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Danish Cancer Society

TUMOR PATHOPHYSIOLOGY AND THE RESPONSE TO RADIATION AND HYPERTHERMIA

ESR 3, AU: Folefac Charlemagne Asonganyi
Supervisor Prof: Michael Robert Horsman
Institution: Aarhus University Hospital

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SUB OBJECTIVES OF THE PROJECT

- Investigate the relationship between various tumor pathophysiological parameters on the interaction between radiation (**photons and protons**) and **hyperthermia**.
  - Use tumor and mouse models to determine the importance of the time interval between the application of radiation (SBRT) and heat (39-44°C). (**Mice model** -CDF1 & **Tumor type**-C3H mammary carcinoma).

    Establish the minimal, maximum temperature and the time interval needed to enhance radiation response with less toxicity.

- Perform mechanistic studies to understand this heat-radiation (SBRT) interaction
  - **Blood flow, oxygenation/hypoxia.**
  - **DNA repair, direct/indirect killing, and immune effect**).
- Investigate the potential of hyperthermia to be used as an **adjuvant for re-irradiation treatment.**
  - Understand the role of thermotolerance and step-down heating.

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HANDS ON TRAINING ON RELEVANT TECHNIQUES TO MY MAIN PROJECT

- Combining some existing antitumor therapists to treat different tumor sizes (50-400 mm3) of C3H mammary carcinoma.
  - Anti-Cytotoxic T Lymphocytes Associated protein-4 (anti-CTLA4) checkpoint inhibition (10 mg/Kg * 4) along with:
    - High single dose proton radiation (20 Gy)
    - OXi4503 Vascular Disrupting Agent (VDA) (50 mg/kg * 4)
    - Single thermal dose of Hyperthermia (42.5 Degree, 1 hr)

Priyanshu M Sinha, Folefac Charlemagne Asonganyi, Michael R Horsman.
(Paper in progress for publication).

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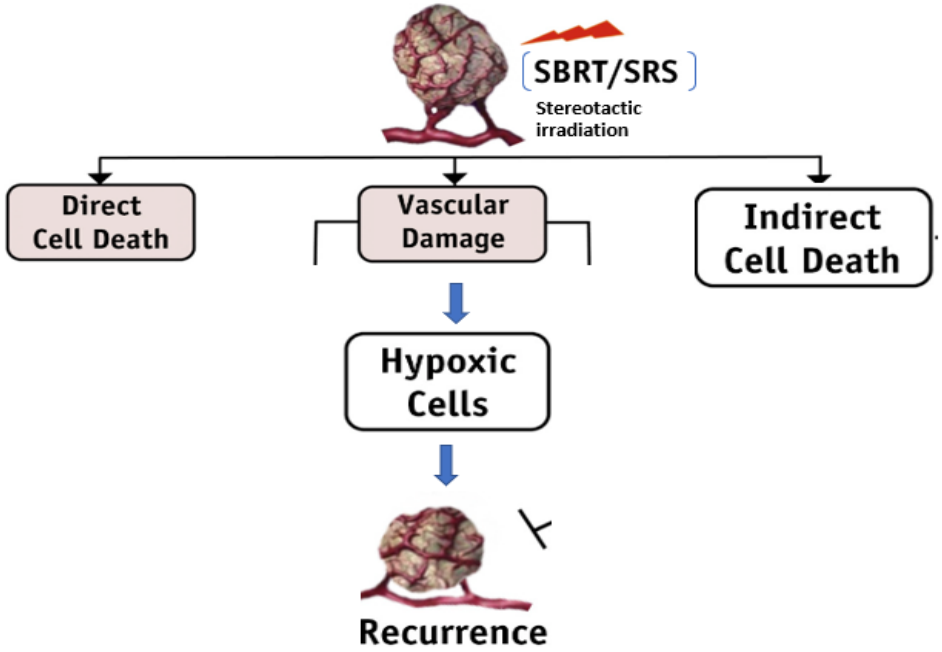
BACKGROUND

INVESTIGATE THE RELATIONSHIP BETWEEN TUMOR PATHOPHYSIOLOGICAL PARAMETERS ON THE INTERACTION BETWEEN RADIATION AND HYPERTHERMIA

EFFECTS OF SBRT RADIATION TREATMENT

SBRT/SRS

- Can kill cancer cells **directly** and **indirectly**.
- It can also destroy blood vessels which supply cancer cells, contributing to hypoxic cancer cells which may eventually leads to recurrence of primary tumor after treatment.



Adapted from Song et al., 2019. Biological Principles of Stereotactic Body Radiation Therapy (SBRT) and Stereotactic Radiation Surgery (SRS): Indirect Cell Death. Int J Radiation Oncol Biol Phys, Vol. 110, No. 1, pp. 21e34, 2021

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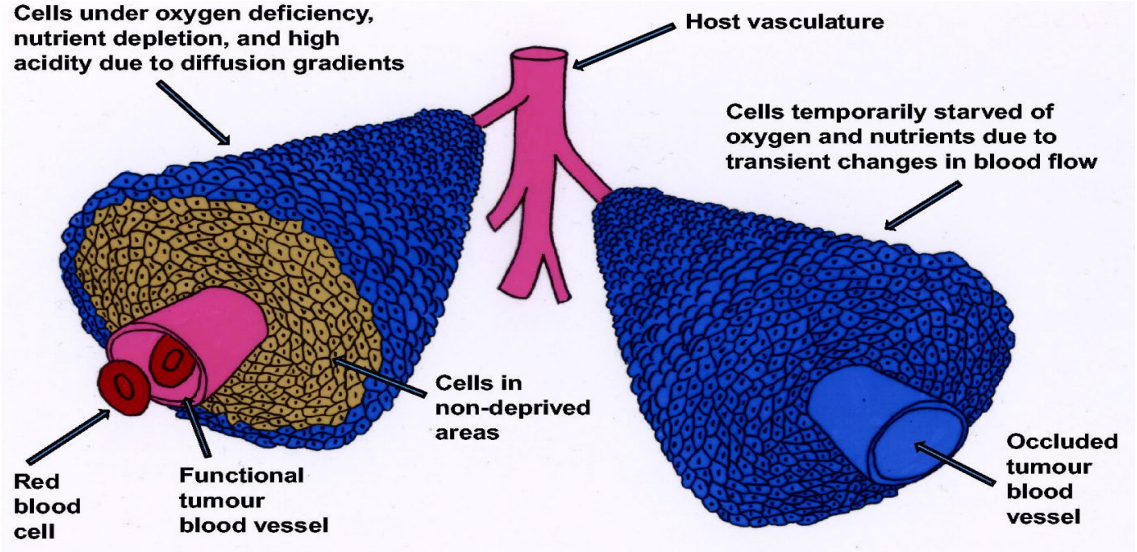
BACKGROUND

THE INTERRELATIONSHIP BETWEEN TUMOUR CELLS AND THEIR VASCULAR SUPPLY



Horsman MR, Mortensen LS, Petersen JB, Busk M, Overgaard J. Imaging hypoxia to improve radiotherapy outcome. Nat Rev Clin Oncol 2012;9:674–87

OTHER POSSIBLE EFFECTS OF SBRT ON TUMOR MICROENVIRONMENT

- Hypoxia (low oxygen) leads to radioresistance.
- Low glucose nutrients, low extracellular acidity, increase level of lactate acid.

➢ Cancer cells in these poor conditions can be kill with hyperthermia temperature (Overgaard J, 1989).

- Combining SBRT with heat can have therapeutic benefits.

Effects of heat:
Radiosensitization of cancer cells, enhancement of radiation (inhibit DNA damaged repair mechanisms) and direct hypoxic cell killing (A.L. Oei et al, 2020).

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BACKGROUND

- How should SBRT and hyperthermia be applied in order to obtain the most therapeutic benefits with less toxicity?
  - What hyperthermia Temperature? What SBRT fraction? What Time interval? What heating duration?

- What has already been done preclinically and what is currently been done in the clinic as far as **SBRT + Hyperthermia** is concern?

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PRECLINICAL AND CLINICAL STUDIES COMBINING SBRT + HYPERTHERMIA

- REVIEW ON THE RATIONAL FOR COMBINING SBRT AND HYPERTHERMIA (**ongoing**)

Folefac Charlemagne Asonganyi, Priyanshu M Sinha, Michael R Horsman, Jens Overgaard.

Observations of previous publications:

- Inconsistency in the application of SBRT + Hyperthermia in both preclinical and clinical studies.

Preclinical studies

- **Different time intervals between SBRT and heat in different studies. Eg 30 mins, 1,2,4 and greater than 4 hours.**
- **Different single studies have used different SBRT Fractions.**

Clinical Studies

- **Different patients received different SBRT fractions in different studies.**
- **Some studies combine hyperthermia and thermal ablation.**
- **Different time intervals between various heat fractions received by patients in the same study.**

WAY FORWARDS

Preclinically apply different fractions of **SBRT** and **hyperthermia temperatures** to see which is the most benefit.

Vary the different temperatures and possible time interval in the process.

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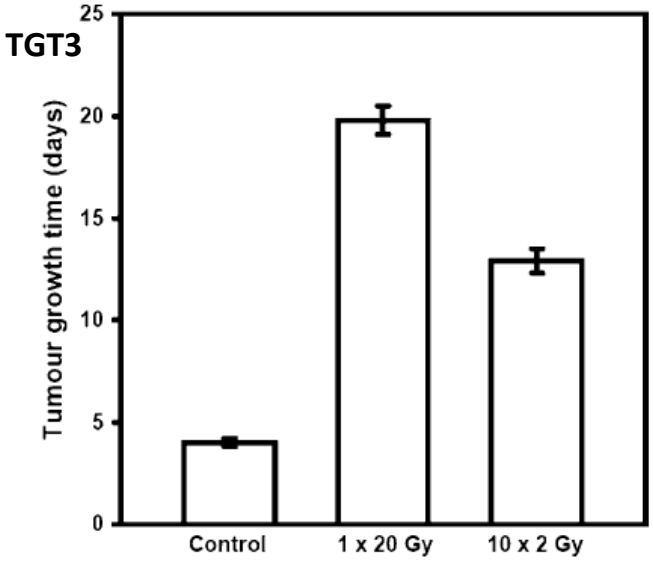
EFFECTS OF STEROITACTIC RADIATION AND HYPERTHERMIA IN PREVIOUS STUDIES IN OUR LAB

❖**C3H mammary carcinoma has responded to both high-dose irradiations and heat in previous studies with CDF1 mice.**

ANIMALS TREATED WITH SINGLE OR FRACTIONATED HIGHER DOSE IRRADIATIONS

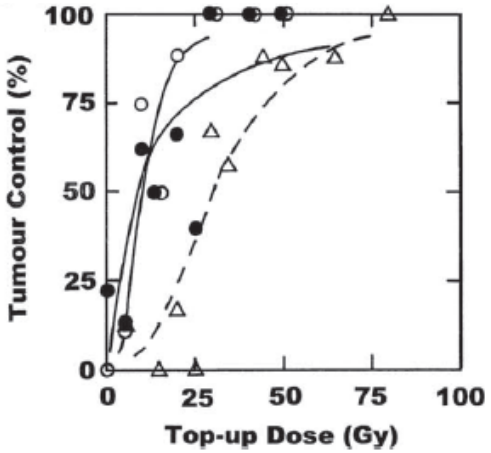


All results show means (+-1 SE) from 8-10 mice.

Horsman et al., 2009

ANIMALS TREATED WITH SBRT FRACTIONS COMBINED WITH HYPOXIA MODIFIERS

Treatment groups	Day 0	Day 3	Day 7	3 days after day 7. TCD50 values for clamp top-up dose
Δ	15Gy	15Gy	15Gy	→ 29.7
o	15Gy	15Gy	15Gy +heat (H)	→ 10.1
●	15Gy +heat	15Gy +heat	15Gy +heat(H)	→ 8.6



Thomas R. Wittenborn & Michael R. Horsman, 2015

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METHODOLOGY

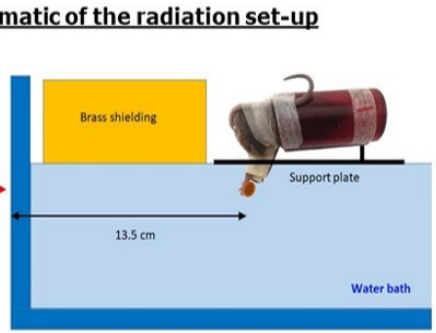
2

	Schedules		
	Day 0	Day4	Day 7
Radiation (R) doses / Fractions 5, 10, 15, 20 Gy	1 R	2 R	3R
Hyperthermia (H)	1 R	2R	3 R+H after 30 mins H=41.50C for 1 hour

3

Photon source

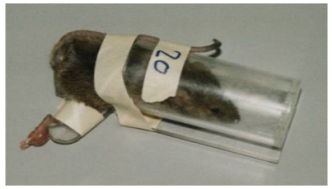
Experimental Proton source



Restrained non-anaesthetised CDF1 mouse with tumor bearing foot immersed in a waterbath. Tumor only irradiated, the remainder of the animal being shielded

1

Implant tumor material C3H mamary tumor in the right rear foot of CDF1 mouse.



Around 2-3 weeks later tumors reach desired 200 mm3 range (day 0) treatments started

$$\pi/6 \times L \times W \times H$$

Tumor Volume

4

Endpoints:
Tumor growth time to 3 (TGT3) 0r 5 times (TGT5) their starting treatment volume or 90 days

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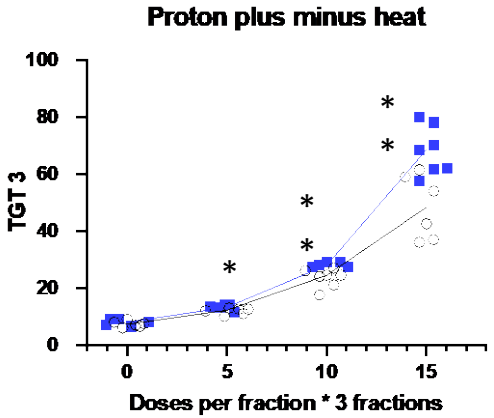
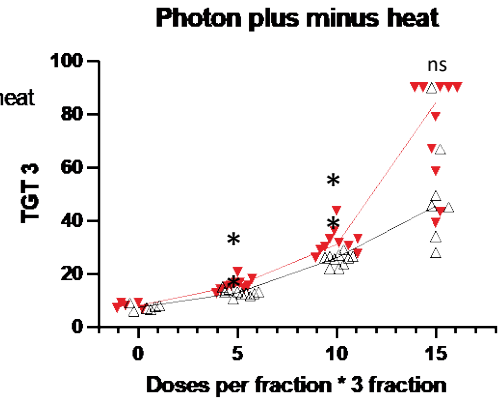
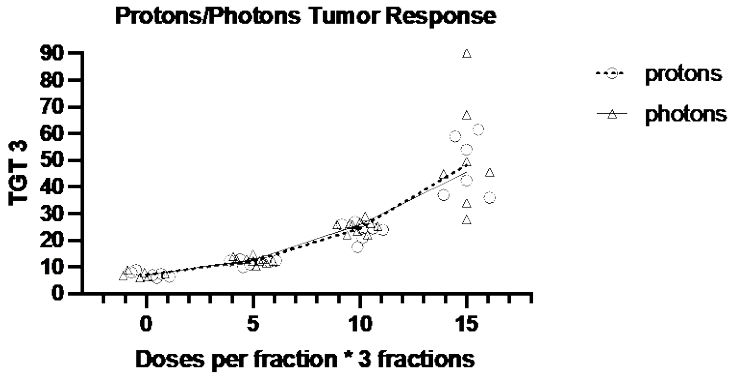
PRELIMINARY RESULTS OF PROTON AND PHOTON SBRT X3 FACTIONS WITH AND WITHOUT HEAT







- **p<0.05; **p<0.01; ns not significant*

- No difference in tumor response between photon and protons SBRT 3F

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INTERIM CONCLUSION

(1) The is optimum beneficial effect of combining hyperthermia with SBRT for both photon and proton at the time interval of 30 mins, heating duration 1 hour.

