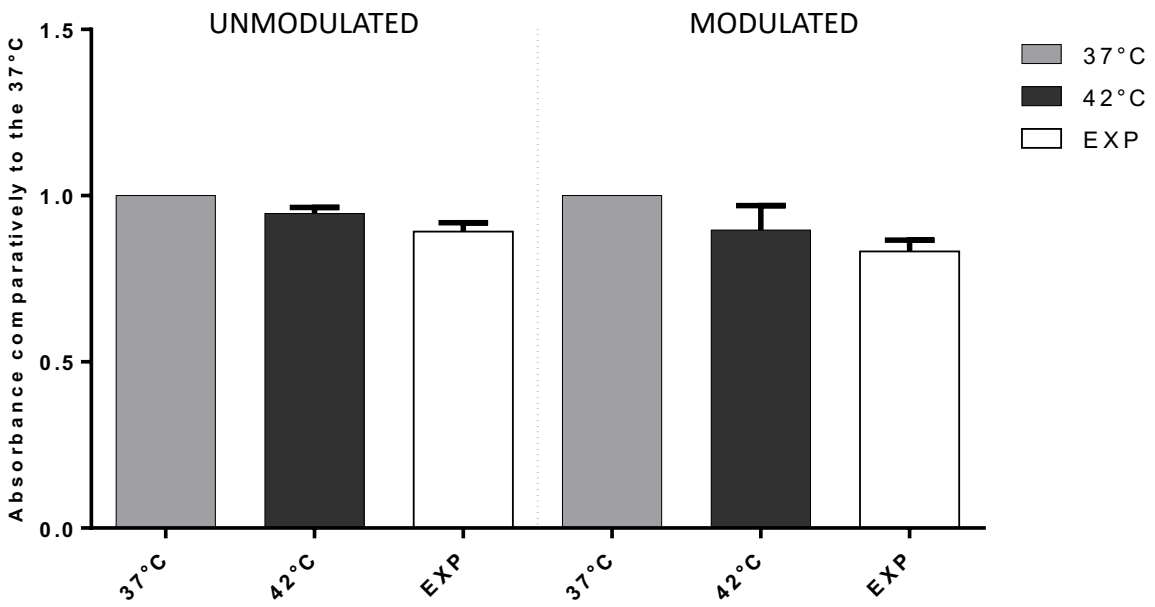
RF = 13.56 MHz

AMRF = 13.56 MHz, Mod = 100 Hz, Mod. Index = 50%

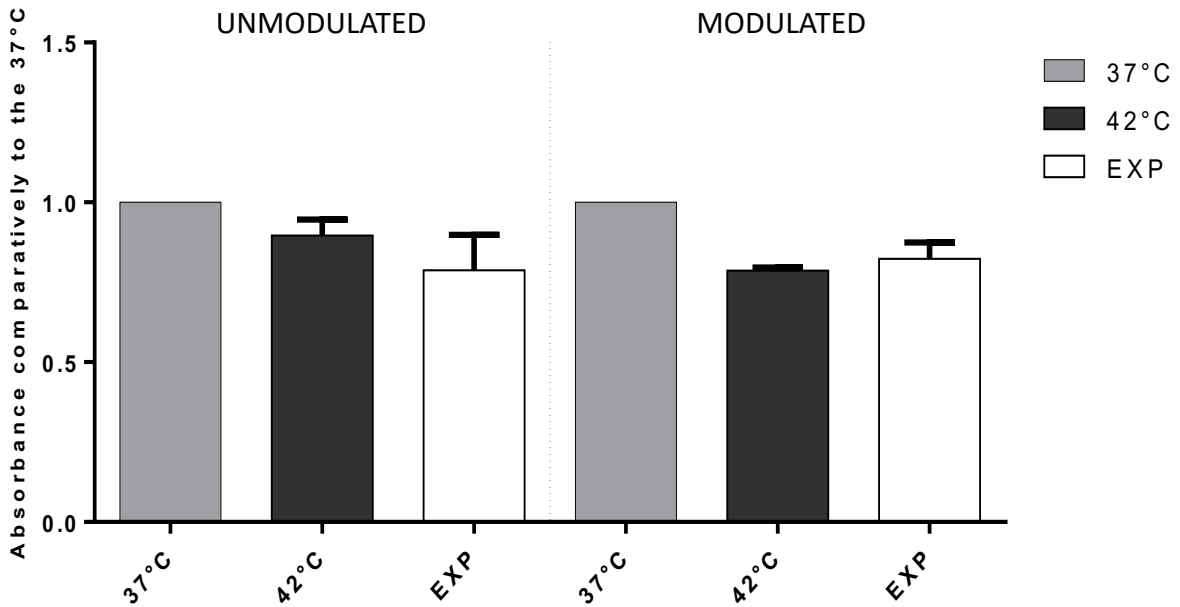
MTT Results

24 hours

Without RT



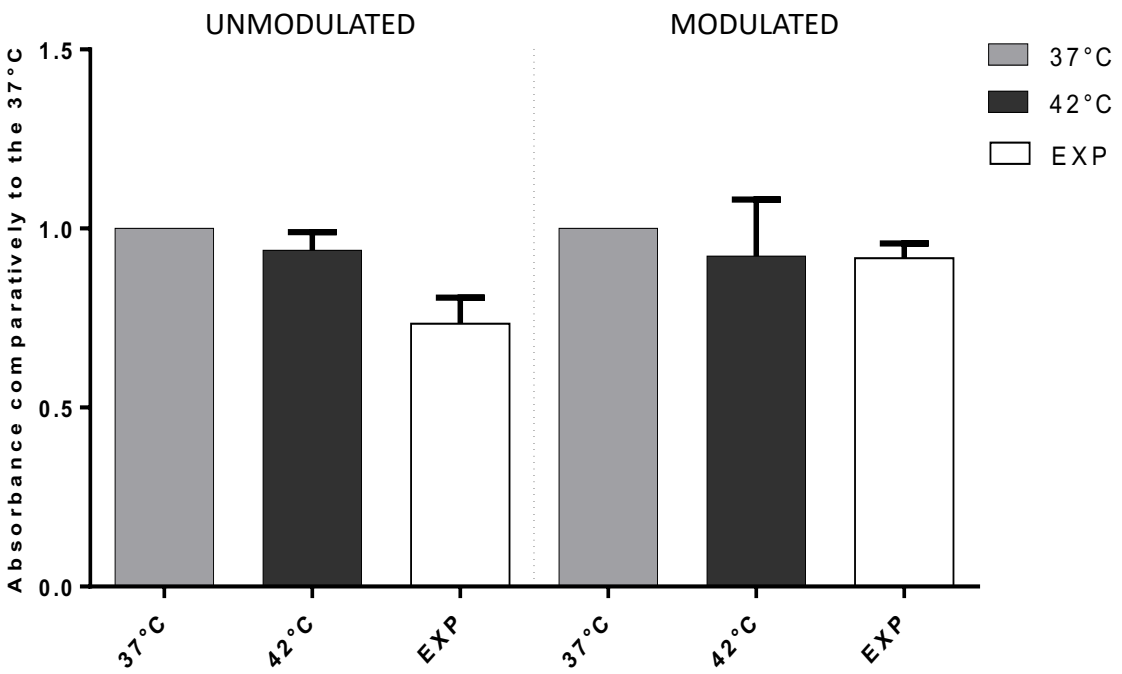
With RT



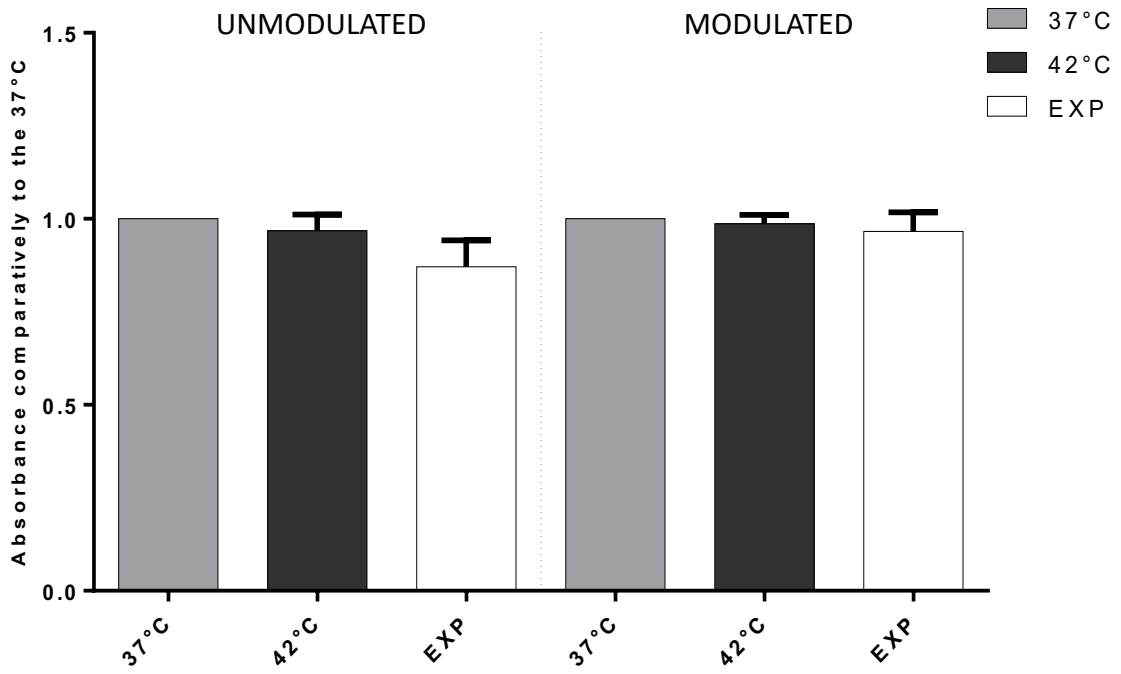
MTT Results

48 hours

Without RT

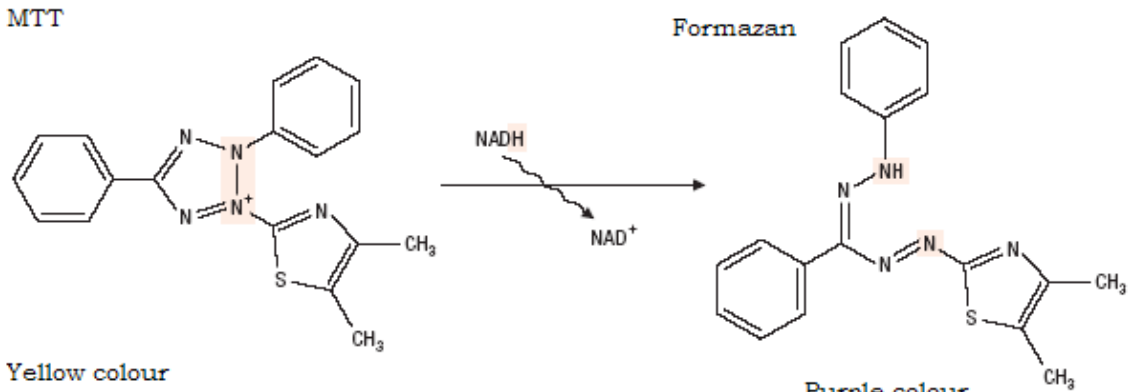


With RT



Comments - A

Higher viability rate after AMRF + RT ?!



- Ca^{2+} monitoring (Fluo-4 AM)[2]
- Ca^{2+} involvement in the mechanism of action (channel blockers)

Electrical model of the cell membrane and ion channels

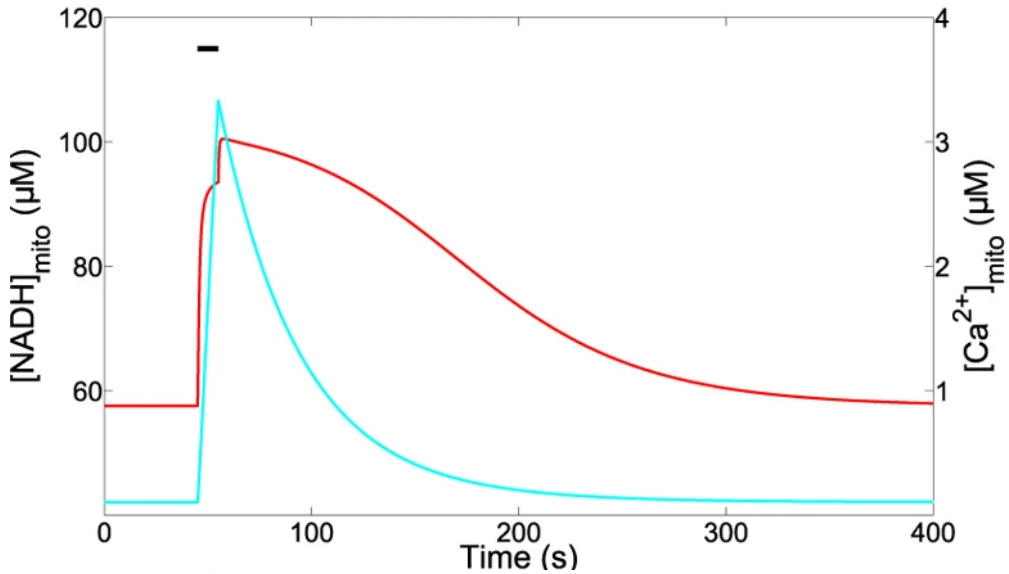
Wust, Peter, et al. "Non-thermal effects of radiofrequency electromagnetic fields." *Scientific Reports* 10.1 (2020): 13488.

Open Access | Published: 18 January 2016

Interplay Between Intracellular Ca^{2+} Oscillations and Ca^{2+}-stimulated Mitochondrial Metabolism

Benjamin Wacquier, Laurent Combettes, Guy Tran Van Nhieu & Geneviève Dupont