(2) The cut-off point for the experiment after 90 days (about 3 months) of mice receiving treatment does not show the effects of heat when 3x20Gy ionization irradiation is administered.

(3) SBRT for **Photons and proton** when applied with hyperthermia seems to have the same effects on cancer cells.

(4) For tumor studies (**tumor delay growth**), the benefits of **SBRT plus heat is seen,** but in normal tissues studies (**data not shown**), hyperthermia + SBRT group shows no statistically significant damage of healthy tissues compared to SBRT group alone.

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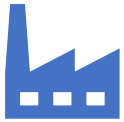
FUTURE PROSPECTIVES

Perform toxicity study (acute toxicity). (Ongoing)

Change treatment schedules (vary temperatures and time intervals)



Perform mechanistic studies

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THANKS FOR YOUR KIND ATTENTION

THE END!

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ESR4 Azzaya Sengedorj

Elucidate the effects and mechanisms of hyperthermia in combination with radiotherapy on the innate and adaptive immune system in pre-clinical model systems

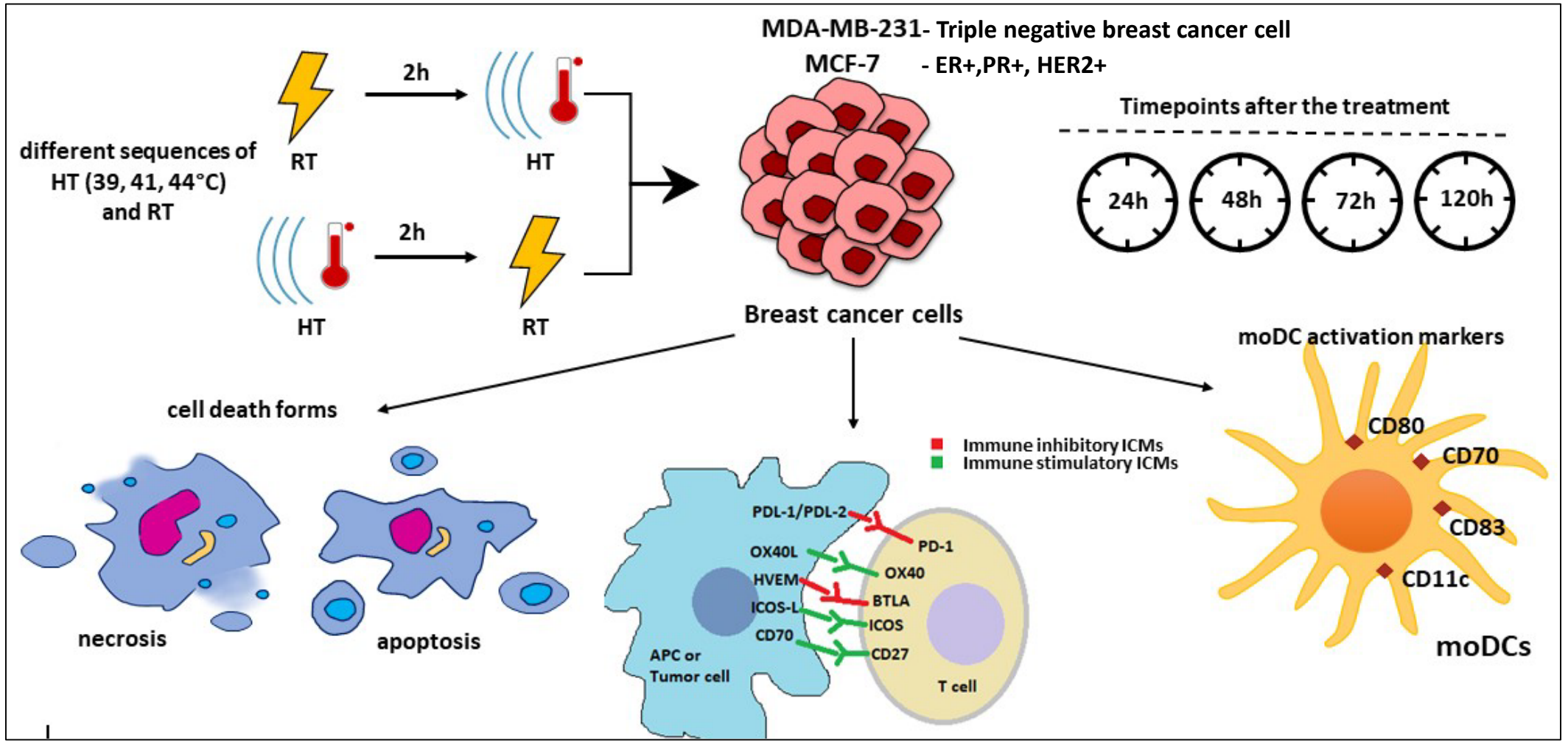
Universitätsklinikum Erlangen (UKER),
Department of Radiation Oncology, Translational Radiobiology,
Universitätsstr. 27, 91054 Erlangen, Germany

Universitätsklinikum Erlangen

Main objective of the project

- To study the effect of hyperthermia treatment in combination with RT on the innate and adaptive immune system
- To investigate if the sequence of HT and RT (either using RT before HT or vice versa) affects differently the immune system
- To determine the effect of HT in combination with RT in induction of anti-tumor immune response by using preclinical and *in vivo* model systems

Effect of hyperthermia and radiation therapy sequence on cell death and the immune phenotype of breast cancer cells



Sengedorj et.al, The Effect of Hyperthermia and Radiotherapy Sequence on Cancer Cell Death and the immune phenotype of Breast Cancer Cells. *Cancers* **2022**, *14*, 2050. https://doi.org/10.3390/cancers14092050

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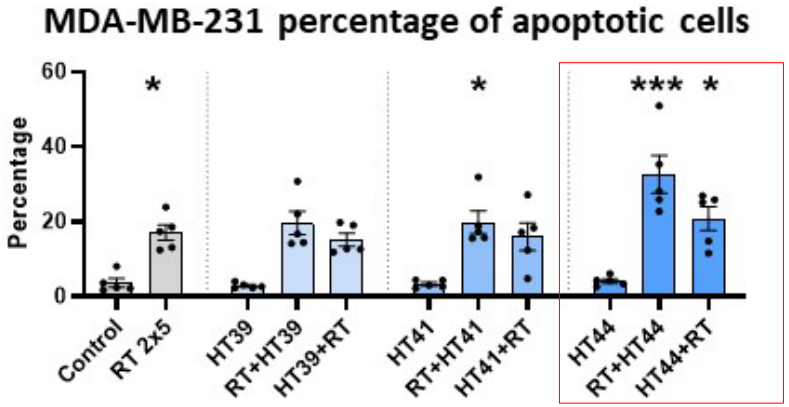
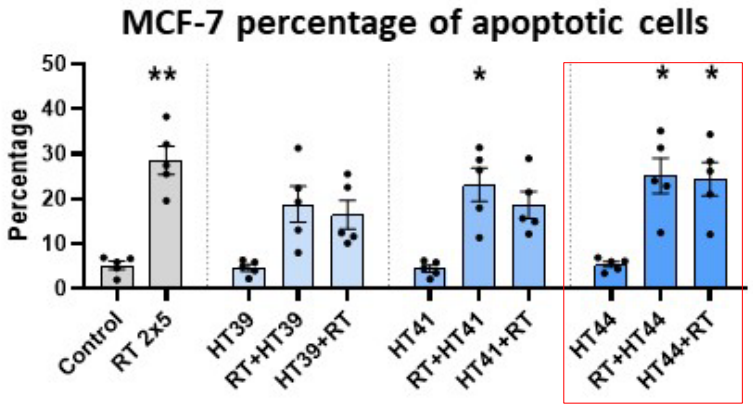
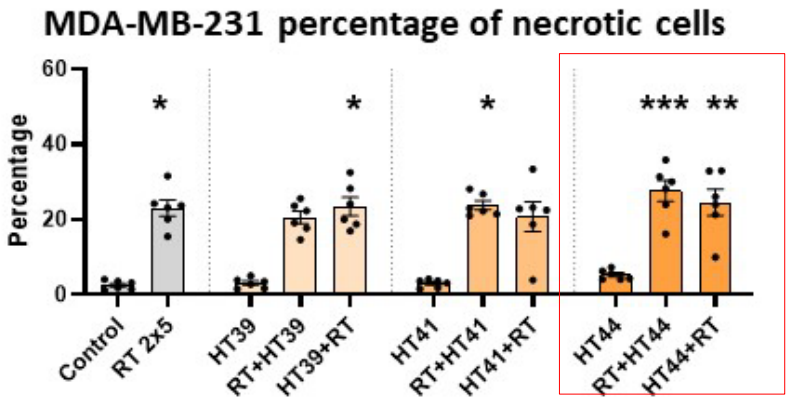
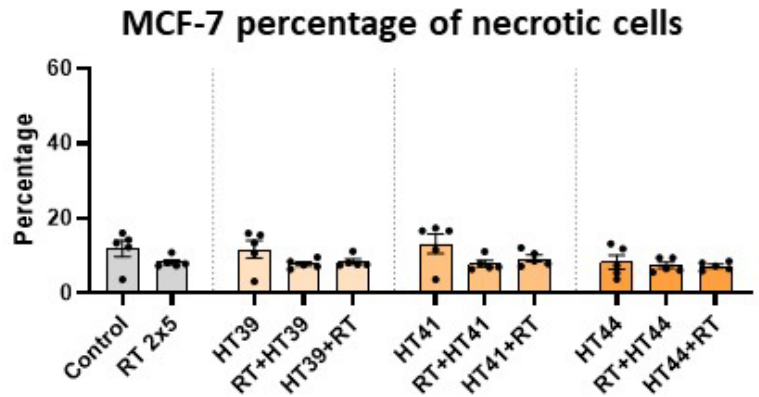
RESULTS

The sequences of HT and RT didn't significantly affect the induction of cancer cell death in MCF-7 and MDA-MB-231 cells









HT in combination with RT significantly induced both apoptosis and necrosis in MDA-MB-231 cells, and apoptosis in MCF-7 cancer cells

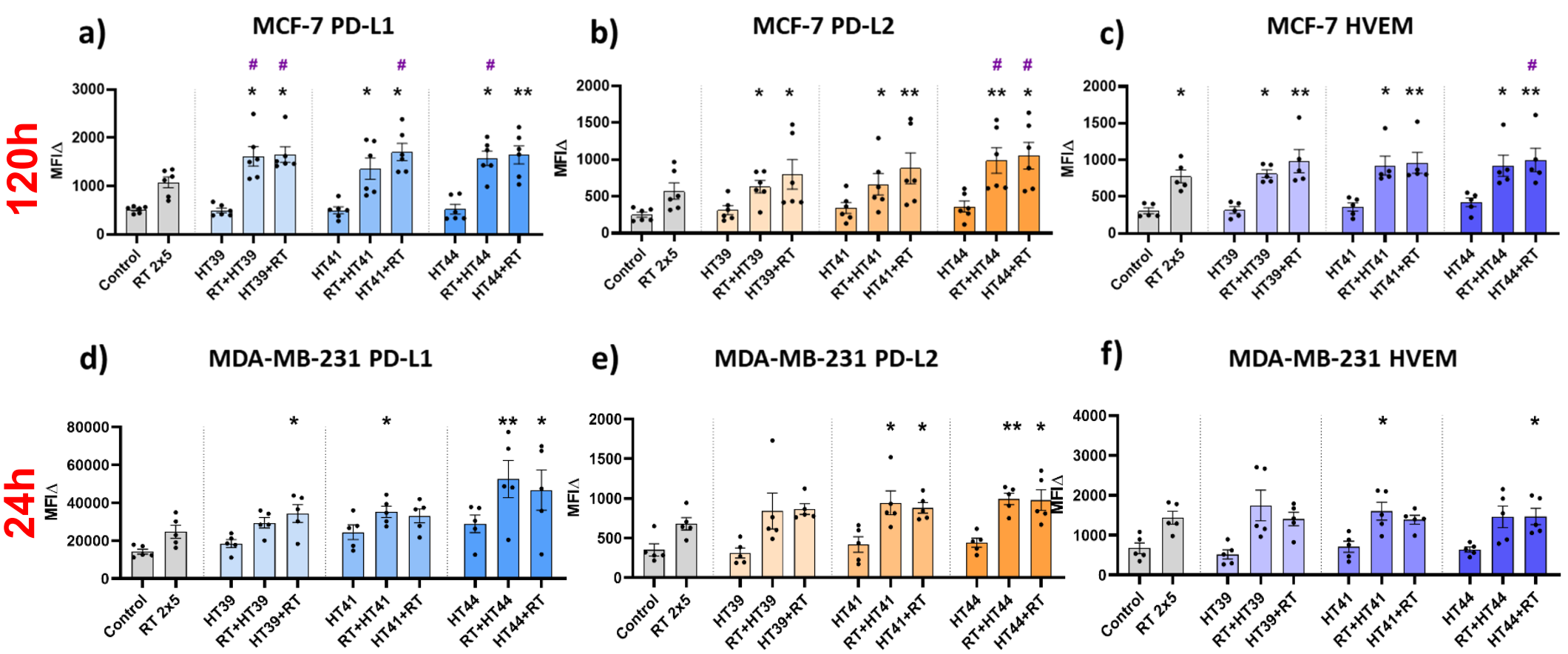
Figure 3: **Cell death of breast cancer cells 120h after the respective treatments**. Mean ± SD are presented from at least five independent experiments. Statistical significance was calculated by using a Kruskall-Wallis test with Dunn's correction * ($p<0.1$), **($p<0.01$), *** ($p<0.001$).

Sengedorj et.al, The Effect of Hyperthermia and Radiotherapy Sequence on Cancer Cell Death and the immune phenotype of Breast Cancer Cells. *Cancers* **2022**, *14*, 2050. https://doi.org/10.3390/cancers14092050

RESULTS:

HT in combination with RT upregulates the expression of inhibitory immune checkpoint molecules in breast cancer cells

Expression of Immune checkpoint molecules in different timepoints



HT boosts the RT's immunosuppressing effect, thus using ICI additional to the RT combined with HT is better

Due to the specific dynamic of ICMs, starting the immunotherapy based on the kinetic of IC molecule expression might be beneficial

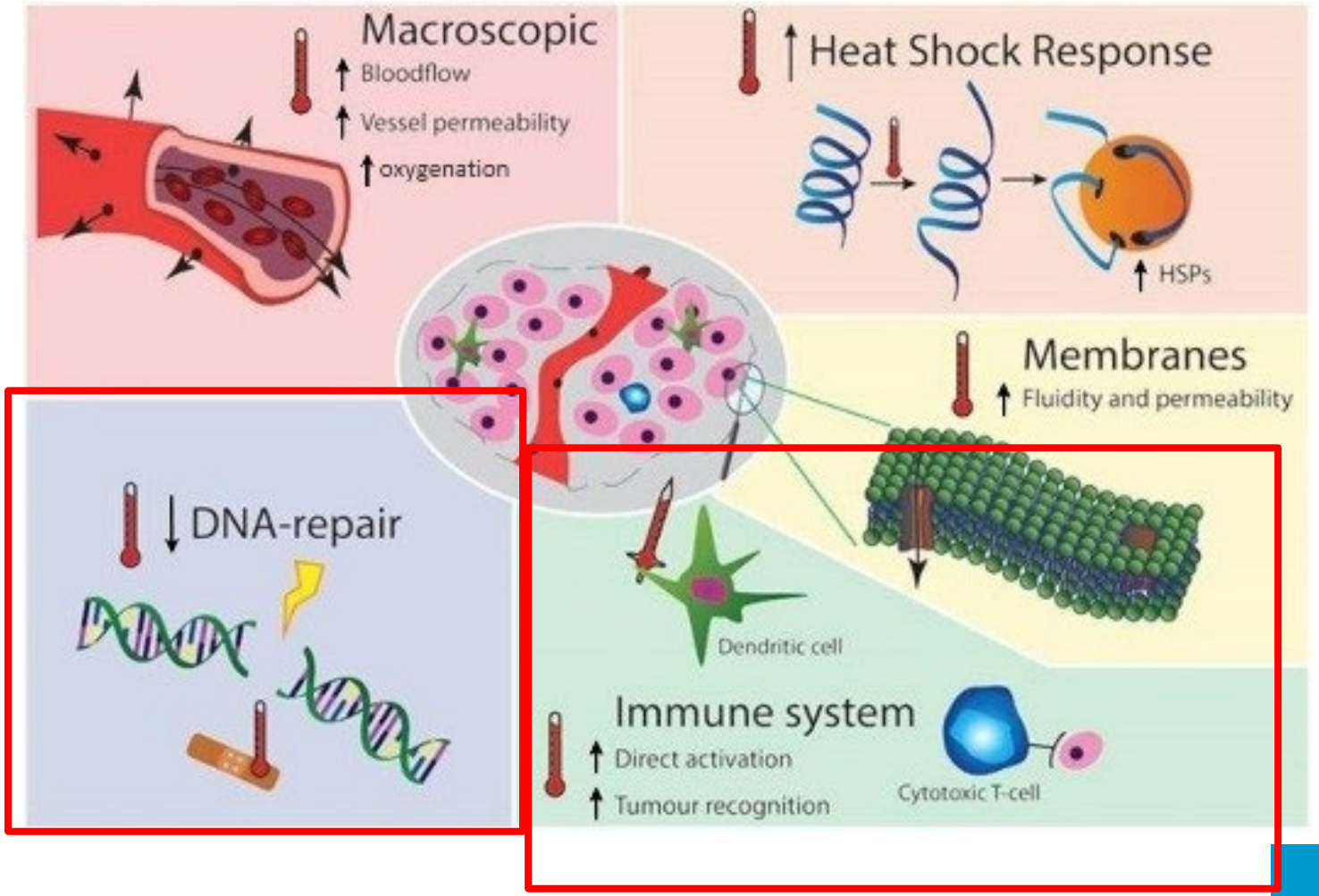
Figure 5: **The expression of inhibitory immune checkpoint molecules (PD-L1, PD-L2, HVEM) on MCF-7 (a-c) and particularly PD-L2 on MDA-MB-231 (e) breast cancer cells at 24h and 120h after the treatments.** Mean ± SD are presented from at least five independent experiments. Statistical significance is calculated by using Kruskall-Wallis test with Dunn's correction * (p<0.1), **(p<0.01), *** (p<0.001). RT alone was compared with combinational treatments (HT+RT and RT+HT) by Mann Whitney U test, # (p<0.1).

Sengedorj et.al, *Cancers* **2022**, *14*, 2050. https://doi.org/10.3390/cancers14092050

Secondment in Amsterdam UMC

Dr. Przemek Krawczyk

Amsterdam UMC



* Horsman MR *et al. Clin Oncol* (R Coll Radiol). 2007;19:418-26, and van den Tempel N *et al. Int J Hyperthermia*. 2016;32:446-54

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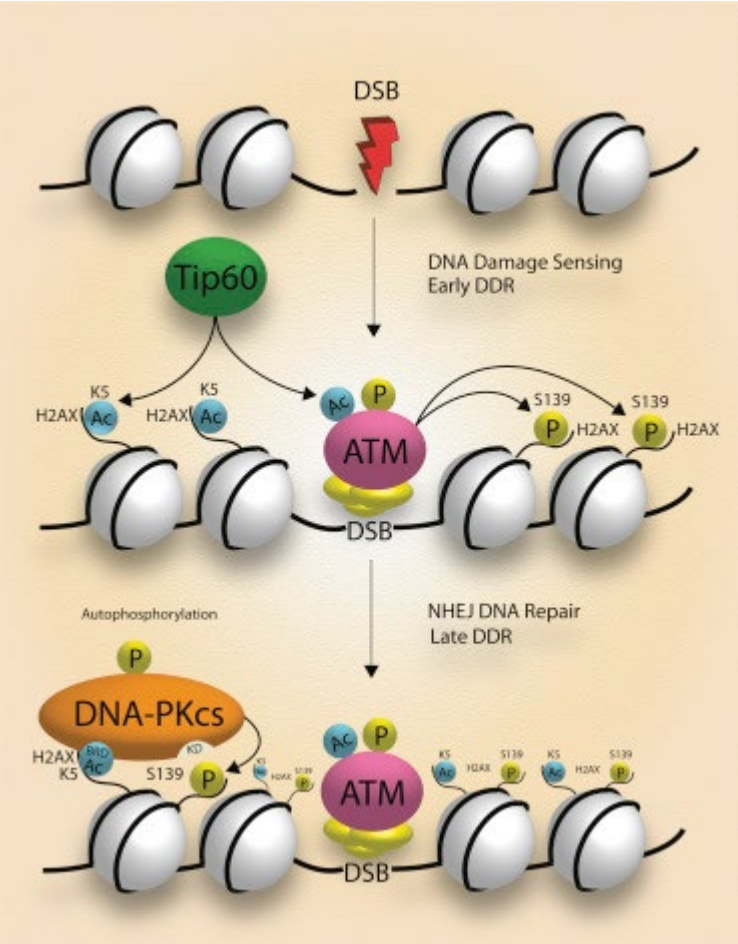
OBJECTIVES

How does the combination of HT and RT affect the DNA damage of cancer cells?

- Analyze yH2AX formation after our treatment setting
- Detection of micronuclei after the treatments
- Analyze the changes of immune related genes after HT
- Analysis of ICM expression on tumor cells after HT and RT
- Investigate whether micronuclei formation is affected by HT and RT, and if this formation activates cGAS STING pathway and changes ICM expression on tumor cells

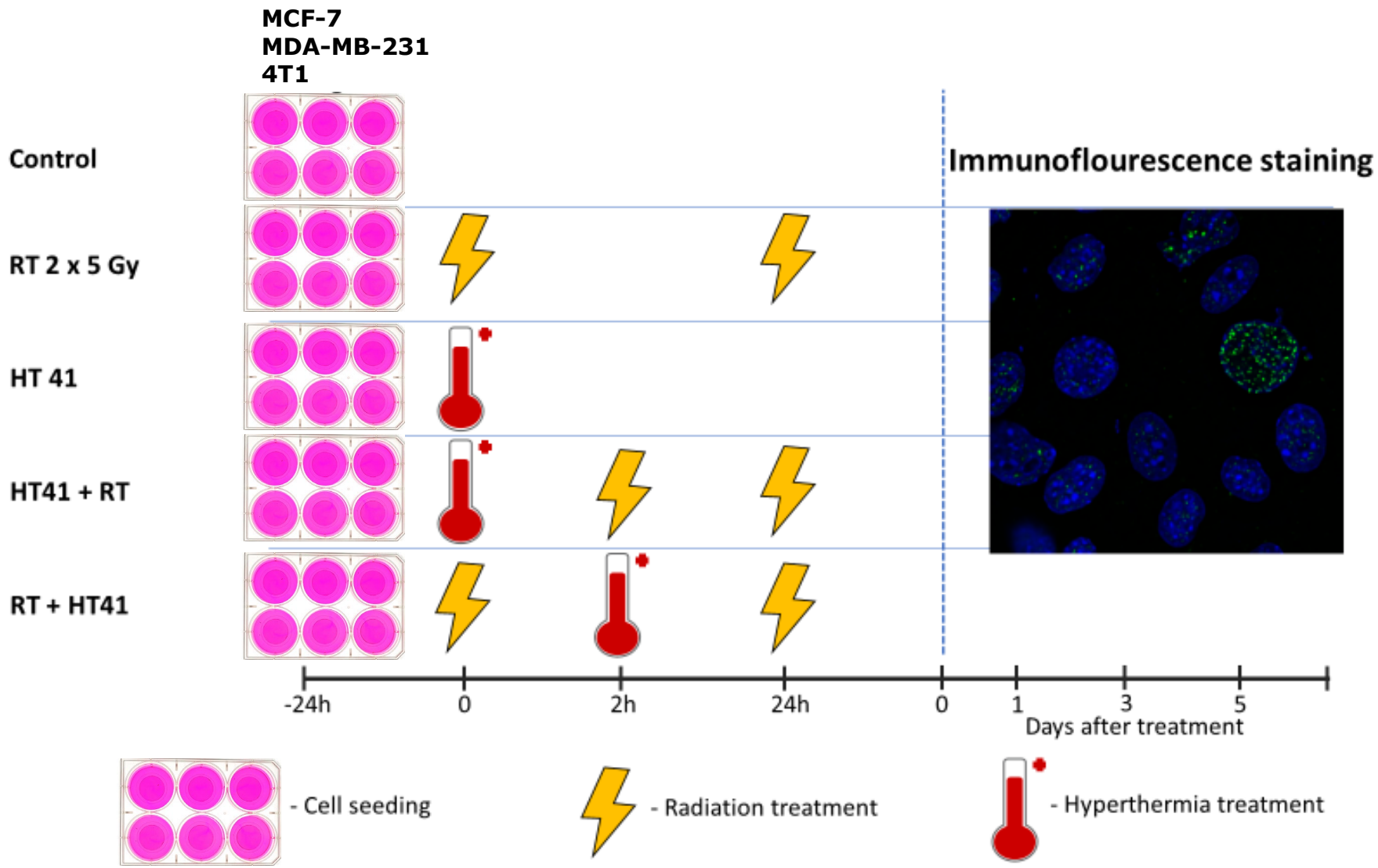
yH2AX is a sensor for DNA double strand breaks



- yH2AX- phosphorylation of the Ser-139 residue of the histone variant H2AX
- Senses double strand break on DNA, and further activates the DNA damage repair mechanism
- Immunofluorescense detection of yH2AX is very sensitive and reliable method to detect DSBs (double strand break)

https://doi.org/10.1016/j.chembiol.2015.05.014

Immunofluorescence detection of yH2AX



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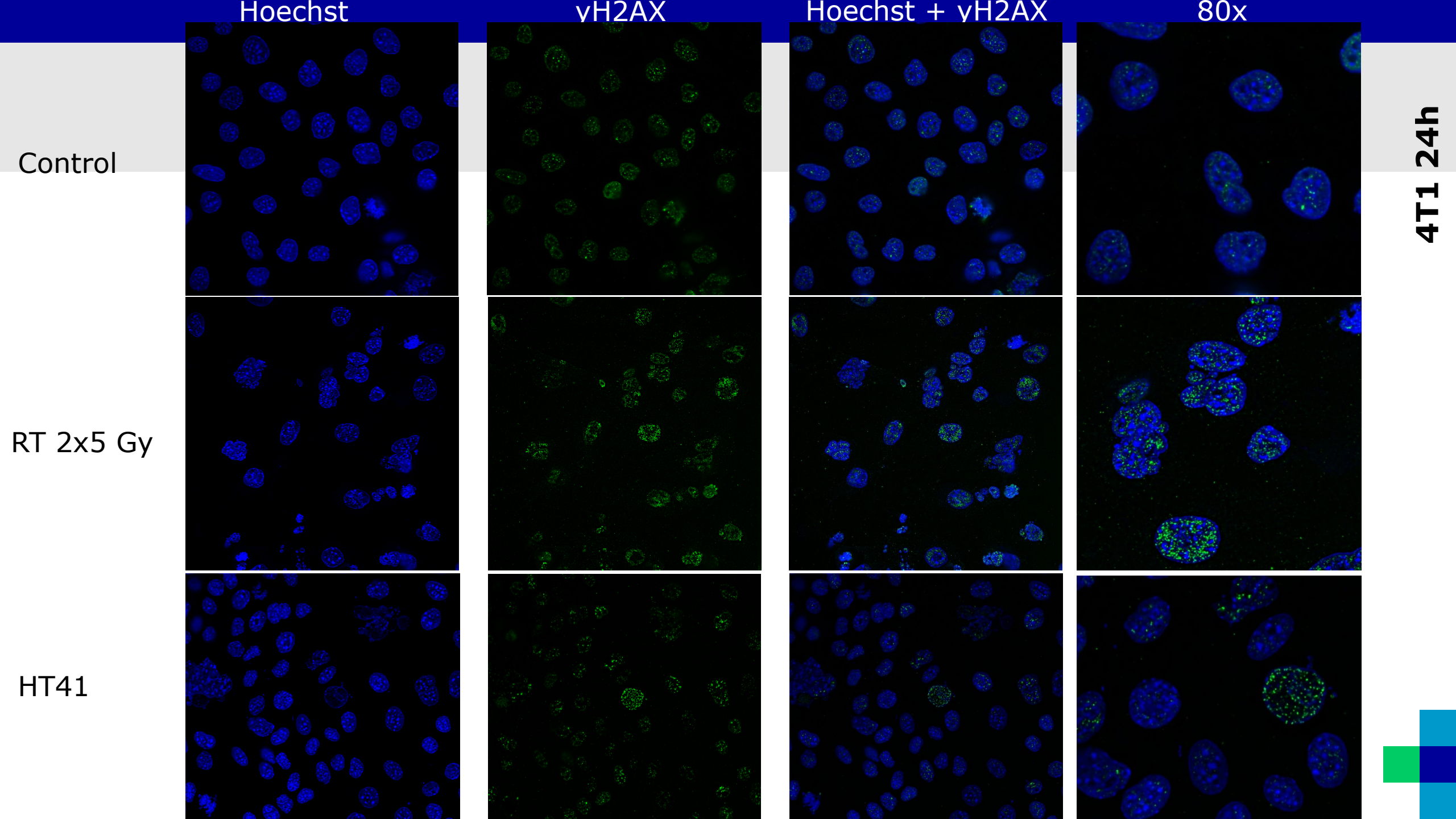
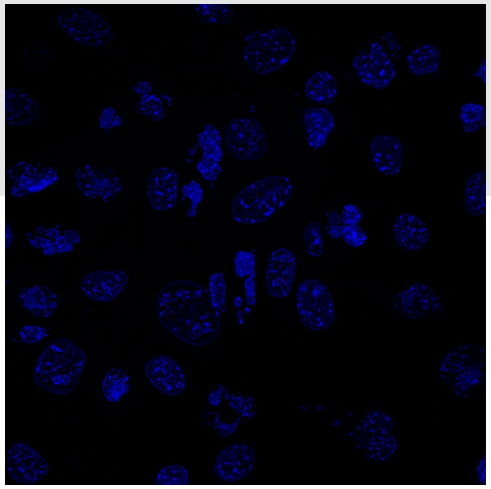
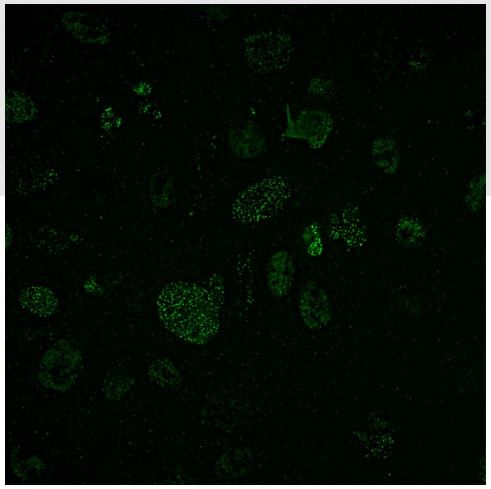
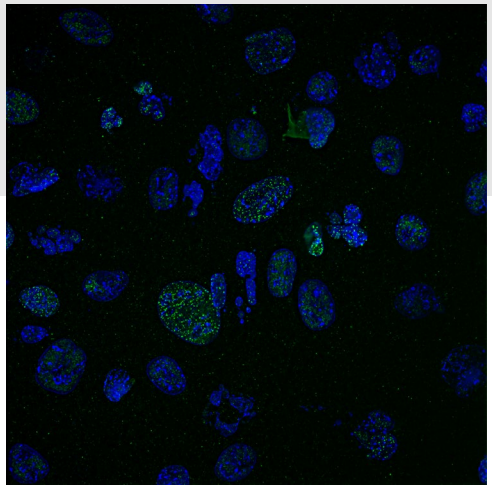
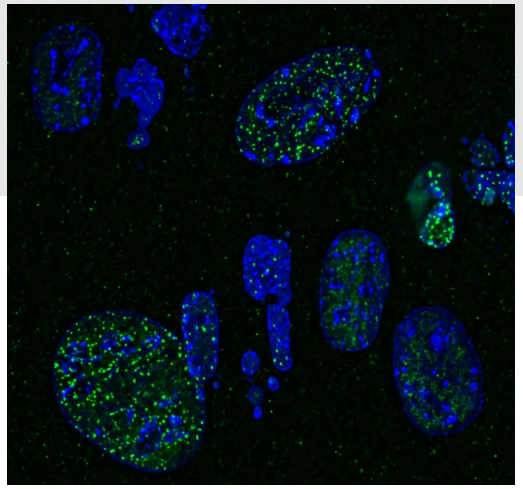
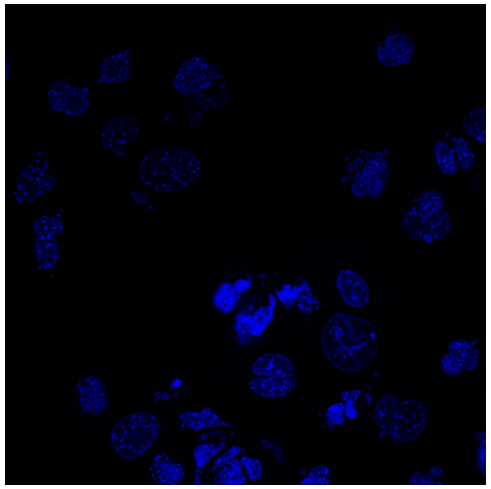
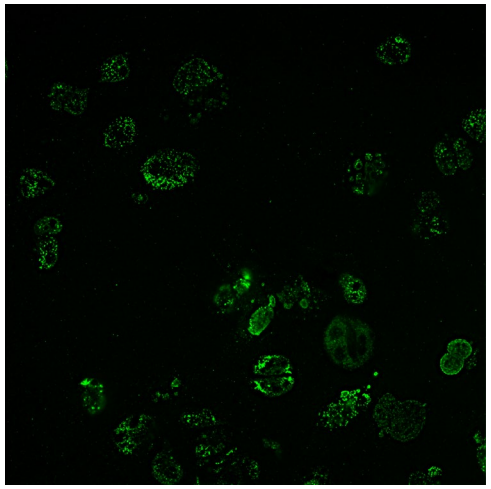
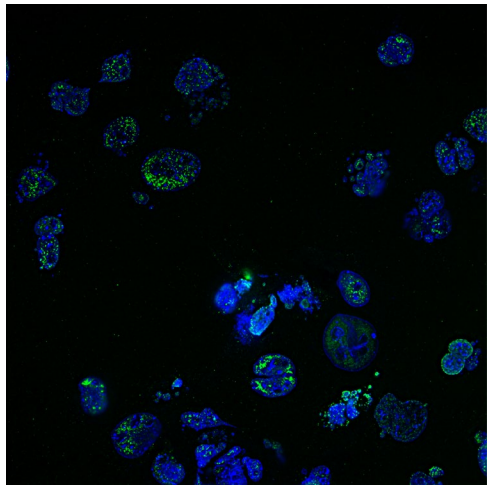
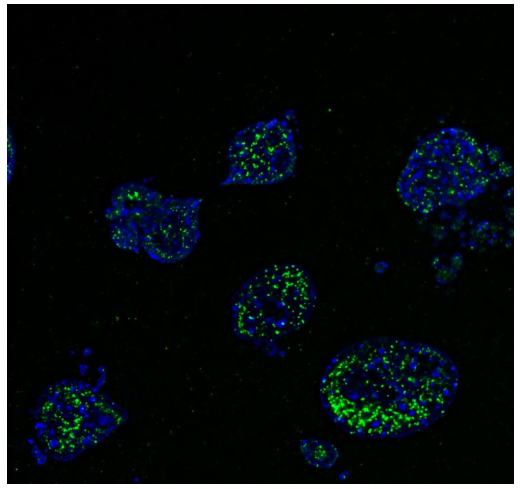