Scientific Reports **6**, Article number: 19316 (2016) | Cite this article



(1) Wacquier, Benjamin, et al. "Interplay between intracellular Ca2+ oscillations and Ca2+-stimulated mitochondrial metabolism." *Scientific reports* 6.1 (2016): 1-16

(2) Andocs, G., et al. "Comparison of biological effects of modulated electro-hyperthermia and conventional heat treatment in human lymphoma U937 cells." *Cell death discovery* 2.1 (2016): 1-10.

HYPERBOOST

Approach No2- IncuCyte

- RF
- RF + RT
- AMRF
- AMRF + RT

Treatment

+ RT doses screenings

IncuCyte

- 4-day Monitoring
- Apoptosis and Necrosis (1,5ul Annexin V, 250nM YOYO3)

30.000 cells/well and
10.000 cells/well

RT = 8Gy

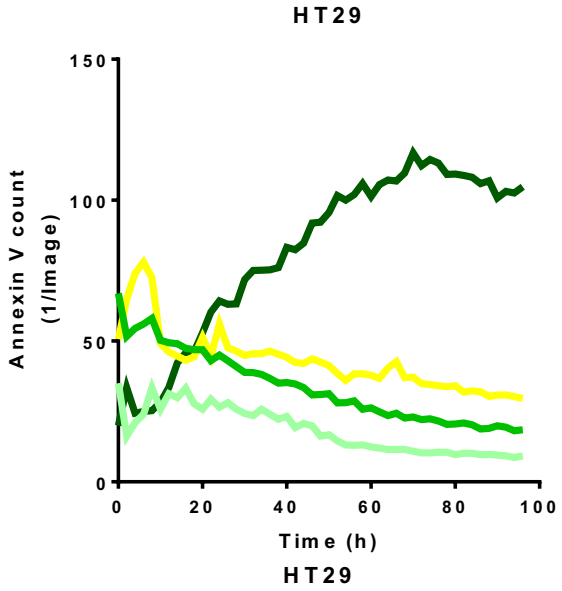
Treatment duration = 65 min

RF = 13.56 MHz

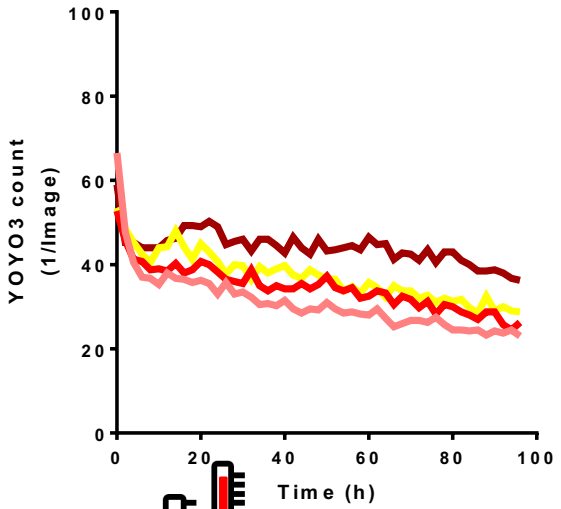
AMRF = 13.56 MHz, Mod = 100 Hz, Mod. Index = 50%

Apoptosis & Necrosis

Unmodulated



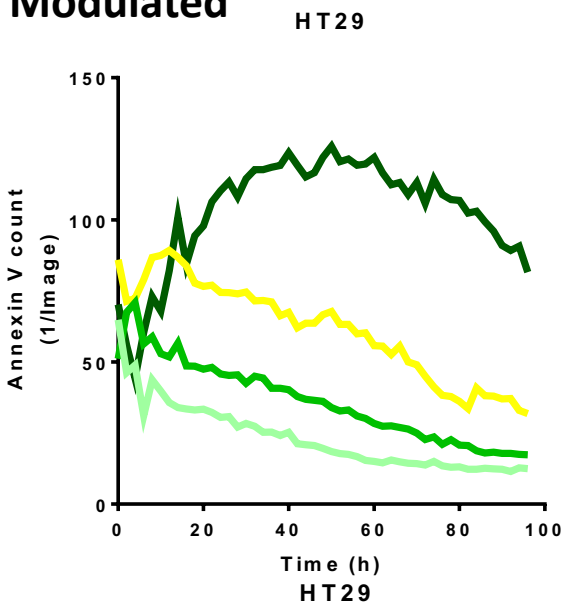
Experimental vs 37: $p < 0.01$
Experimental vs 42: $p < 0.05$