Hoechst
γH2AX
Hoechst + γH2AX
80x
Control
RT 2x5 Gy
HT41
4T1 24h

	Hoechst	yH2AX	Hoechst + yH2AX	80x
RT+41				
HT41+RT				

4T1 24h

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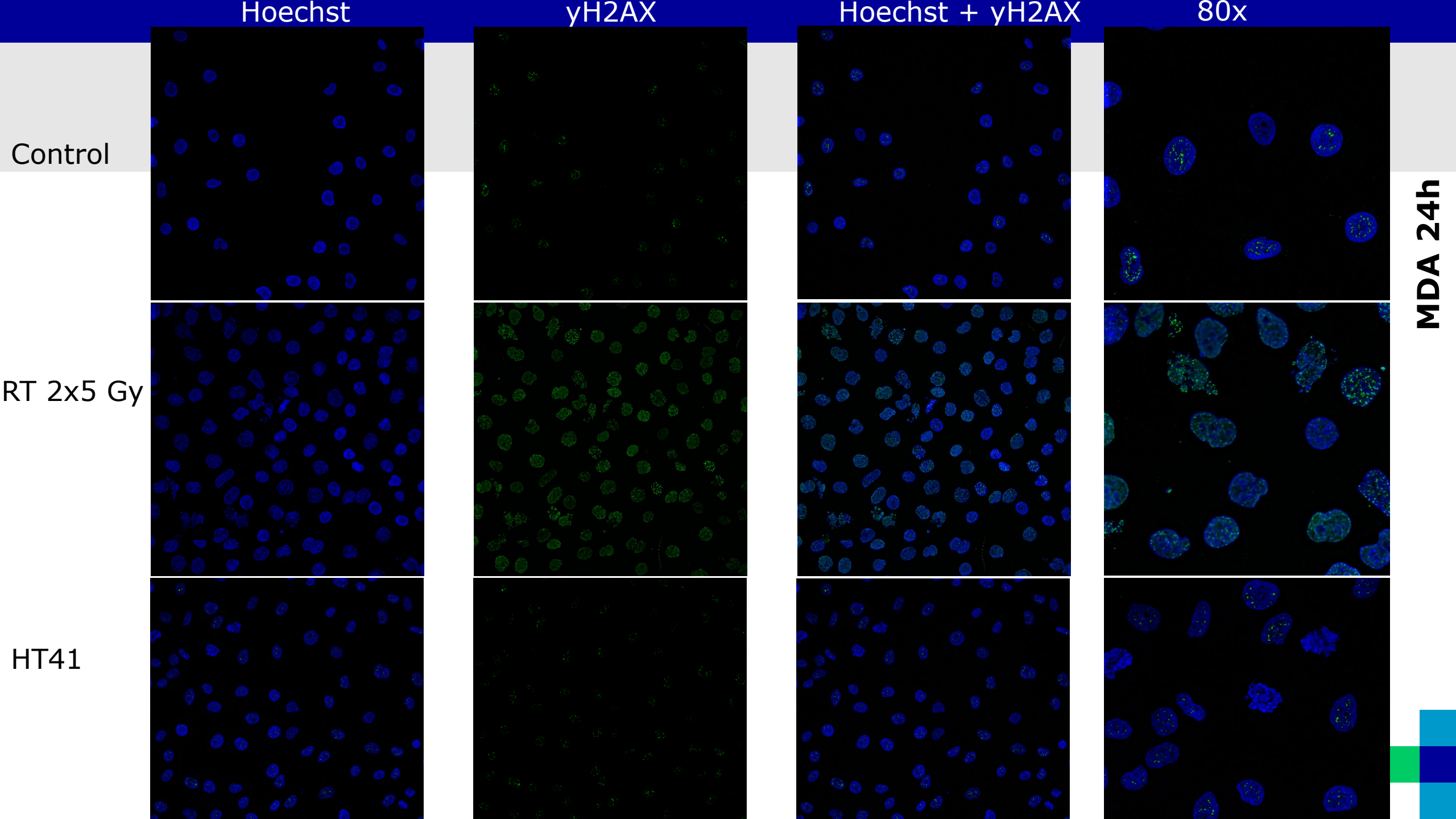