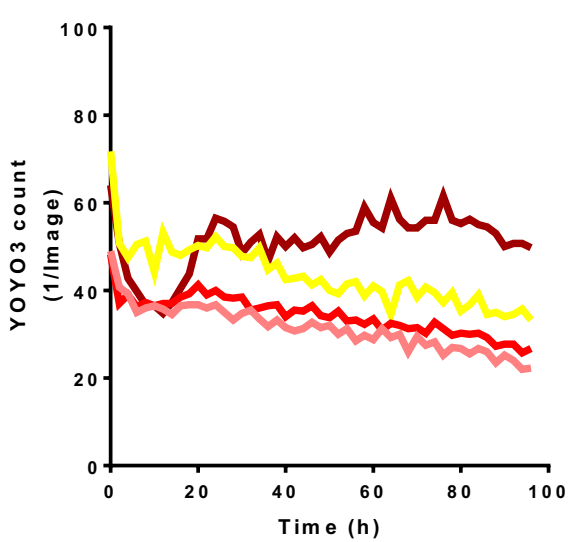
Experimental vs 37: *NS*
Experimental vs 42: *NS*

Modulated

30.000 cells/well



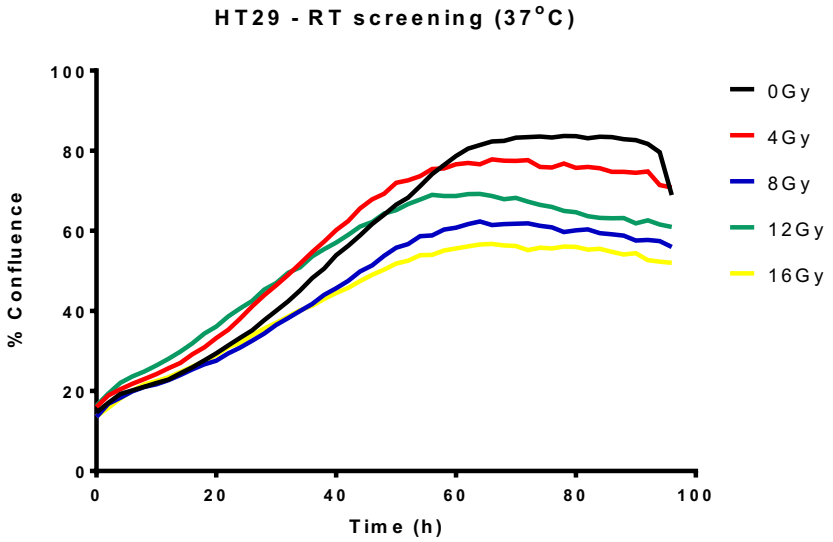
Experimental vs 37: $p < 0.0001$
Experimental vs 42: $p < 0.001$

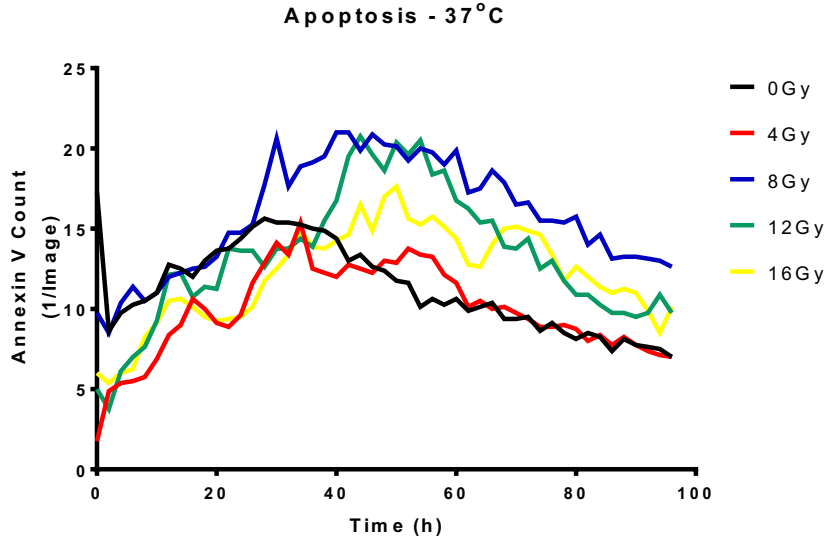


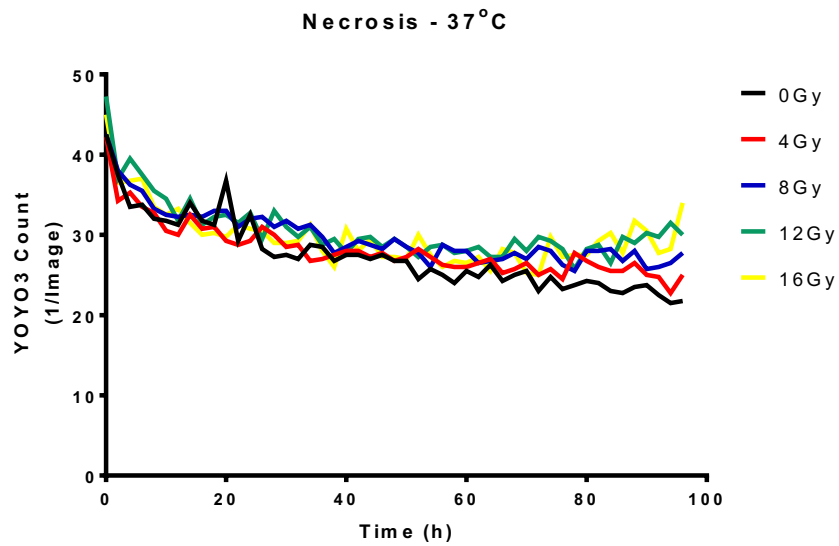
Experimental vs 37: $p < 0.001$
Experimental vs 42: $p < 0.001$

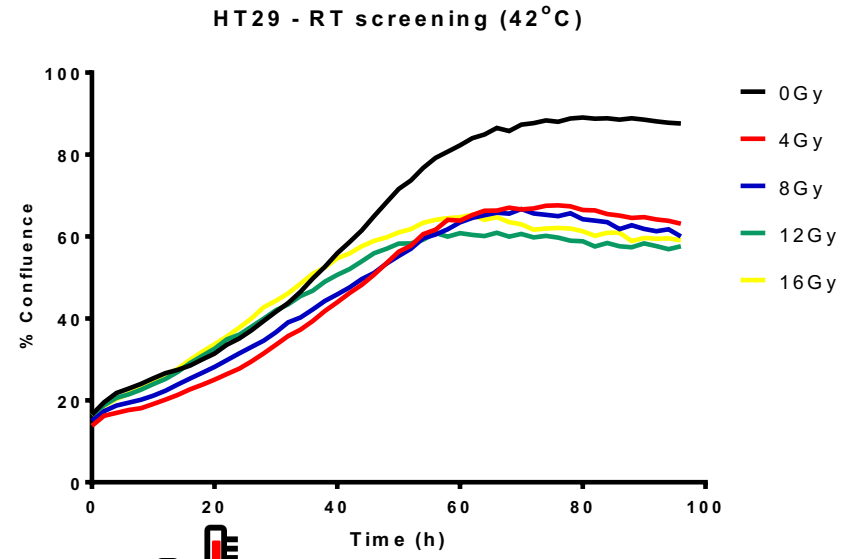
HYPERBOOST

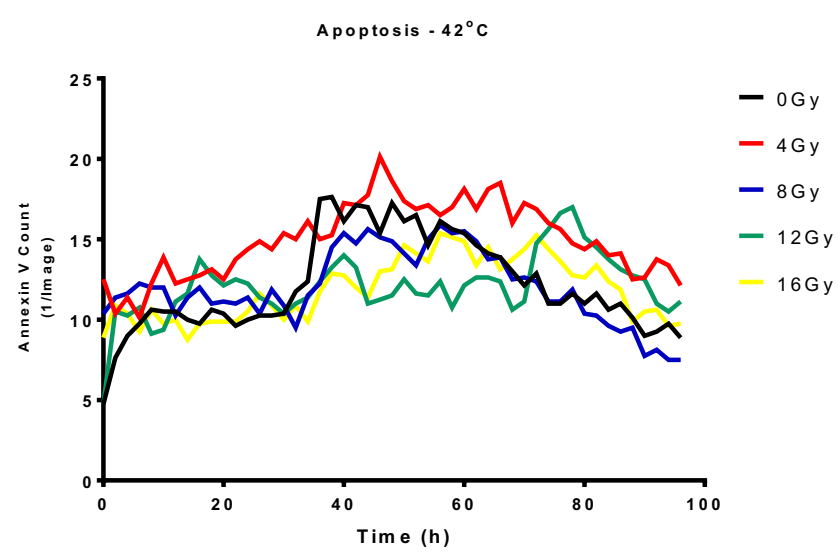
RT screening

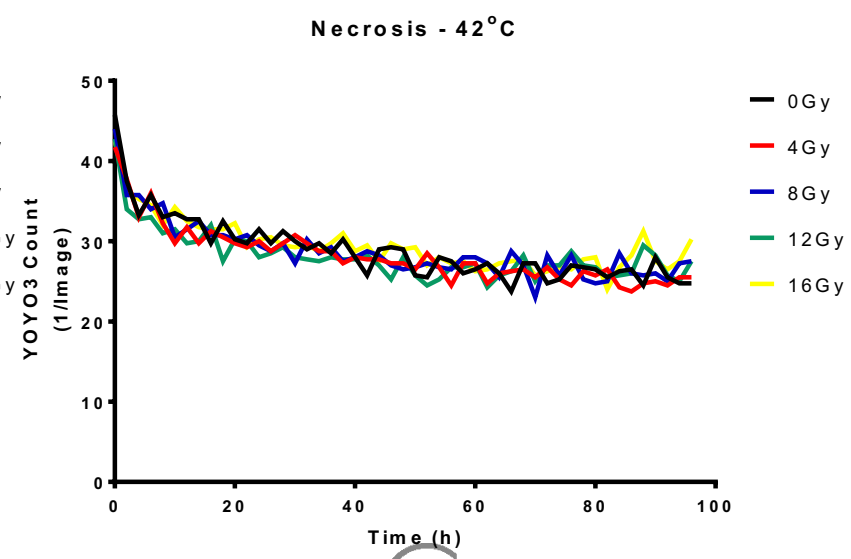












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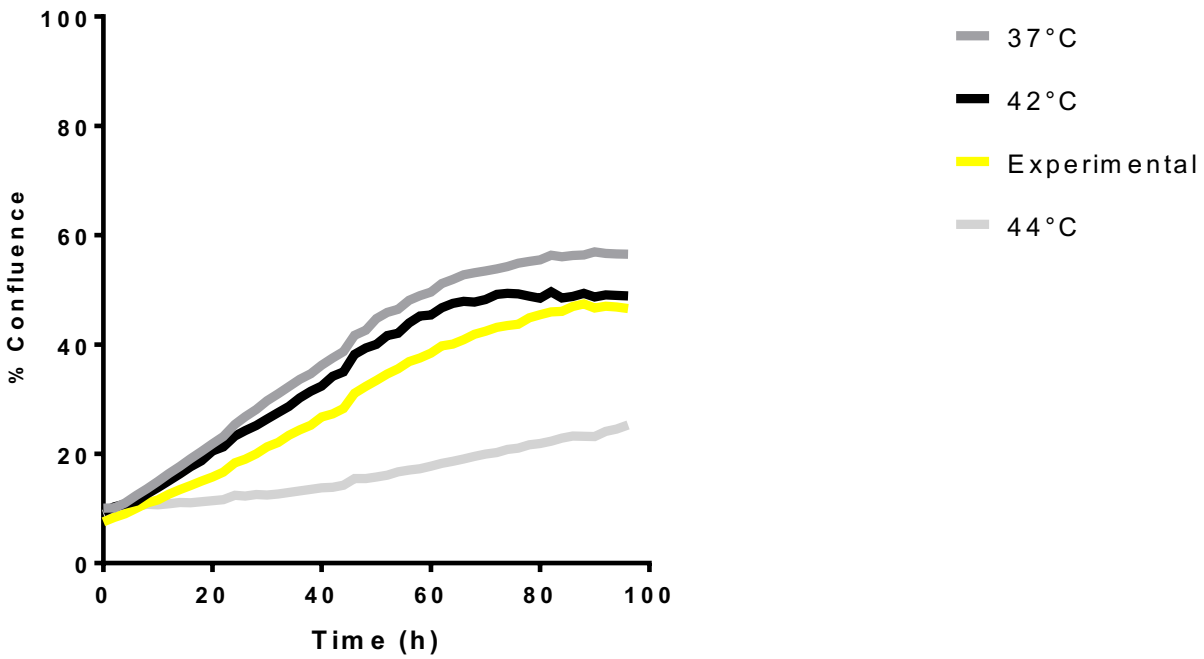
Results - B

Confluence

10.000 cells/well
RT = 8Gy

Unmodulated

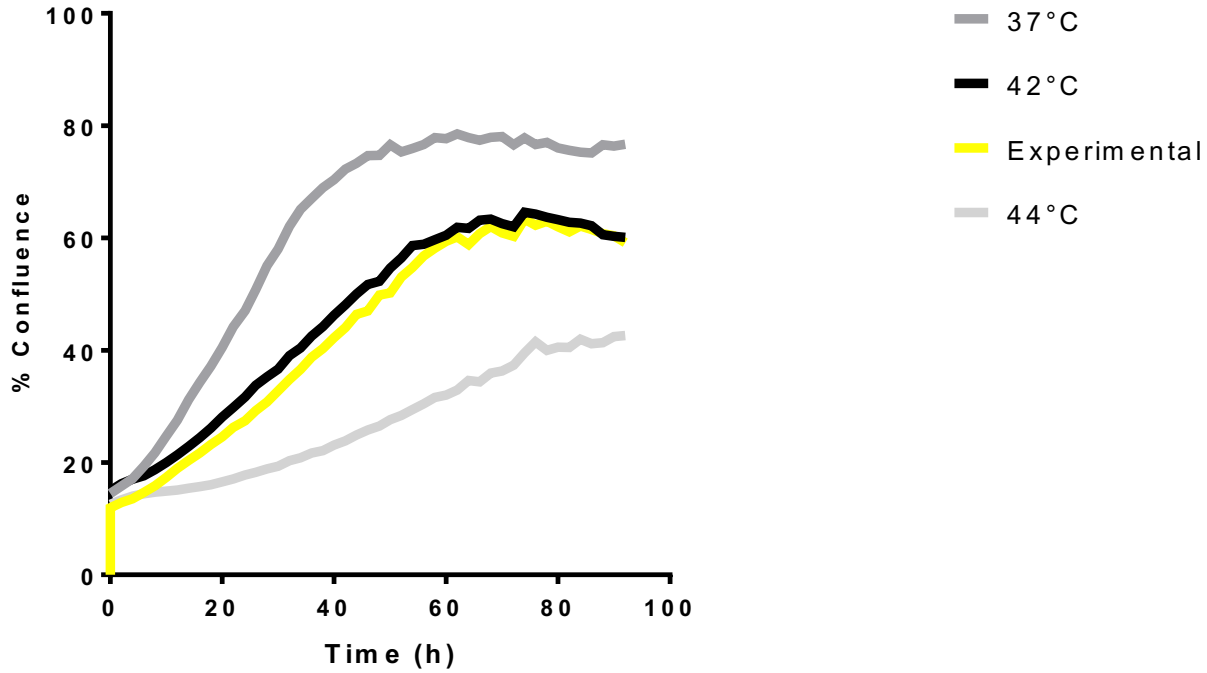
HT29



Experimental vs 37: $p < 0.0001$
Experimental vs 42: $p < 0.001$

Modulated

HT29



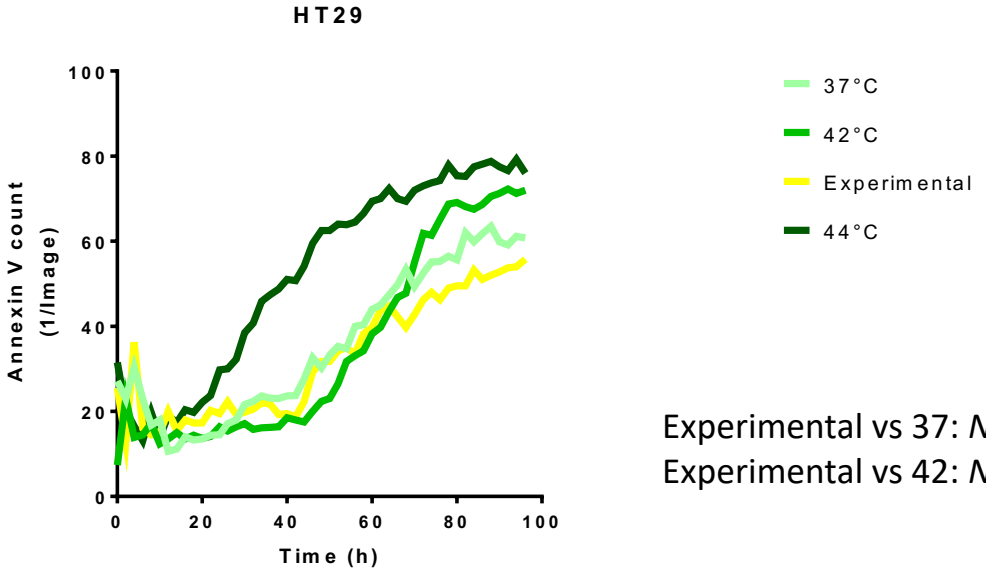
Experimental vs 37: $p < 0.001$
Experimental vs 42: *NS*