Hoechst
yH2AX
Hoechst + yH2AX
80x
Control
RT 2x5 Gy
HT41
MDA 24h

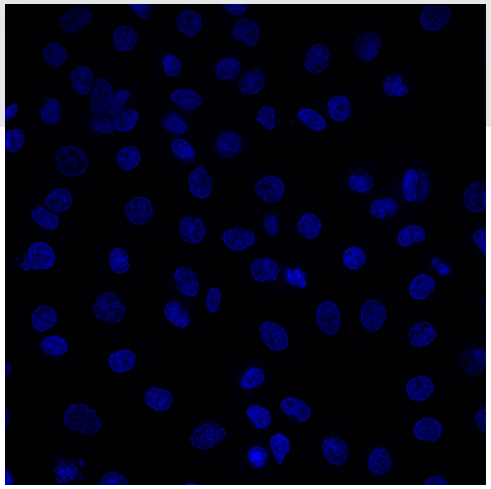
Hoechst

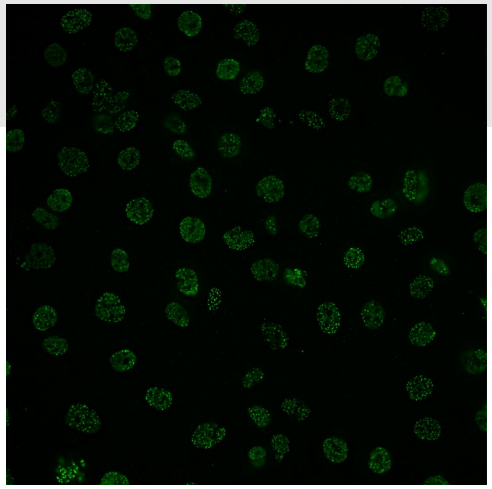
γH2AX

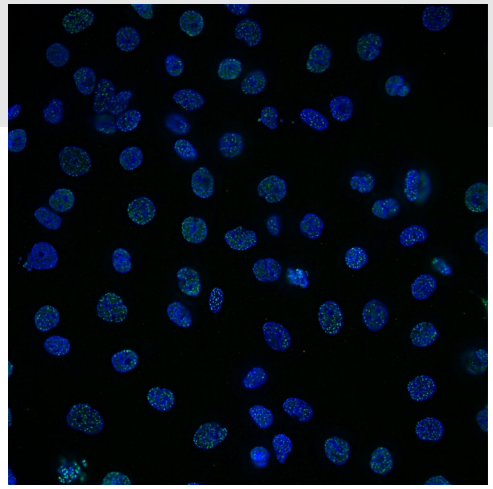
Hoechst + γH2AX

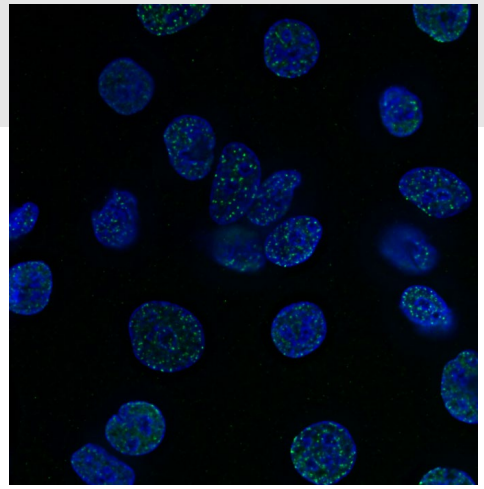
MDA_MB_231 24h

RT+41

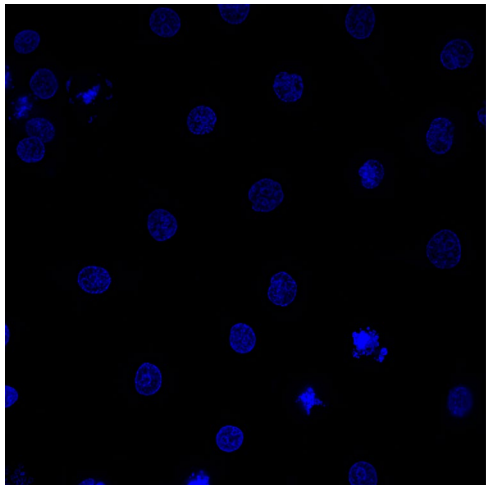


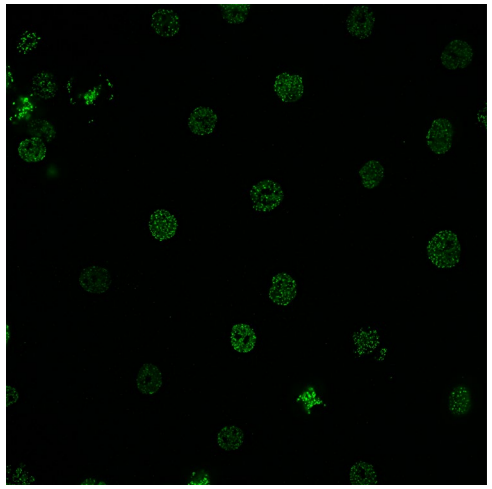


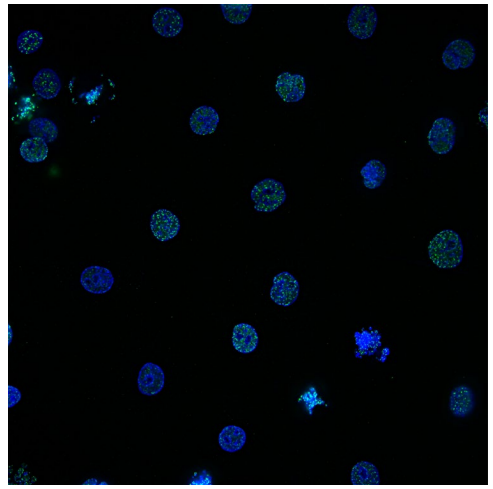


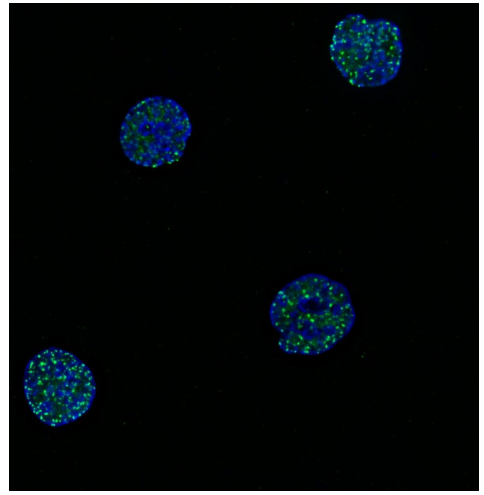


HT41+RT









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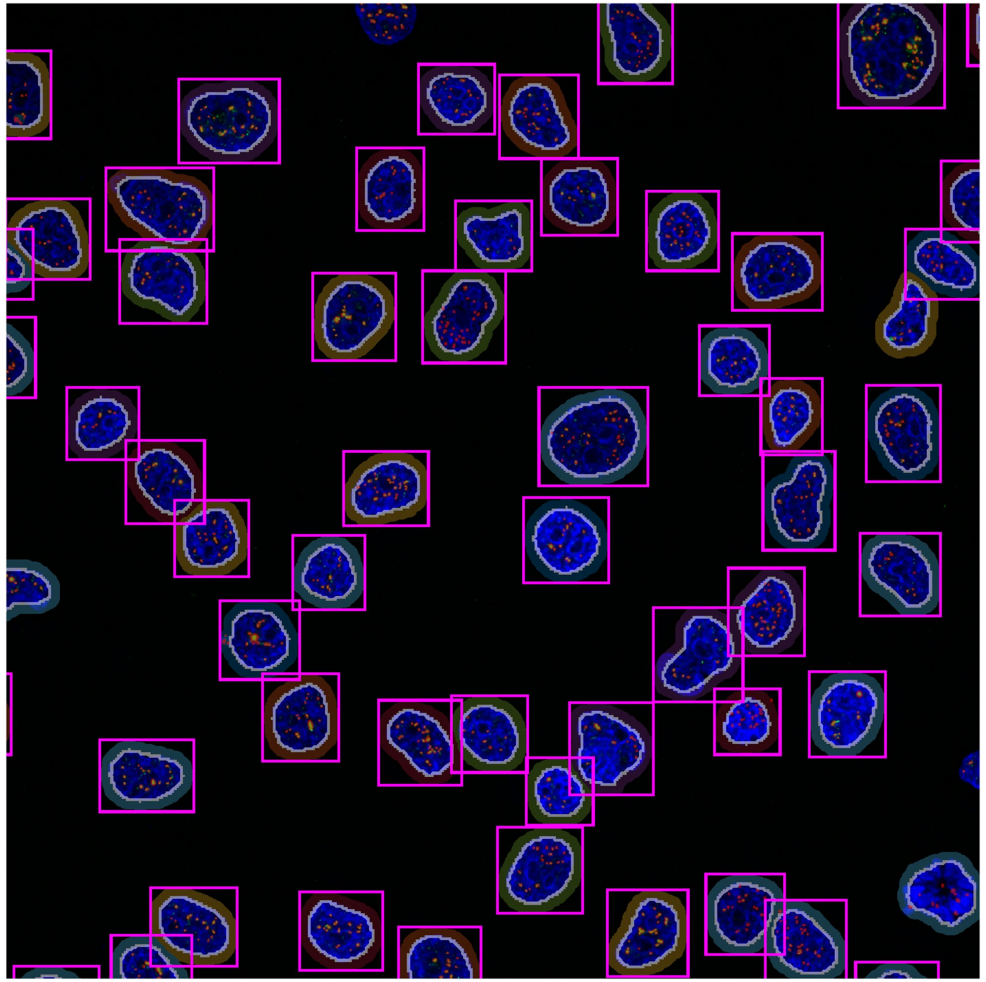
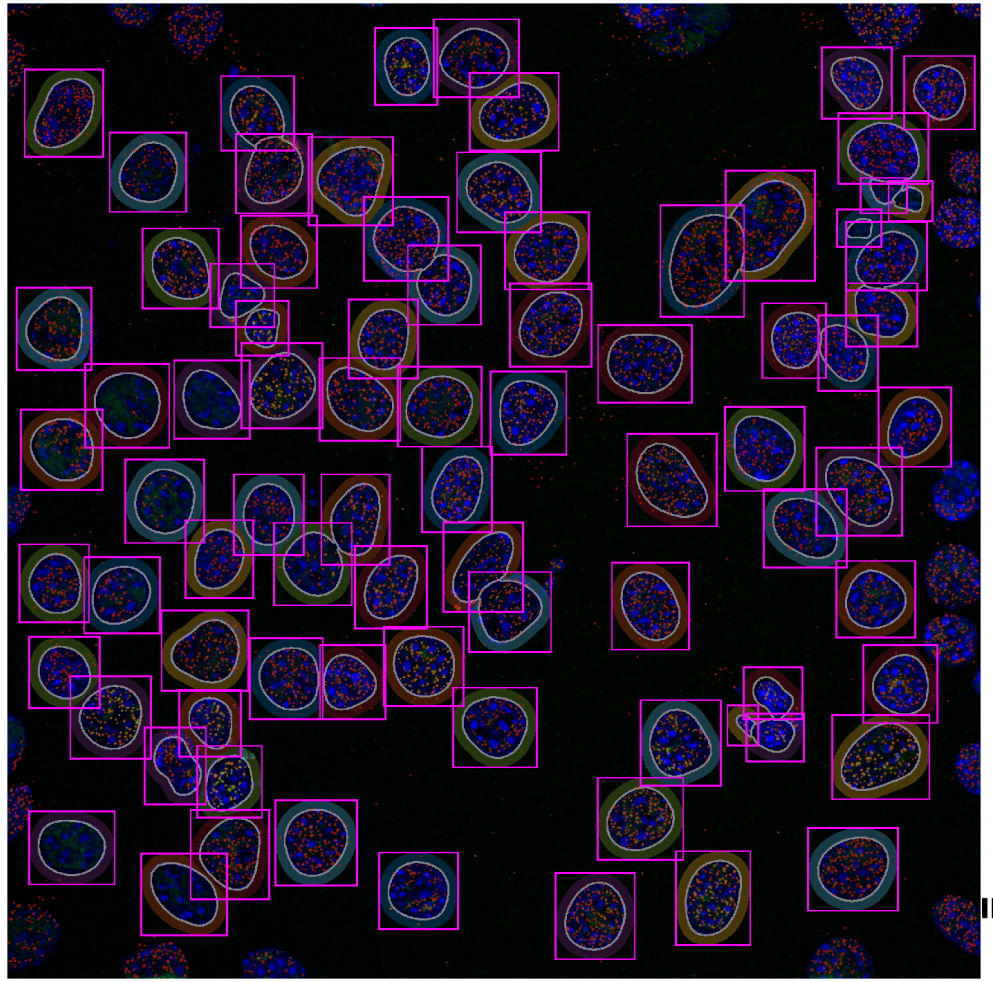
yH2Ax foci count using CI Imaging

Around 3000 cells from each condition of each cell line (3000*3*5= 45000)

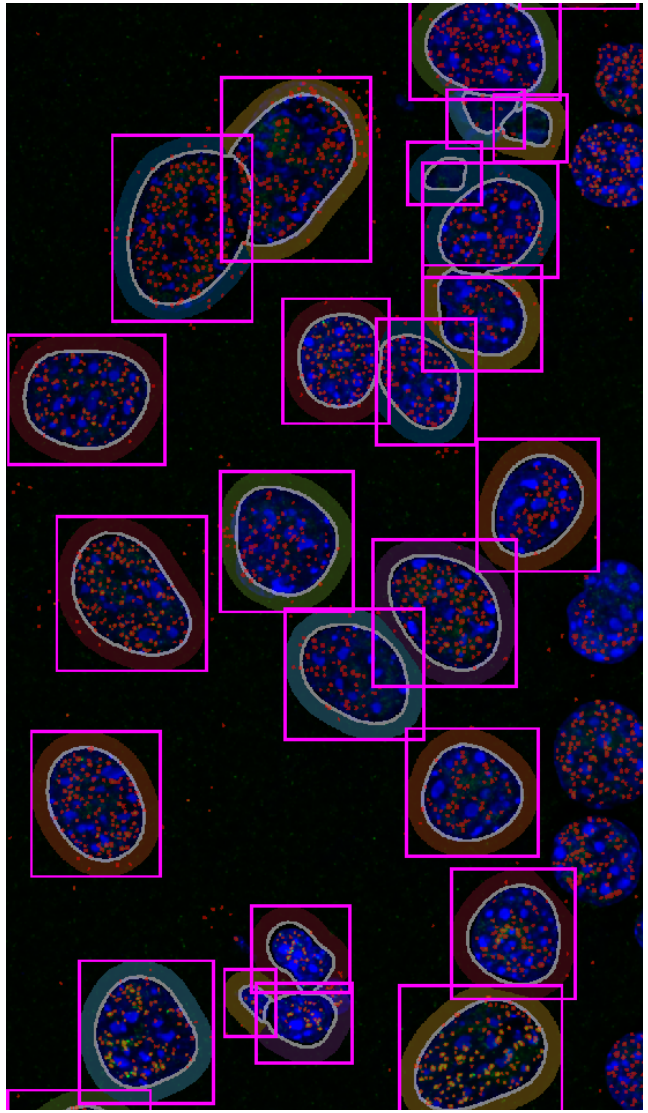
- MDA-MB-231 (human breast cancer cells)



- 4T1 (mouse breast cancer cells)



yH2AX foci detection steps

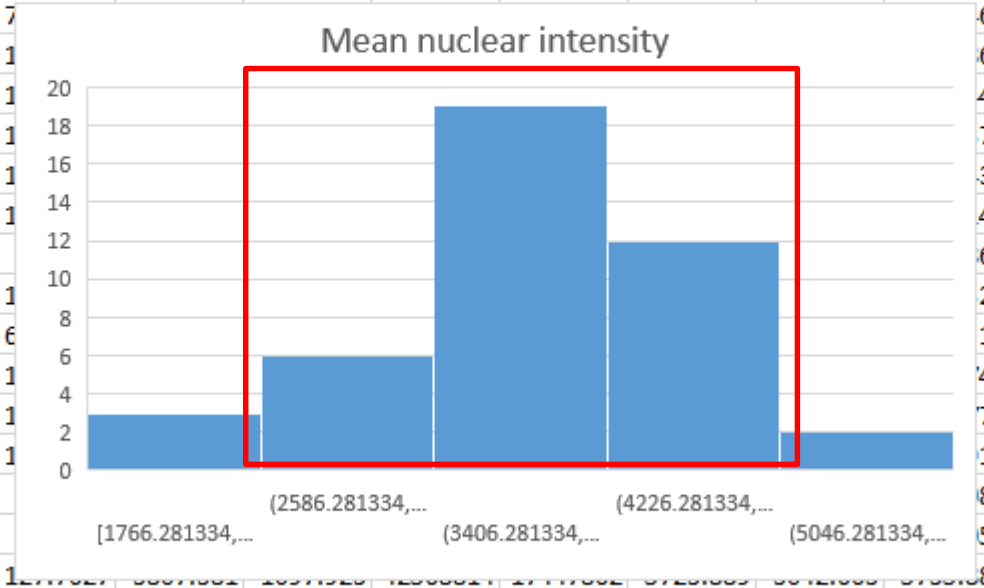


After the CI Imaging analysis

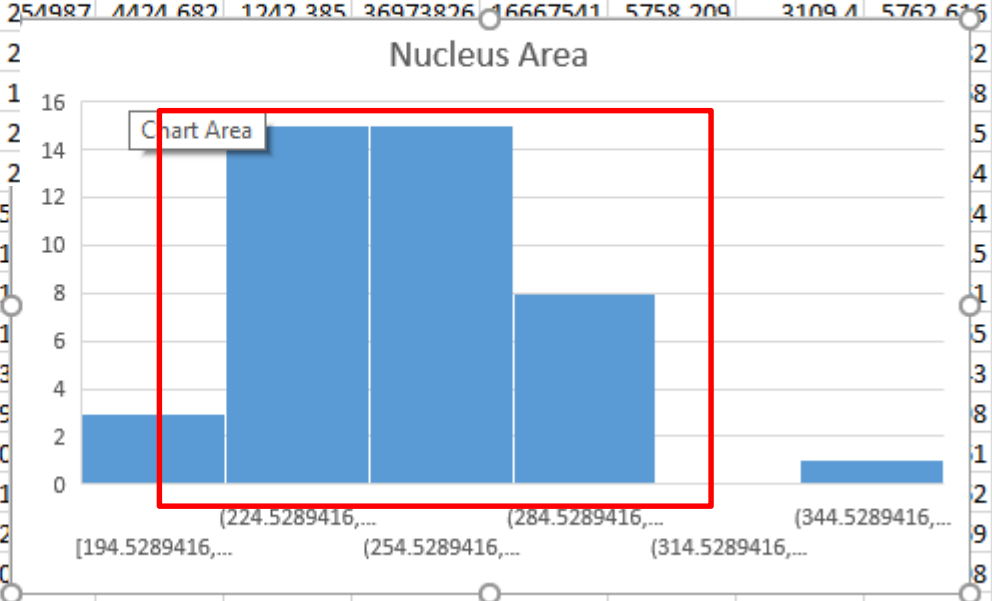
The results were sorted according to their size and intensity

Small and low intensity nucleus were filtered out from the result

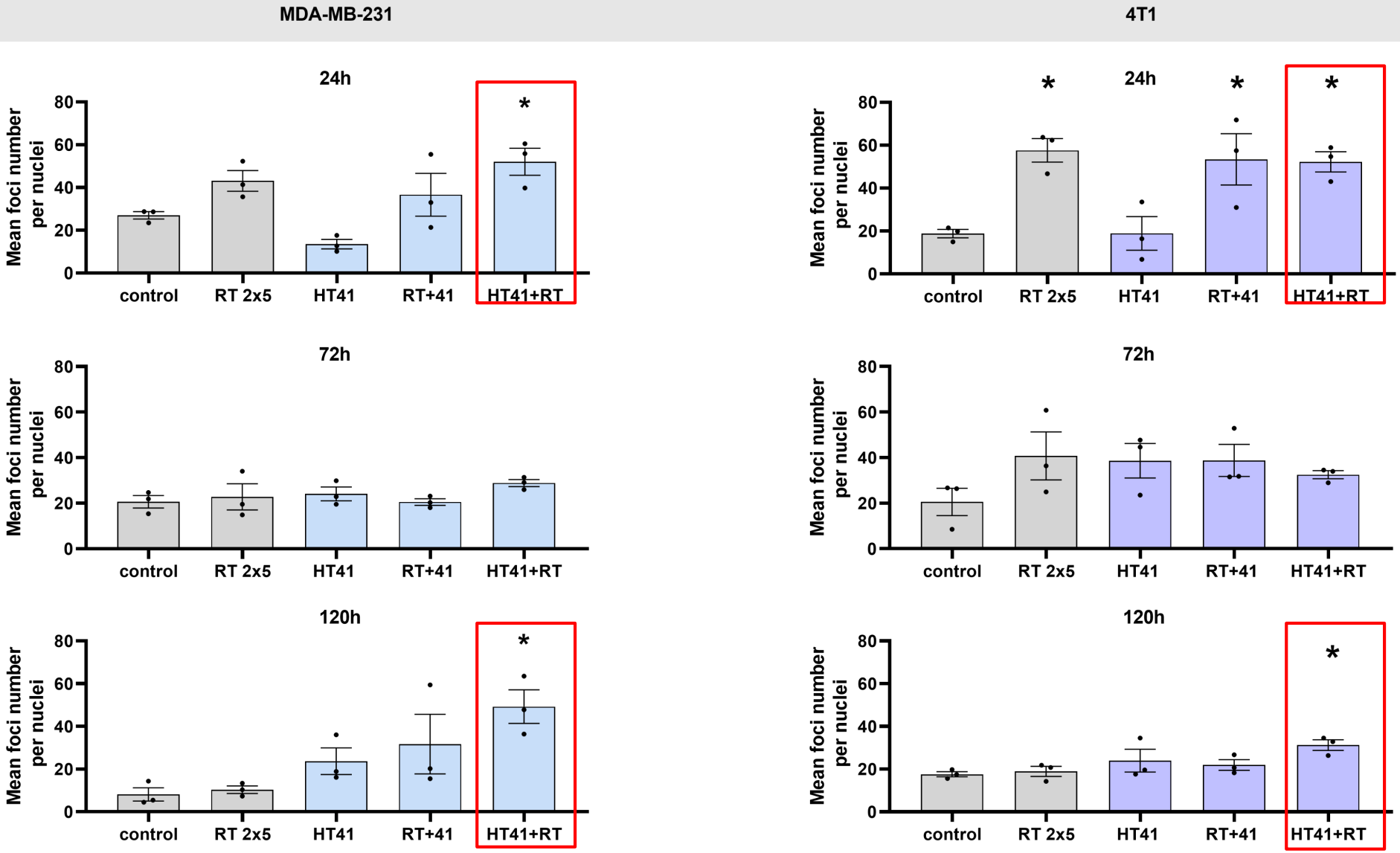
MeanCytc	StdCytopl	MeanNucl	StdNucleu	MeanNucl	StdNucleu	MeanNucl	StdNucleu	MeanCell	StdCellInt	MeanNucl	StdNucleu	M
74.36765	47.9794	354.3687	219.9657	1766.281	1413.747	21595092	23440952	5408.961	3001.853	5404.912	3010.553	1
103.7744	36.61373	270.0369	140.9006	2050.524	862.444	24004009	17720594	5319.216	3033.165	5303.984	3047.973	1
124.2173	11.95979	269.4689	35.8121	2490.151	648.8529	25303640	6970965	5593.25	2945.127	5600.177	2953.355	2
126.9339	18.32233	284.805	73.71294	2808.581	790.1255	29335241	7372152	5618.937	2966.651	5626.968	2974.67	2
113.2551	24.77909	248.415	7							61	2984.189	2
105.8503	36.38203	262.7839	1							61	3018.41	1
108.5838	33.66202	270.6705	1							48	3015.405	1
115.5304	35.34045	267.4073	1							77	2964.087	2
121.3577	35.78607	287.001	1							36	3079.928	2
105.9103	32.41018	264.2082	1							48	2985.424	2
107.7414	26.27238	250.4784								62	2933.979	
114.0687	31.88814	290.002	1							21	2977.239	2
107.7874	20.35246	229.902	6							15	2990.942	1
131.0382	30.88306	304.2553	1							43	3171.788	245913
105.4771	32.41497	273.1612	1							77	3025.432	37121
109.6013	25.81225	237.9076	1							15	3002.396	12.6511
104.2941	27.04193	262.3597								86	3028.376	19.6463
109.5526	28.49642	263.5783								51	3065.022	254987
118.6719	28.44526	309.979	12							81	3057.691	2
121.8959	28.98967	284.6851	185.5495	3809.672	993.6726	39810686	25176891	5341.665	3004.946	5326.464	3019.722	1
113.3223	22.77365	246.214	89.49371	3850.226	944.1455	35226325	13744396	5630.925	2986.486	5638.798	2994.724	2
122.6618	24.95813	281.9606	104.5613	3898.273	779.9585	40043950	13915817	5482.359	3204.267	5496.179	3216.989	2