HYPERBOOST

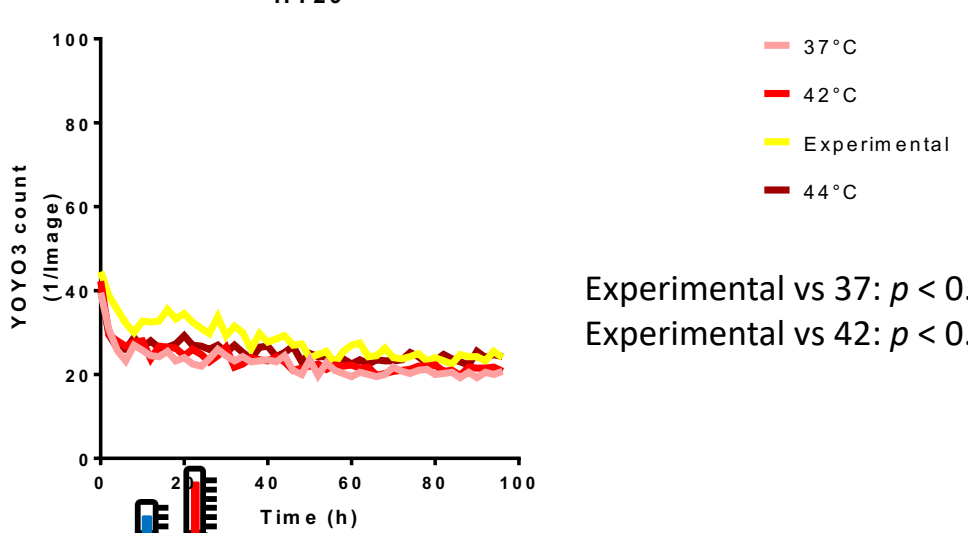
Apoptosis & Necrosis

10.000 cells/well
RT = 8Gy

Unmodulated

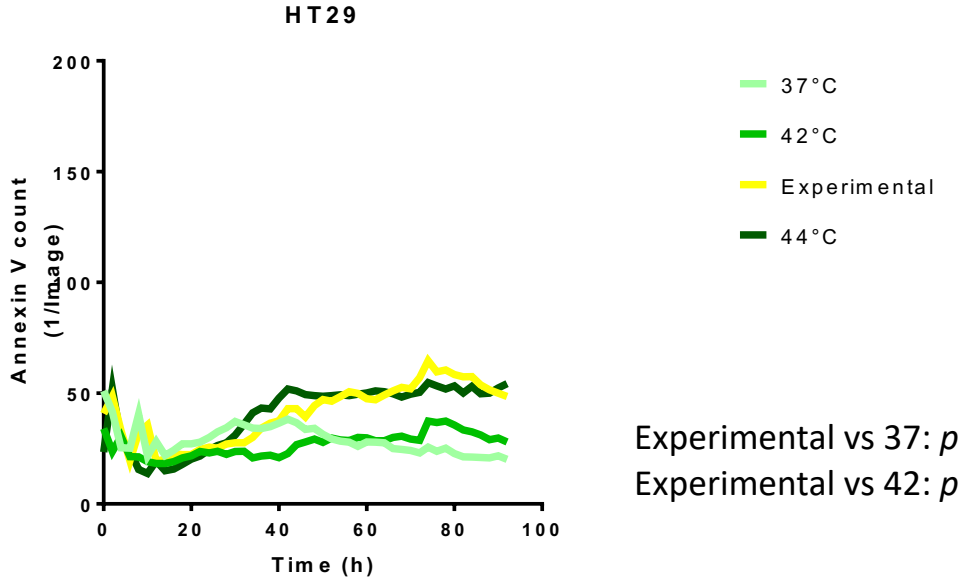


Experimental vs 37: *NS*
Experimental vs 42: *NS*

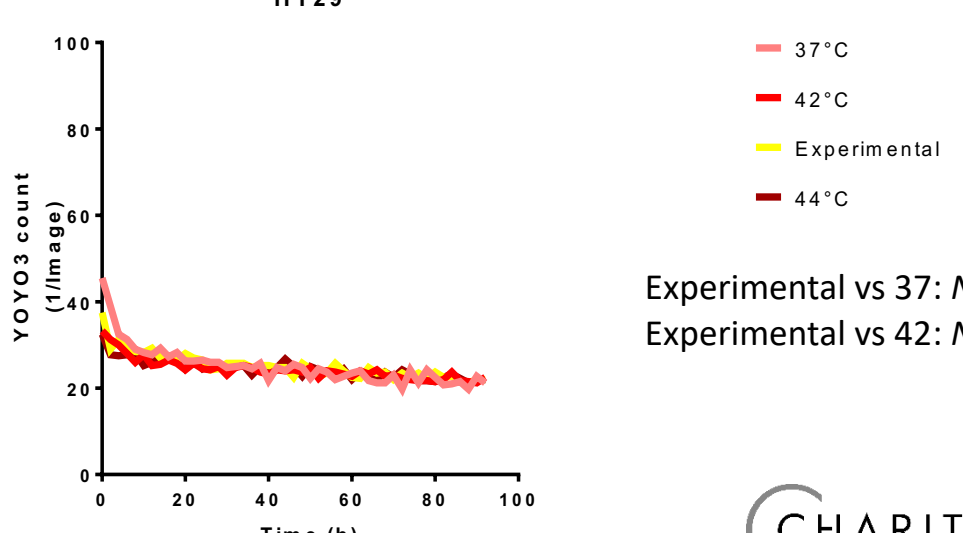


Experimental vs 37: $p < 0.0001$
Experimental vs 42: $p < 0.0001$

Modulated



Experimental vs 37: $p < 0.001$
Experimental vs 42: $p < 0.0001$



Experimental vs 37: *NS*
Experimental vs 42: *NS*

Comments

- Results confirm the effect of RF on HT29 compared to temperature alone (42^{o}C WB)
- AMRF seems to cause significantly higher cell death when compared to temperature alone
- AMRF/RF HT enhanced the effect of RT

Plan

- Unravel the role of Calcium in the mechanism of non-temperature induced effects
- Investigate the involvement of other factors in the AMRF/RF HT-related cell death
- Introduce new cell lines to the setting (HCT116, U87 & U343)

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MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT

e-mail: paraskevi-danai.veltsista@charite.de

University of Zurich[UZH]

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Analysis of thermal enhancement parameters

Hyperboost Consortium Meeting

Adela Ademaj
PhD student
Prof. Dr. med. Oliver Riesterer
Principal Investigator
Radio-Onkologie-Zentrum KSA-KSB

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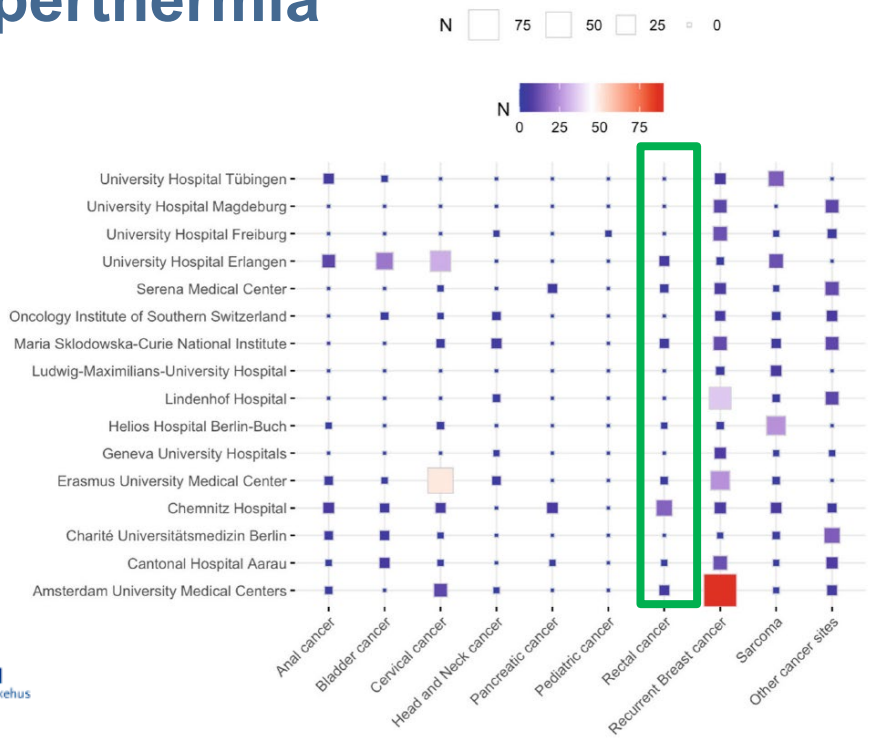
- ❑Planned multinational retrospective clinical study in breast cancer patients
- ❑Real world analysis of quality of life in cancer patients treated with hyperthermia combined with radio(chemo)therapy
- ❑Secondments at Amsterdam UMC

Multinational data collection of rectal cancer patients treated with radio(chemo)therapy + hyperthermia

- Patterns of care analysis in EU clinical centers:
  - In total, 8 clinical centers reported to treat **rectal cancer** with hyperthermia (HT) in combination with radio(chemo)therapy (RCT) :

    37 patients per year



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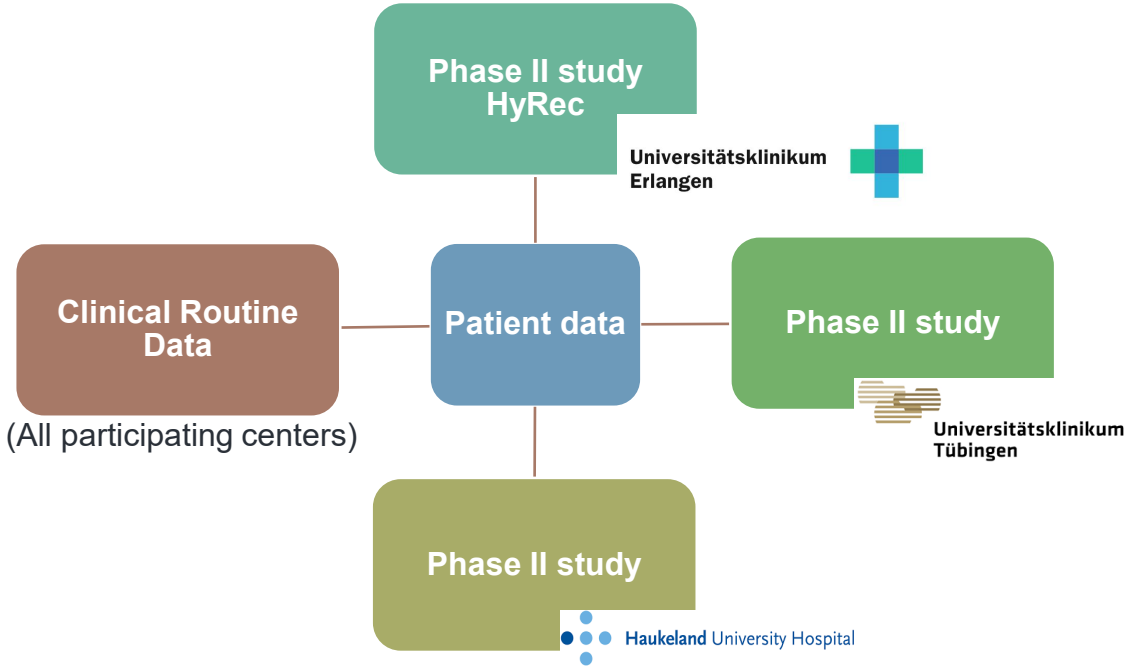
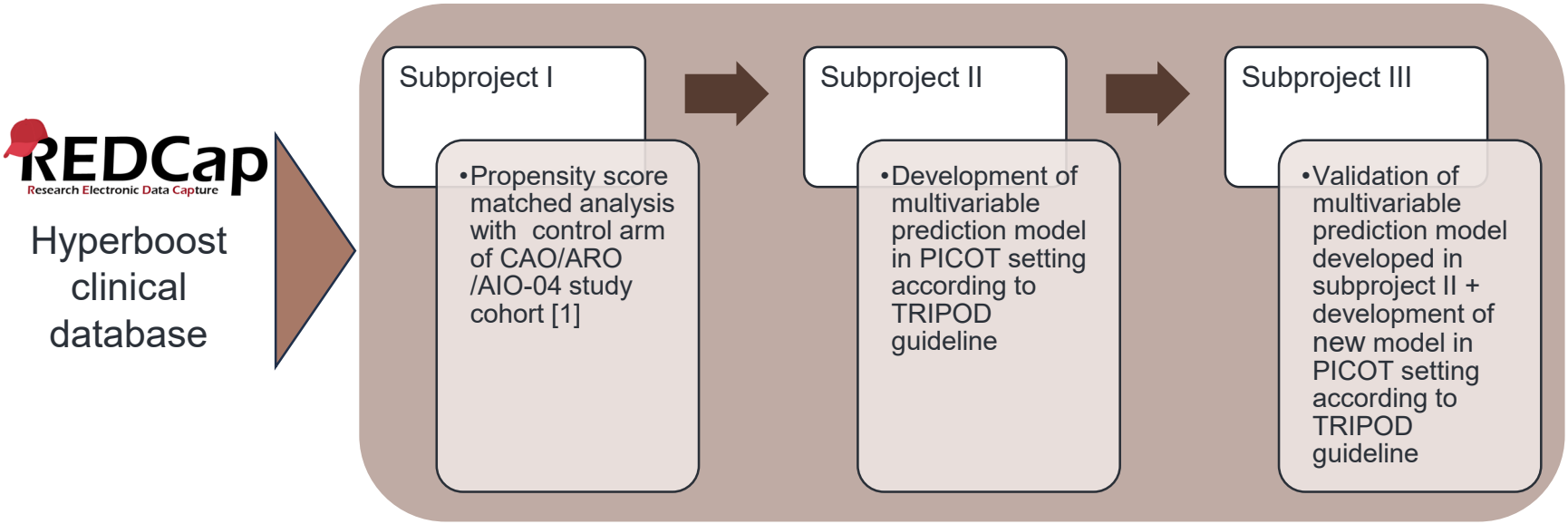
Retrospective and prospective observational clinical study in rectal cancer: current status

- Swiss Ethics Committee has approved the study
- Local ethics application in Germany is being processed
- Ongoing discussion to include recurrent rectal cancer patients treated in Netherlands



Subprojects of planned rectal cancer study



[1] Rödel et al. The Lancet. Oncology vol. 16,8 (2015): 979-89.

Inclusion and exclusion criteria of planned rectal cancer study

Inclusion criteria

- Male and female rectal cancer patients older than 18 years old
- All locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) patients receiving RCT or RT only with HT
- Patients who treated with a radiative HT device according to a geometric or simulation-based treatment plan
- The clinical outcomes for three subprojects are measured according to this protocol

Exclusion criteria

Documented objection of subsequent use of personal health data

Subproject I

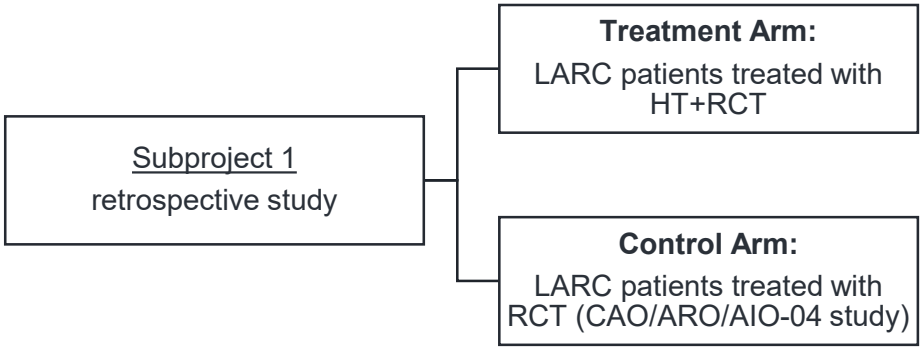
Subproject II

Subproject III

RCT: radio(chemo)therapy; RT: radiotherapy; HT: hyperthermia

Design of subproject I: Propensity score analysis for comparison of 3-year DFS rate

Null hypothesis (H0):
the 3-year disease free survival (DFS) rate in LARC patients treated with HT in combination with RCT (treatment arm) is the same as in patients treated with RCT alone (control arm) [1].



Sample size calculation:
By assuming a difference of 10% between two treatment study arms based on literature data [2,3, 4], a power of 80 % and a two-sided significance level of 0.5 %, a sample size of **536 patients** in total is required to demonstrate superiority in DFS rate between two study arms.

[1] Rödel et al. The Lancet. Oncology vol. 16,8 (2015): 979-89.
[2] Ott et al., Cancers 2021 Mar 13;13(6):1279
[3] Gani et al., Radiother Oncol 2021, 159, 155-160
[4] Rödel et al. The Lancet. Oncology, 13, 679-687

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Design of subproject II: Development of prediction model for pathological complete response

Null hypothesis (H0):
the developed multivariable model does not achieve an area under curve (AUC) over 0.75 in predicting *pathologic complete response (pCR)* status for LARC patients.

Sample size calculation:
With assumed AUC of 0.75, pCR rate prevalence of 19% and five predictor parameters, **346 LARC patients** treated with RCT and HT (with 63 events and 13 events per predictor parameter) are required for the new model development.

Predictor parameters: clinical T-category, clinical N-category, thermal dose expressed as CEM43, total number of HT sessions, and treatment regimen

Design of subproject III: Validation of prediction model and development of new multivariable prediction model

Null hypothesis (H0):
the developed multivariable model does not achieve an area under curve (AUC) over 0.75 in predicting *complete response (pCR or cCR)* for LARC patients.

Sample size calculation:
With assumed AUC of 0.75, pCR rate prevalence of 19% and seven predictor parameters,**484 LARC patients** treated with RCT and HT (with 92 events and 13 events per predictor parameter) are required for the new model development.

Predictor parameters: clinical T-category, clinical N-category, tumor differentiation, thermal dose expressed as CEM43, total number of HT sessions, treatment regimen, time interval between HT and RT

Systematic review and meta-analysis registered in PROSPERO database (CRD42022365439)