46	92.81209	102.0391	15.54758	233.8355	85							
89	135.1777	109.6013	25.81225	237.9076	11							
69	139.6266	105.5424	32.0903	240.4645	11							
94	135.8443	101.7084	30.26901	240.811	11							
78	153.8343	95.89916	35.75793	243.0086	13							
62	109.8803	113.3223	22.77365	246.214	89							
01	93.40607	113.2551	24.77909	248.415	70							
98	132.0064	107.7414	26.27238	250.4784	1							
79	147.0548	109.8193	27.87183	253.7597	12							
71	130.2567	110.7021	26.12584	254.5689	10							
65	102.73	122.1747	19.68143	256.5019	85.25887	4150.995	1498.966	39185096	16585813	5624.316	2931.59	5631.32
38	182.9422	104.2941	27.04193	262.3597	168.965	3664.512	1199.085	36393076	24802128	5351.405	3013.681	5336.086

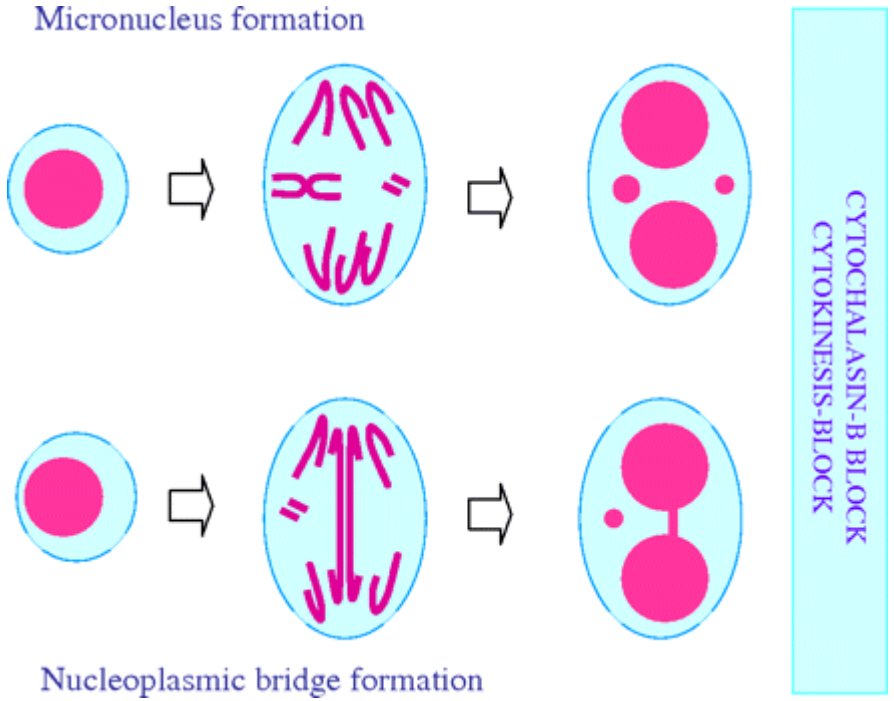


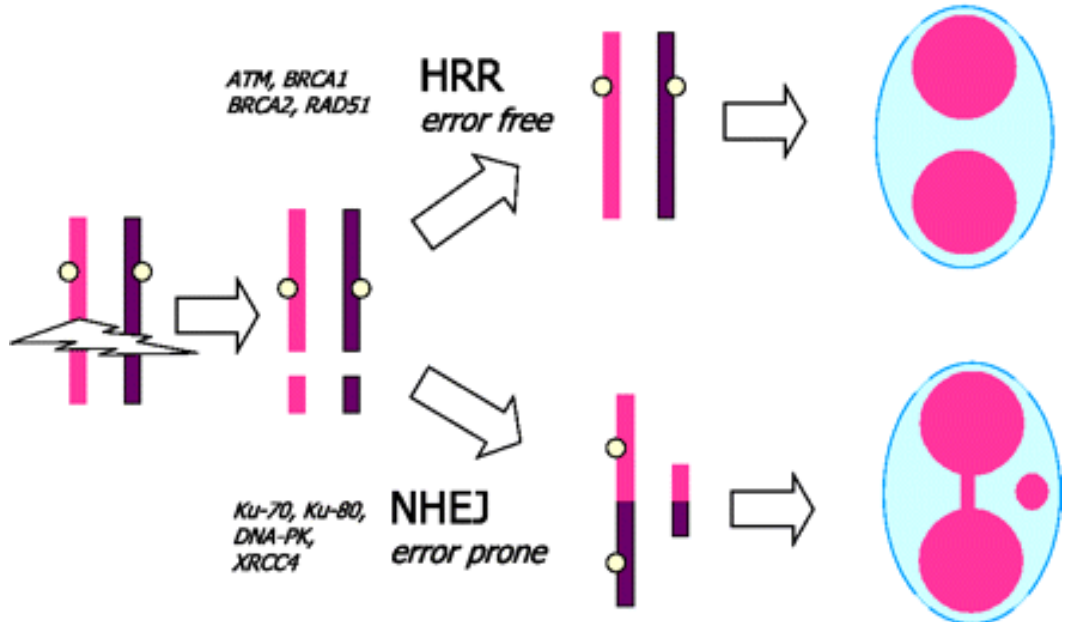
The mean number of DSB foci per nuclei after HT and RT



HT first combination impairs DNA damage more significantly, thus DNA damage repair was significantly delayed in the later timepoint for HT+RT

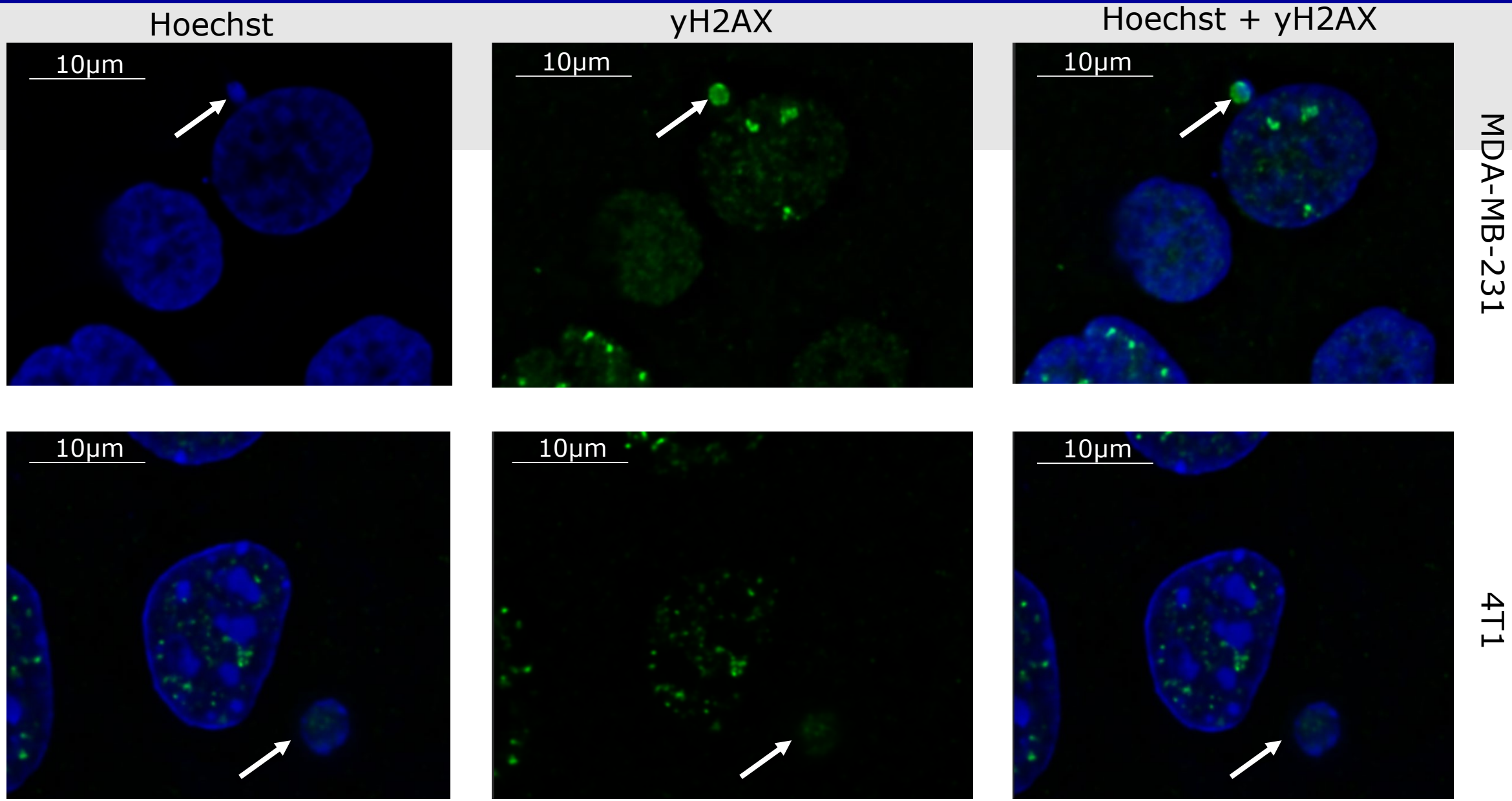
MECHANISM OF MICRONUCLEI





* *Mutagenesis*, Volume 26, Issue 1, January 2011, Pages 125–132, https://doi.org/10.1093/mutage/geq052

yH2AX detection



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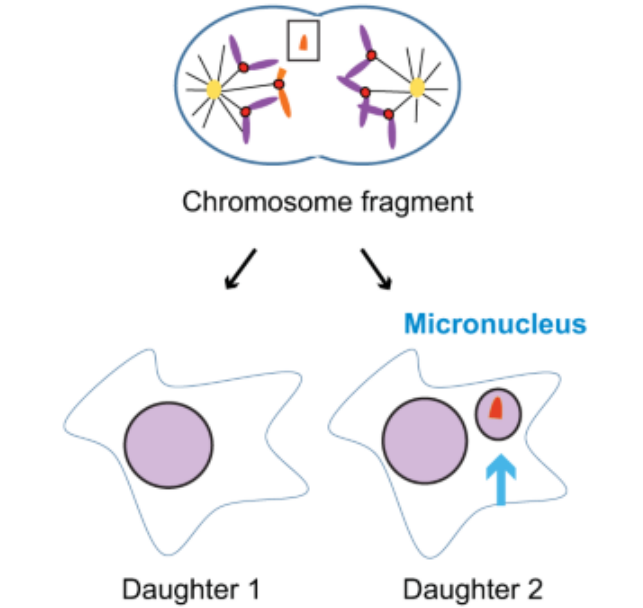
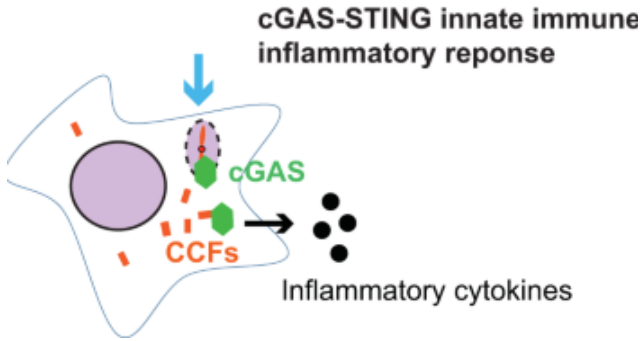
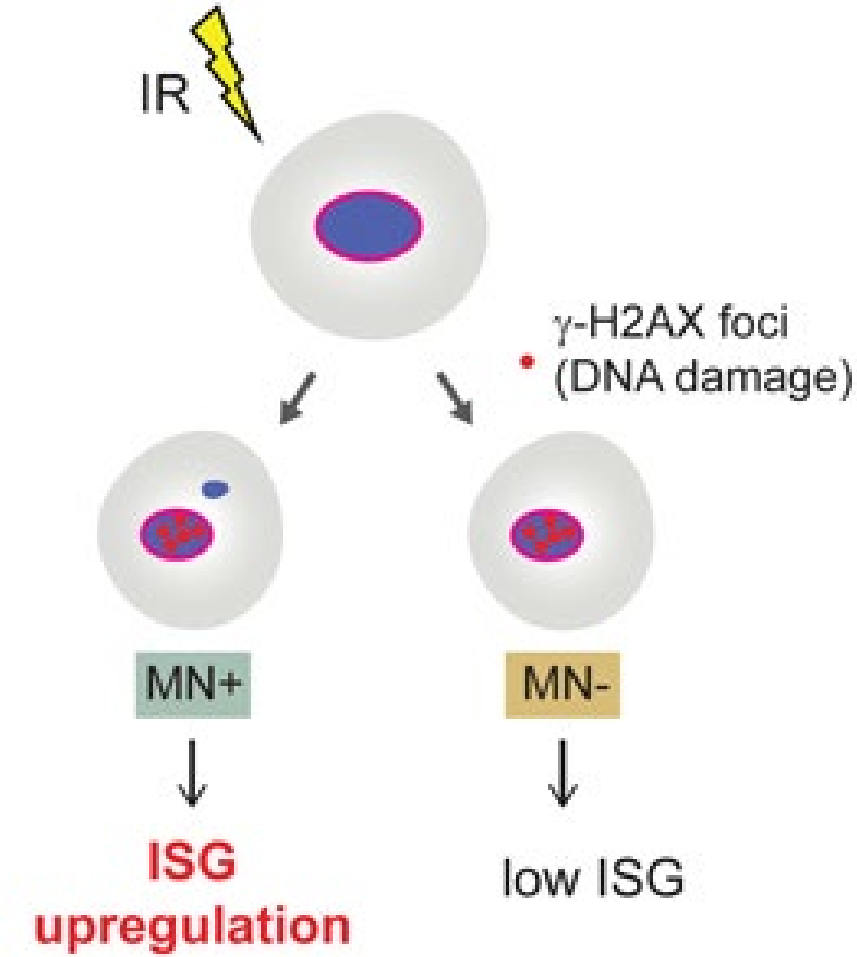
How does the MN affect the immune system?