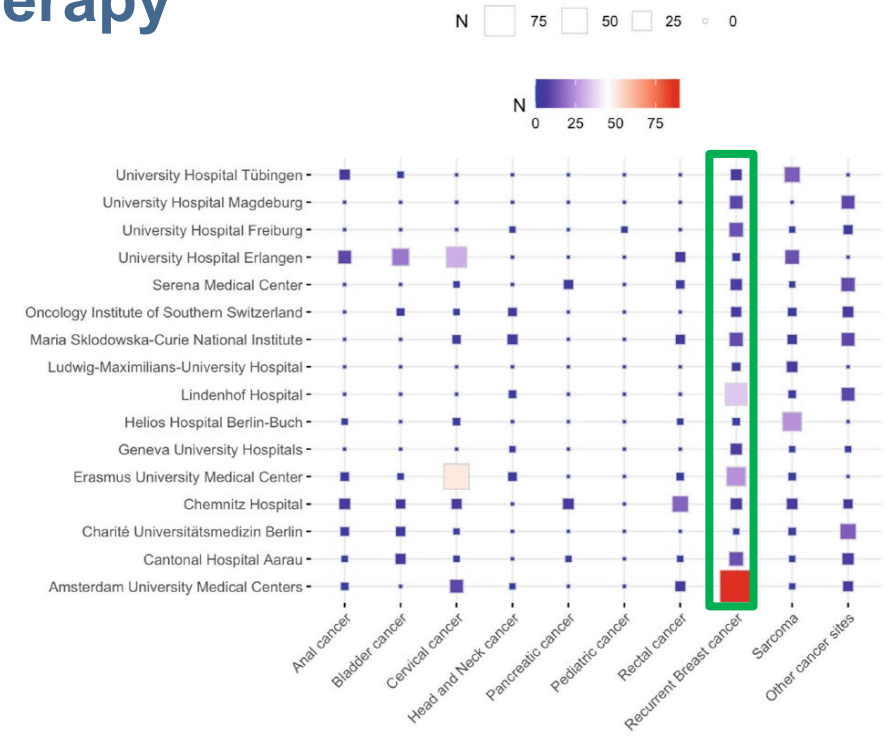
- **Research question:** How does the addition of regional hyperthermia with neoadjuvant radiochemotherapy followed by surgery affect the clinical outcomes in rectal cancer patients?
- **Types of study to be included:** observational clinical study
- **Analysis of subgroups/subsets**: to compare whether the clinical outcomes are associated the thermometric parameters reported in the clinical studies

Authors	pCR rates	Survival outcomes
Schem et al. [5]	29.8%	5-year rectum cancer-specific survival: 73.5% 5-year overall survival: 73.5%
Ott et al. [6]	19%	5-year local recurrence free: 77% 5-year distant metastasis free survival: 49% 5-year overall survival: 75%
Gani et al. [7]	14%	3-year disease free survival: 81% 3-year overall survival: 94%
Maluta et al. [8]	23.6%	5-year disease free survival: 74.5% 5-year recurrence free survival: 94.6% 5-year metastases free survival: 73.2% 5-year overall survival: 86.5%
Rau et al. [9]	14%	38-month overall survival: 86%

Recurrent breast cancer patients treated with hyperthermia combined with radio(chemo)therapy

- Patterns of care analysis in EU clinical centers :
  - All 16 clinical centers included in the survey treat **recurrent breast cancer**: ***235 patients per year***

  ➢ Patients with breast cancer are good models in investigate hyperthermia parameters in large multinational retrospective study



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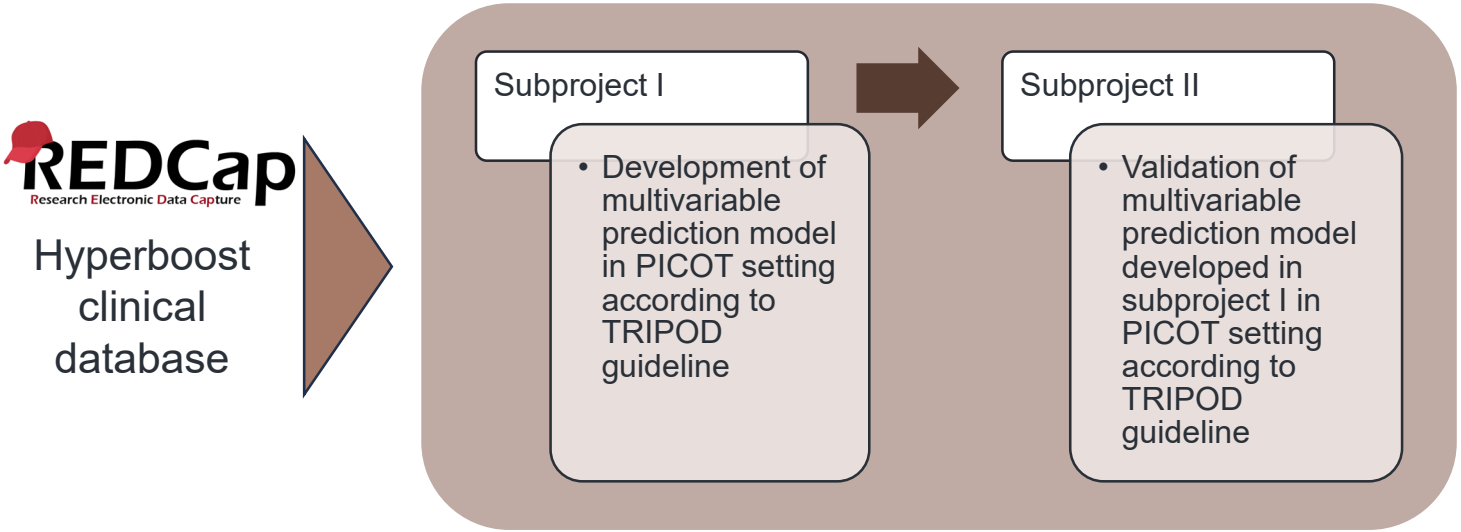
Subprojects of planned breast cancer study



Objective: To establish a thermal dose, temperature metrics, time interval effect relationship of superficial hyperthermia with clinical outcomes.

- Planned: start of patient data collection at Amsterdam UMC

Real world analysis of quality of life in cancer patients treated with hyperthermia

Study design

- Retrospective, single-center

Inclusion criteria

- Patients who received superficial or deep regional HT (≥2 HT sessions) combined with RCT and who returned the *EORTC-QLQ C30 questionnaire* before treatment, immediately after treatment, at 3 and 12 months after treatment

Patient population

Ademaj A et al. Cancers (Basel). 2023 Feb 15;15(4):1241.

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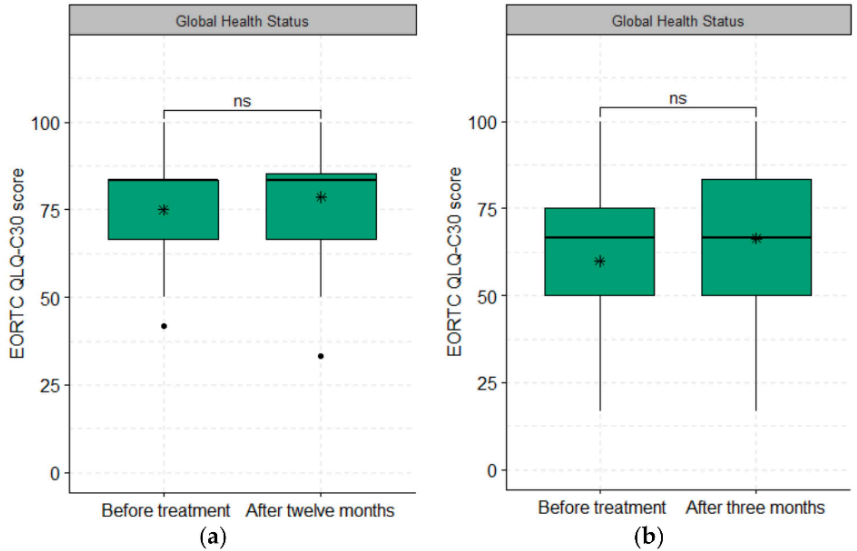
Real world analysis of quality of life: results of global health status patients treated with curative and palliative intent

- The relatively high mean Global Health Status score was maintained in 32 patients treated with curative RCT and HT compared with the EORTC general cancer population
- No significant difference was found for the Global Health Status of 31 patients who received palliative treatment three months after treatment



The global health status scores of (a) 32 patients treated with curative RCT and HT before and 12 months after treatment and (b) 31 patients treated with palliative RCT and HT before and three months after treatment.

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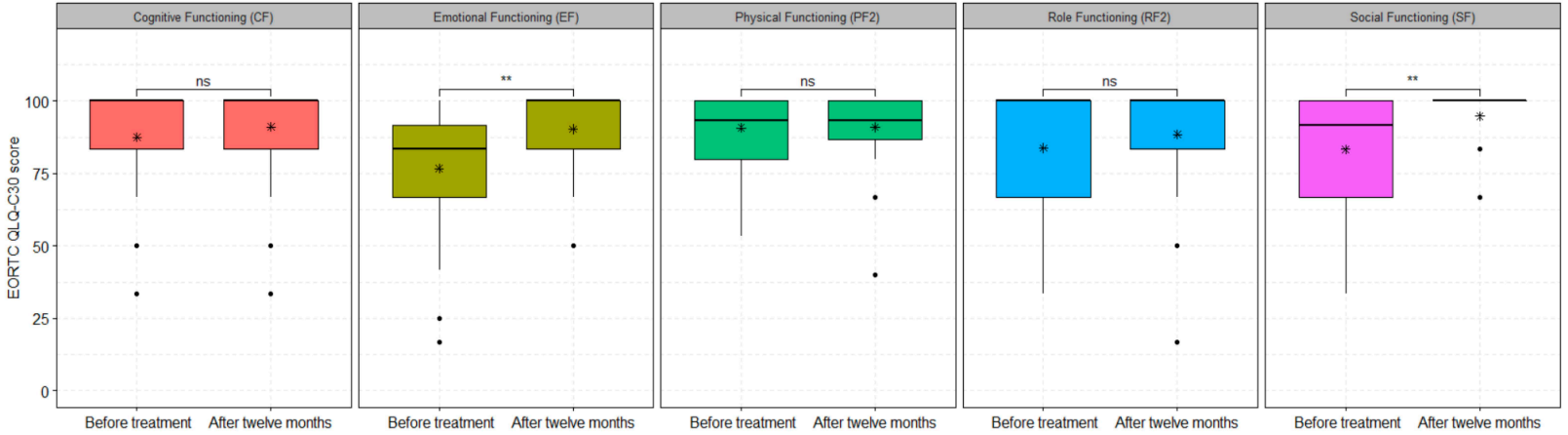
Real world analysis of quality of life: results of functional scale items patients treated with curative and palliative intent



The functional scale scores of 32 patients treated with curative RCT and HT before and 12 months after treatment.

- None of the functional scale items was significantly improved or worsened for 30 patients treated with palliative RCT and HT after three months.

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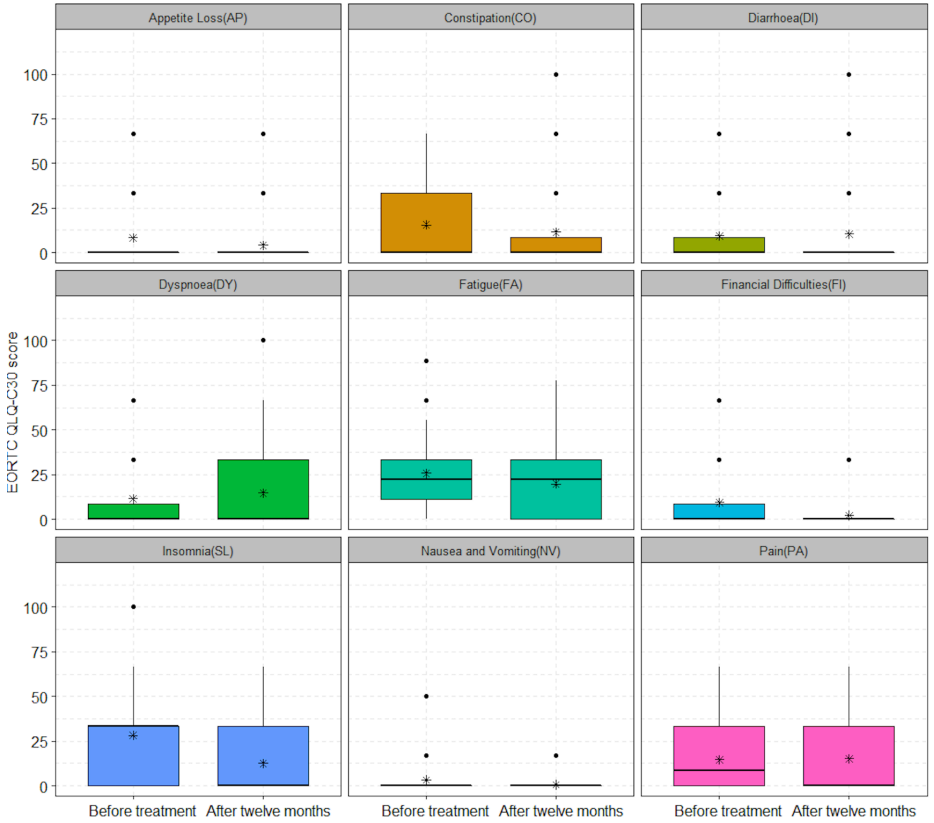
Real world analysis of quality of life: results of symptoms scale items patients treated with curative intent

- The symptom scale items such as AP, CO, FA, FI, NV, and SL were significantly improved 12 months after curative treatment for 32 patients when compared with EORTC general population



The symptom scale scores of 32 patients treated with curative RCT and HT before and three months after treatment

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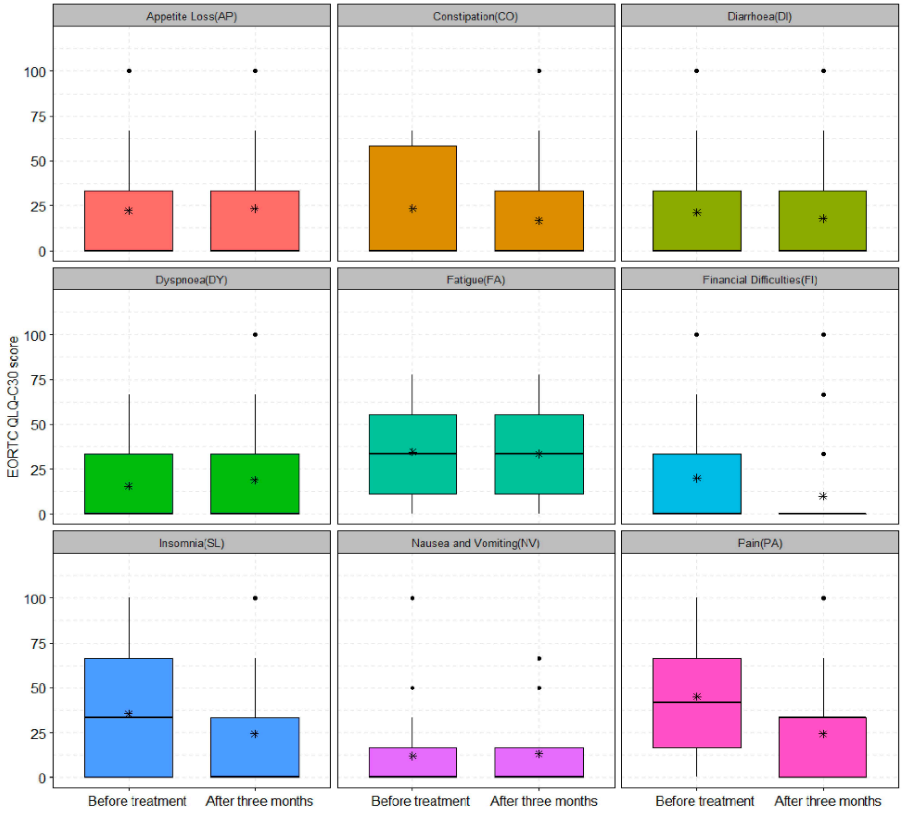
Real world analysis of quality of life: results of symptoms scale items patients treated with palliative intent

- Positive outcomes were obtained after comparing the EORTC general population and 30 patients treated with palliative RCT combined with HT three months after treatment



The symptom scale scores of 30 patients treated with palliative RCT and HT before and three months after treatment

Ademaj A et al. Cancers (Basel). 2023 Feb 15;15(4):1241.

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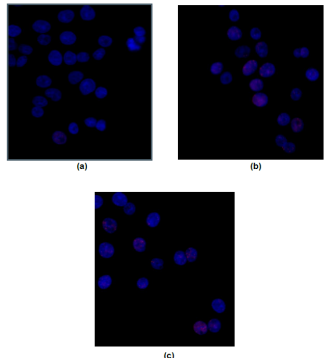
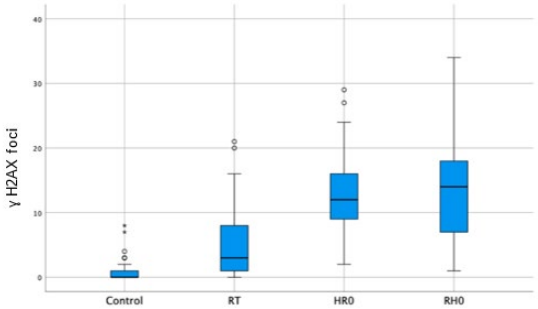
Secondment at Amsterdam UMC: The Effects of Temperature, Sequence, and Time Interval in HT29 cell line

1st treatment condition:

- Control (no treatment)
- Radiotherapy only with 4 Gy **[RT]**
- Hyperthermia (42.3°C for 60 minutes) and radiotherapy with 4 Gy with time interval 0 h **[HR0]**
- Radiotherapy with 4 Gy and hyperthermia (42.3°C for 60 minutes) with time interval 0 h **[RH0]**



Microscope images taken to count ɣH2AX foci: (a) RT (b) HRO and (c) RH0



The mean difference of number of γ-H2AX foci for control; for RT; for HR0; for RH0;

Other treatment conditions with different temperatures and time interval are being investigated

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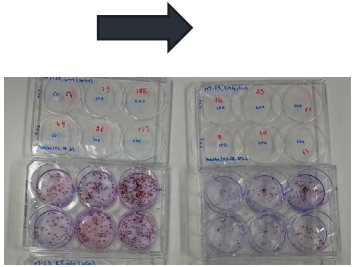
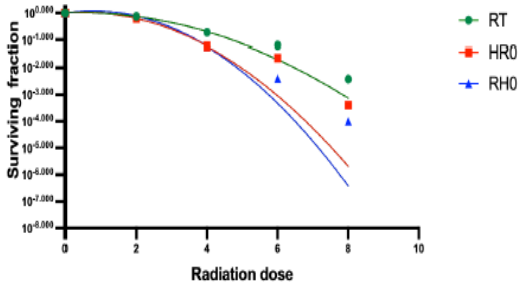
Secondment at Amsterdam UMC: The Effects of Temperature, Sequence, and Time Interval in HT29 cell line

Treatment condition:

- Control (no treatment)
- Radiotherapy only **[RT]**
- Hyperthermia (42.3°C for 60 minutes) and radiotherapy with time interval 0 h **[HR0]**
- Radiotherapy and hyperthermia (42.3°C for 60 minutes) with time interval 0 h **[RH0]**





Other treatment conditions with different temperatures and time interval are being investigated

Questions?