Kwon, M., Leibowitz, M.L. & Lee, JH. Small but mighty: the causes and consequences of micronucleus rupture. *Exp Mol Med* **52**, 1777–1786 (2020). https://doi.org/10.1038/s12276-020-00529-z

*Jiang H, Panda S, Gekara NO. Comet and micronucleus assays for analyzing DNA damage and genome integrity. *Methods Enzymol*. 2019;625:299-307. doi:10.1016/bs.mie.2019.05.015

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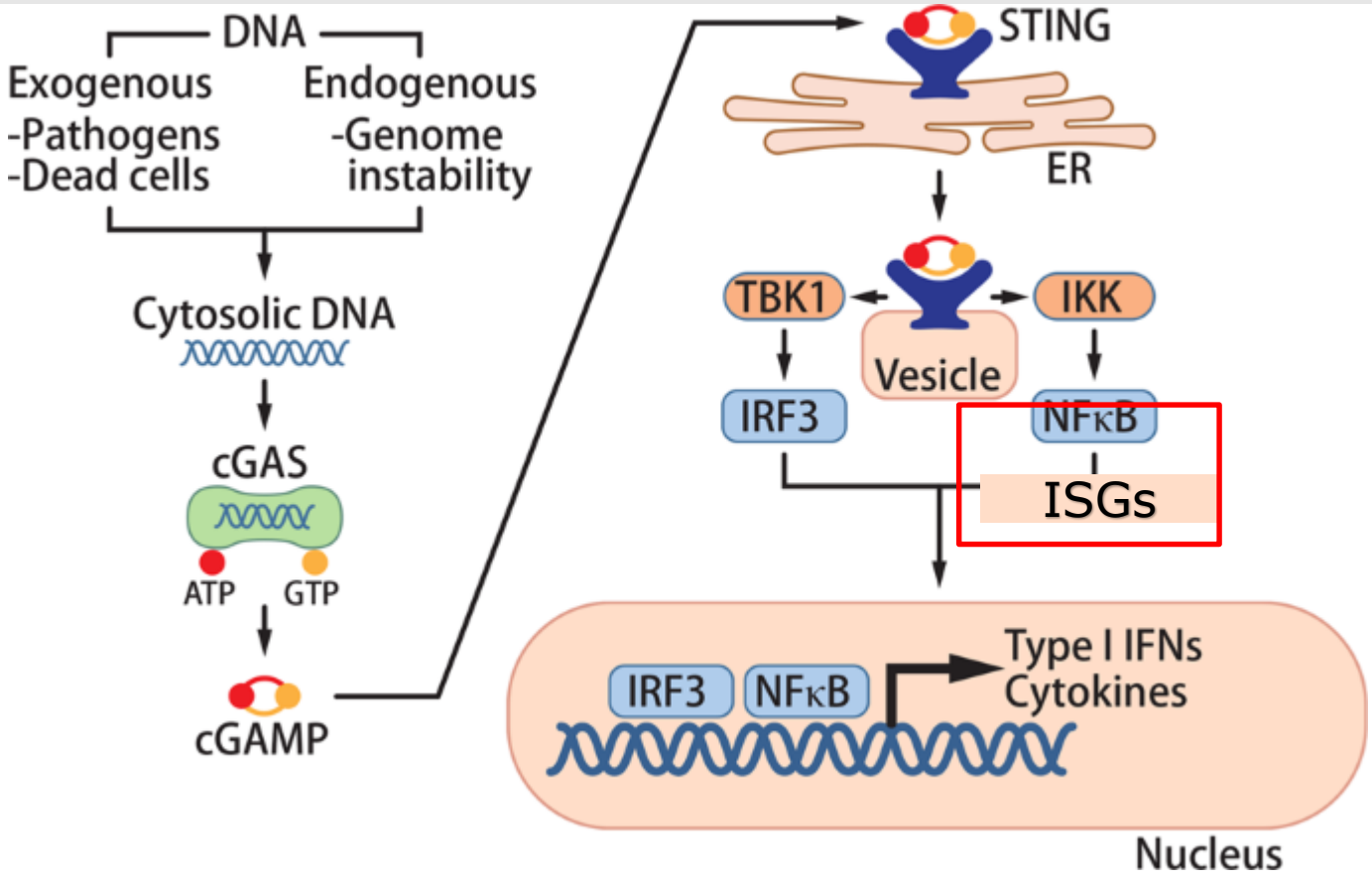
How does MN affect the ICM expression?



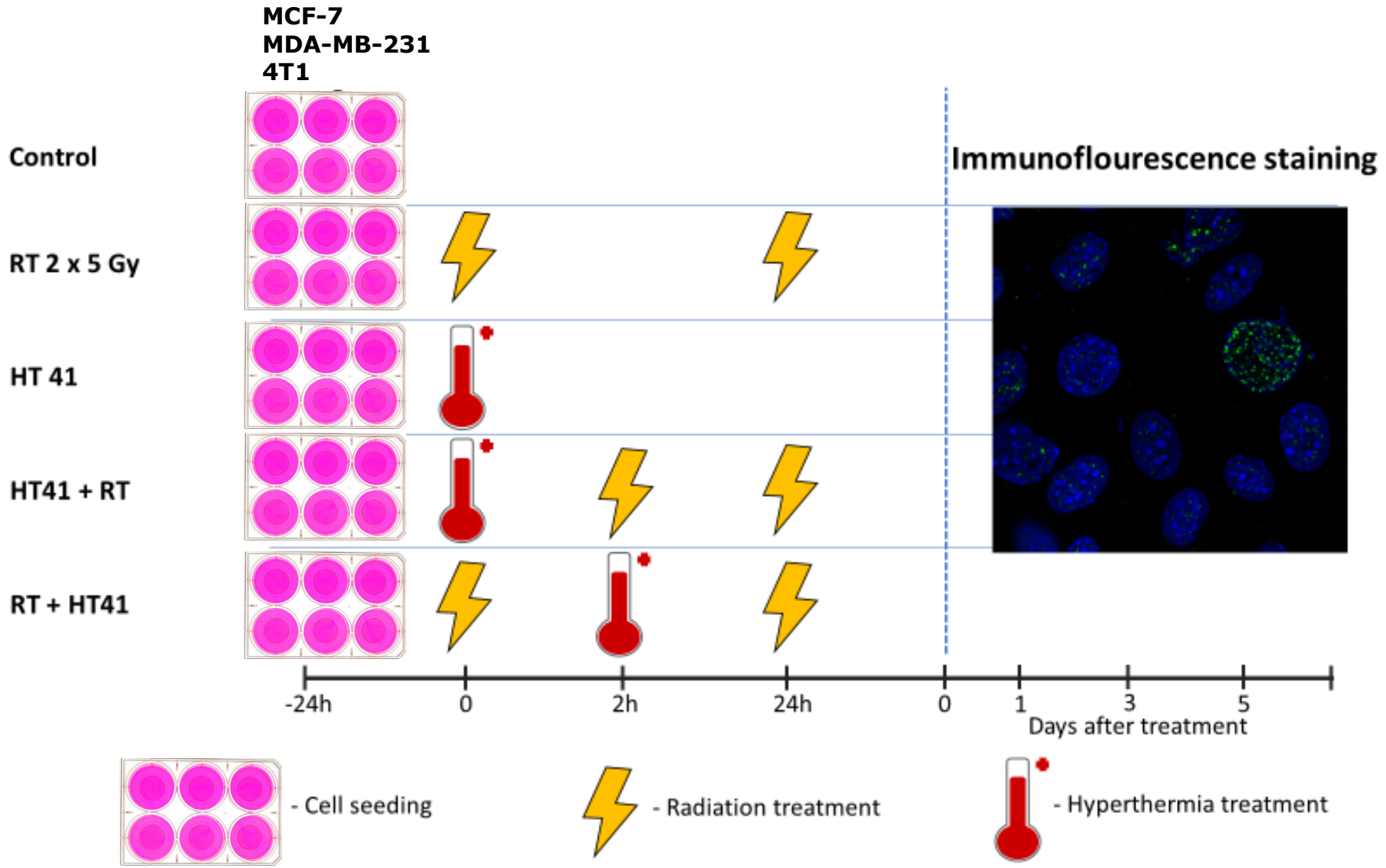
Long exposure of IFN1 exhaust immune cells and promote ICMs expression

PD-L1 and PD-L2, is induced by both Type I and II IFNs

IFNγ induce expression of PD-L1 through activation of JAK/STAT3 and PI3K/AKT pathways

Saleiro D, Platanias LC. Interferon signaling in cancer. Non-canonical pathways and control of intracellular immune checkpoints. Semin Immunol. 2019 Jun;43:101299. doi: 10.1016/j.smim.2019.101299. PMID: 31771762; PMCID: PMC8177745.

Micronuclei detection

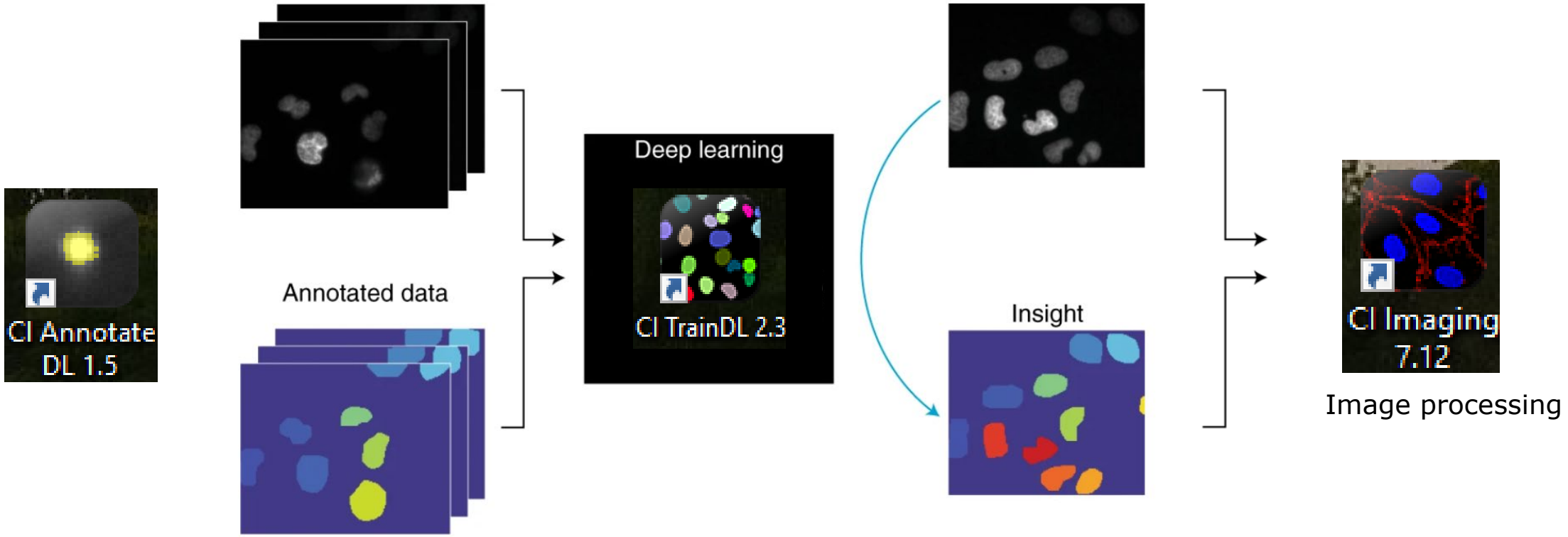


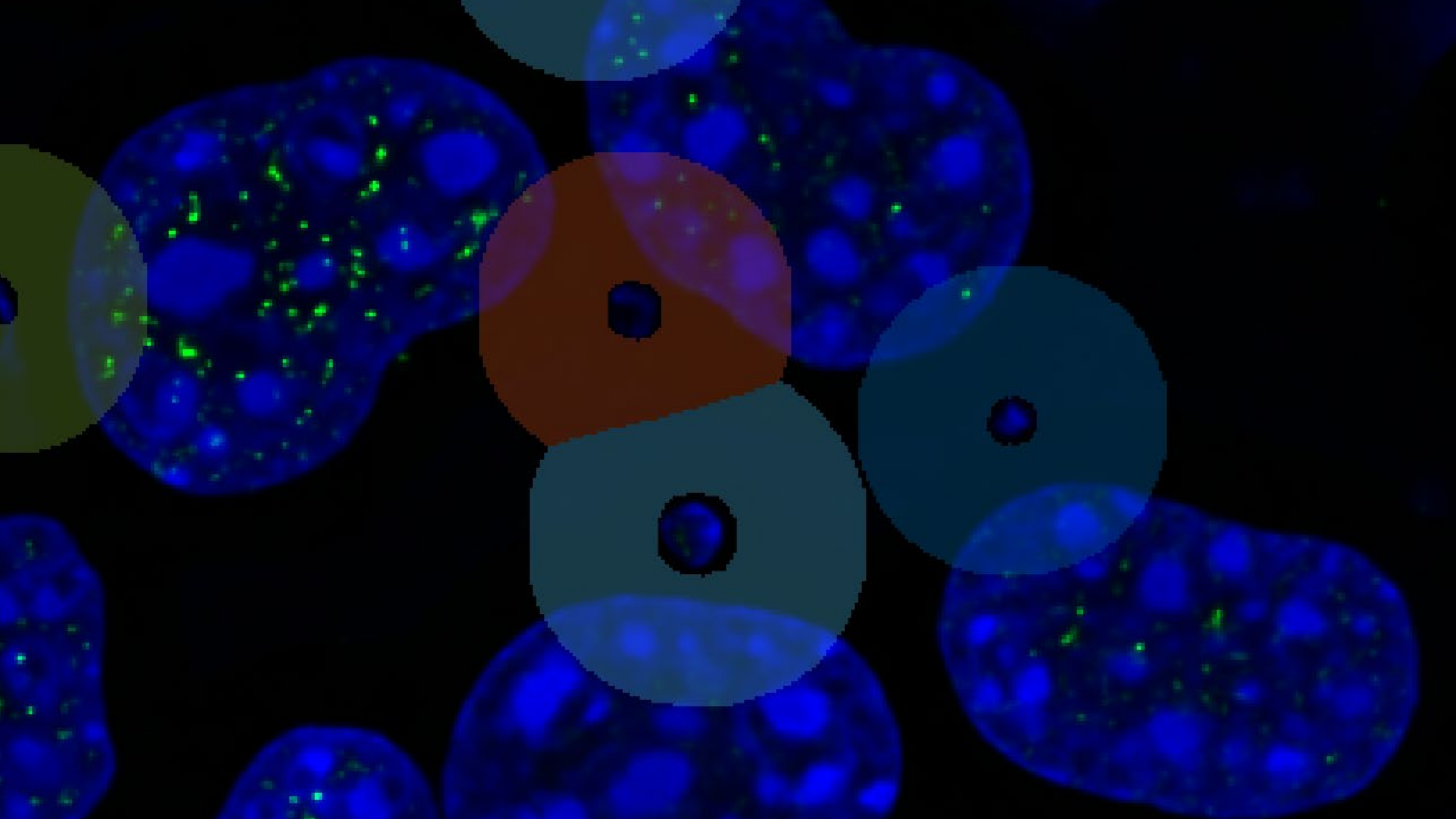
- Timepoints 24h, 72h , 120h
- Detection of micronuclei formation with Hoechst
- MDA-MB-231 MCF-7 and 4T1 cells

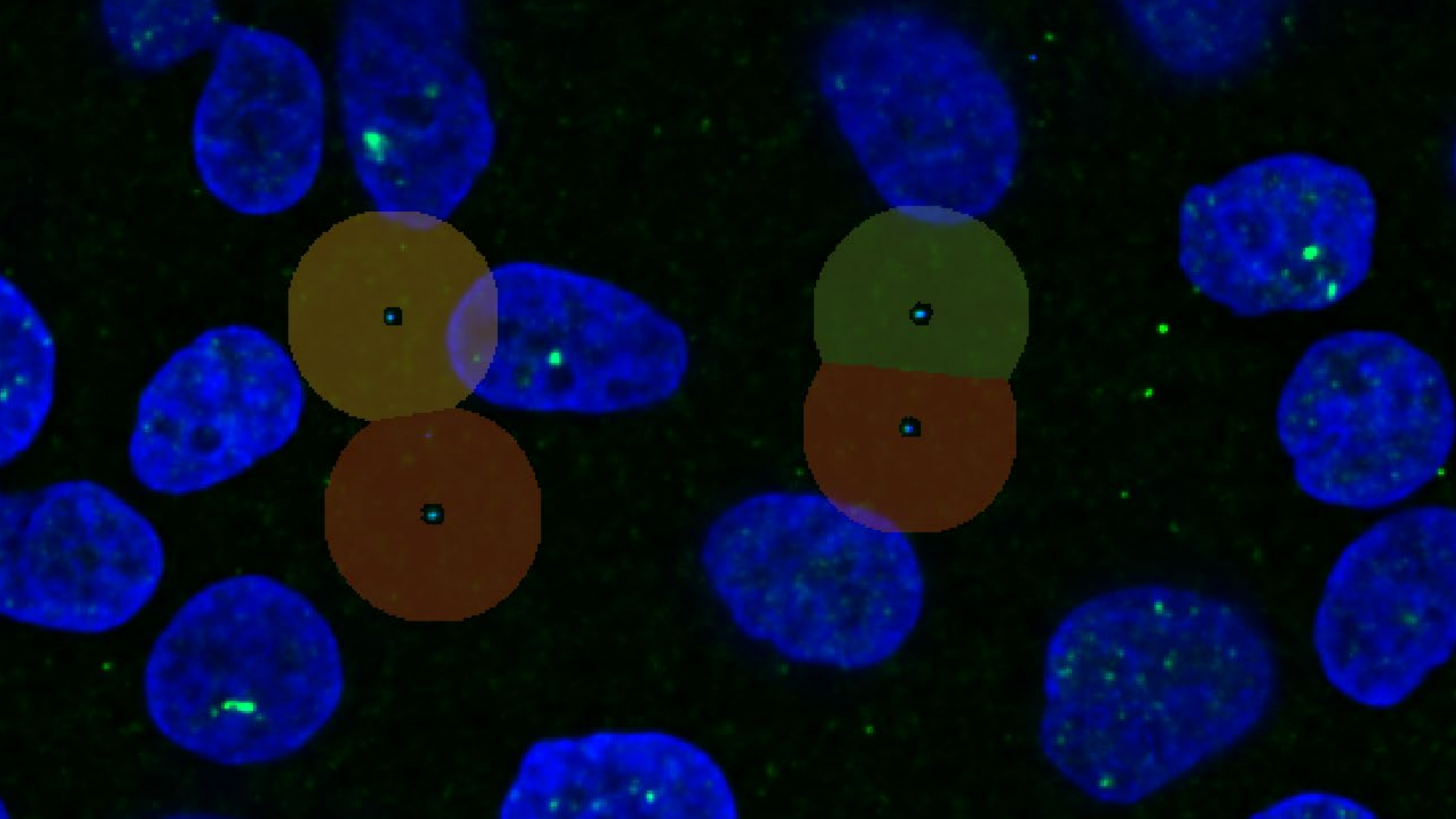
Using Deep Learning tools for Micronuclei detection

- Training new Deep learning model for MN detection
- Creating annotated dataset
- DL training
- New model is used for detection in CI Imaging

Using Deep Learning tools for Micronuclei detection







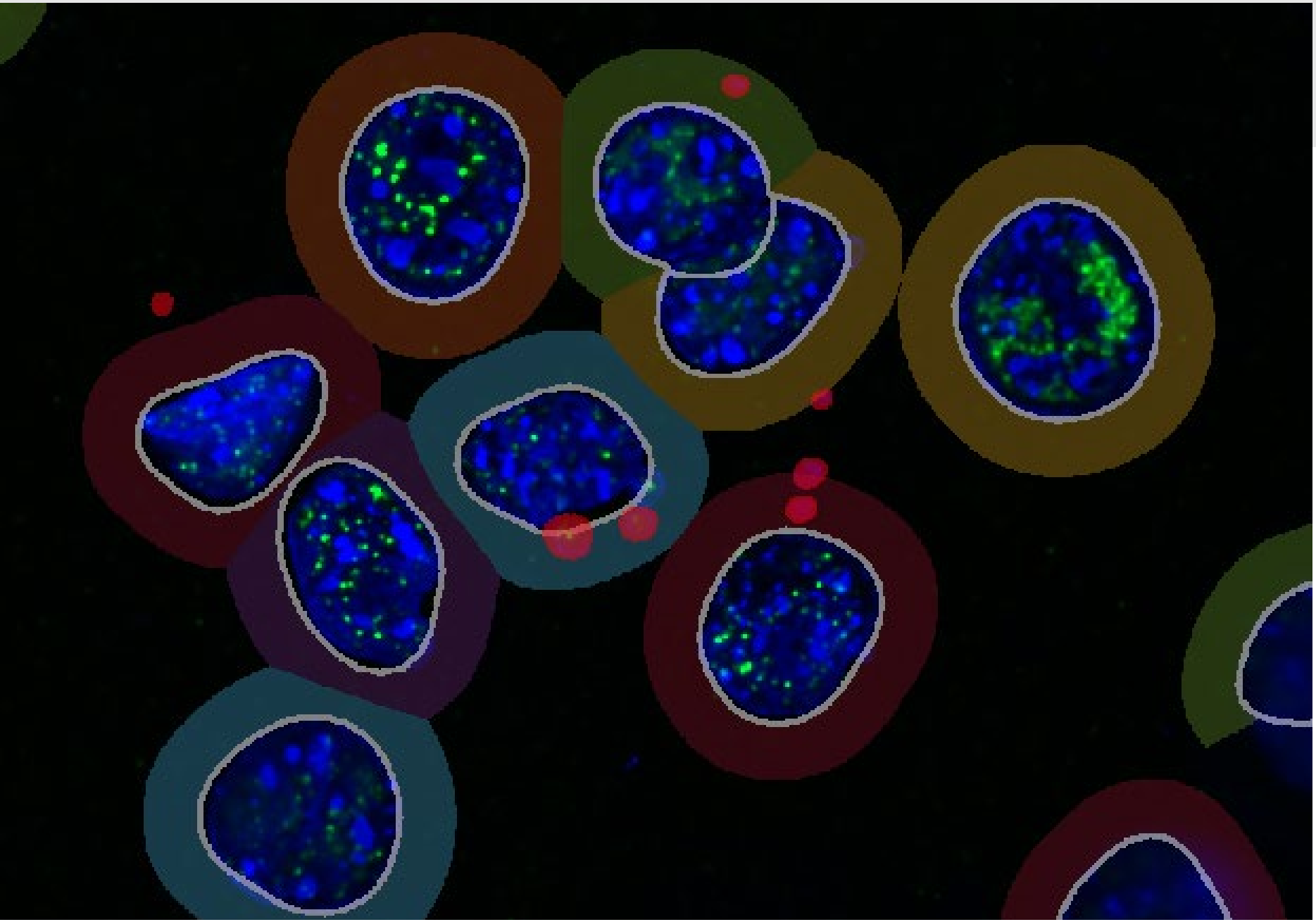
Micronucleus Training

- MDA-MB-231 cell line

- Plus side – apoptotic blebs are not considered as Micronuleis
- Minus side – sometimes less intensity parts are counted as MNs

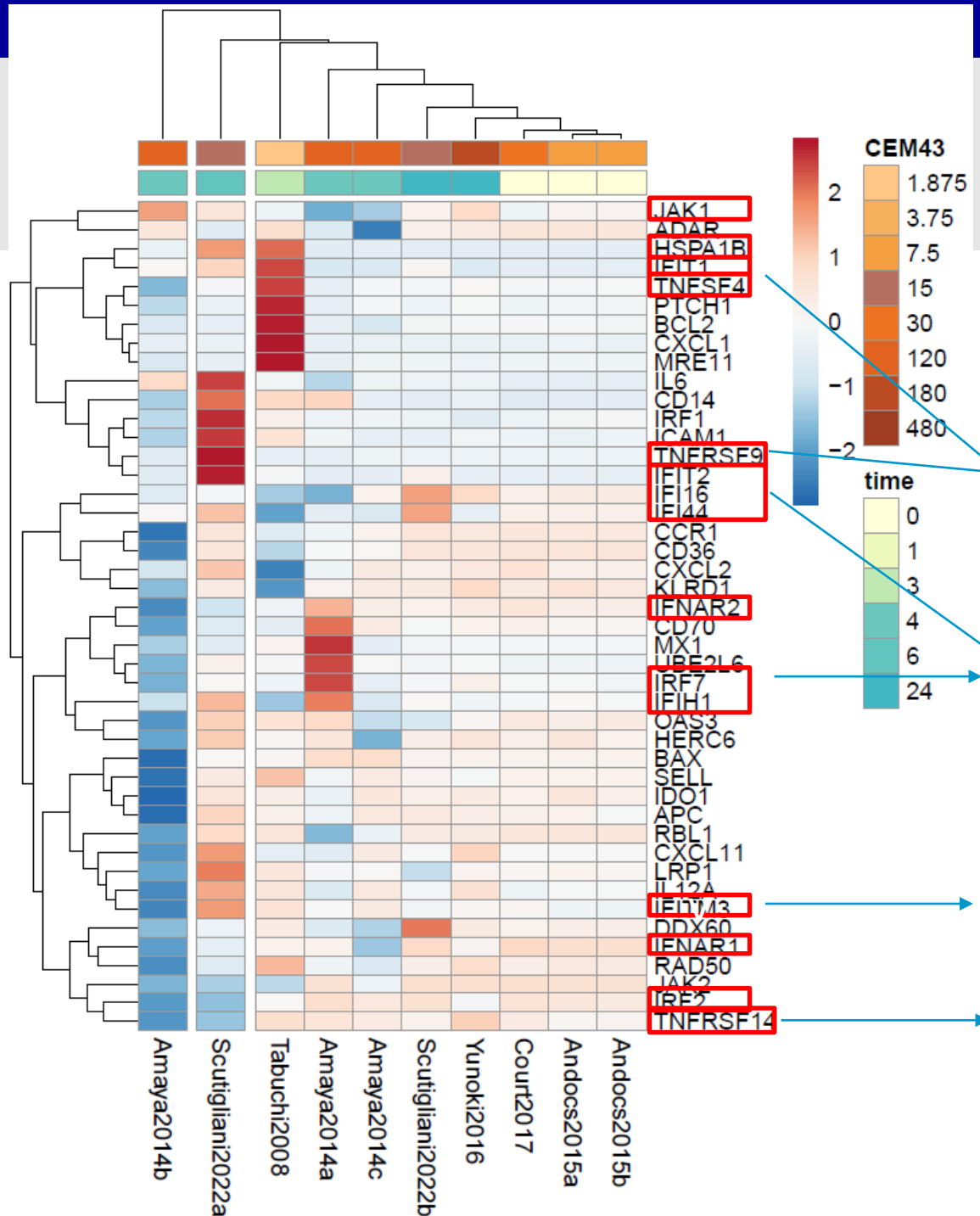
- 4T1 cell line

- Plus side- hyperchromatic regions inside the nuclei are not consideres as MNs anymore
- Minus side – sometimes less intensity parts are counted as MNs



Under process…

Heat map showing fold change of immune related gene expression after hyperthermia treatment



Tumor necrosis factor receptor genes

Interferon regulating factors

Interferon stimulating genes

HVEM

Genes that are responsible for broad immune processes, specifically interferon stimulating genes were upregulated

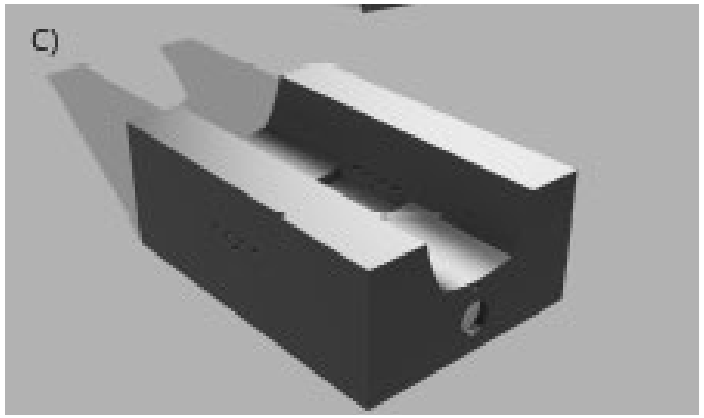
M.Sc. Enzo Scutigliani
Amsterdam UMC, The Netherlands

Amsterdam UMC

Universitätsklinikum Erlangen

NEW MICROWAVE APPLICATOR EXPERIMENT

M.Sc. Benjamin Kahlert
Strahlenklinik,Universitätsklinikum Erlangen



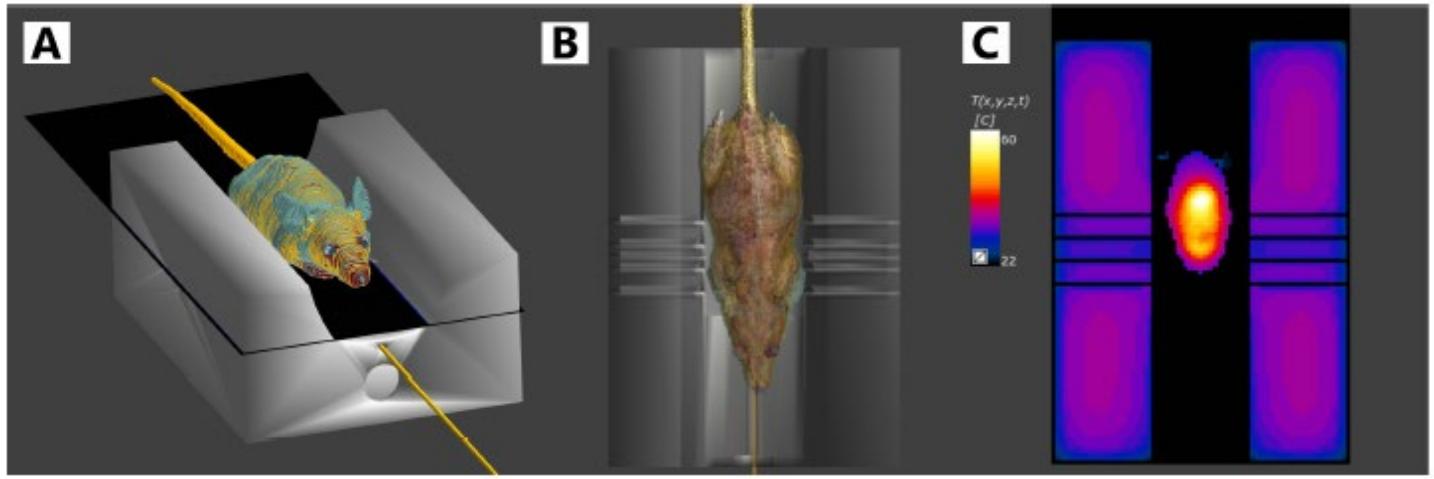


Figure 44: A) Side view of mouse in applicator and shown temperature plane. B) Top down view used in C) for temperature profile.

Conclusion and future plans

- HT combined with RT, in particular when HT is applied before RT it significantly induces more DNA damage, and furthermore impairs DNA damage repair system of cancer cells
- HT combined with RT also affects the expression of immune checkpoint (IC) molecules, this can be explained by different pathways but most significant pathway is cGAS-STING pathway
- The role of Micronuclei formation and how it is activates cGAS-STING pathway and furthermore immune response is under investigation
- Microwave heating applicator for mice is under development, further *in vivo* experiments will be done with this heating method
- Experiments in breast cancer organoids are being considered in the near future

Training experience within the network

- Collaborative work with Dr. Sennewald Medizintechnik, to optimize a microwave hyperthermia applicator for **in vivo** experiments
- Collaborative work with **ESR1**, Amsterdam University Medical Centers, to define immune parameters after HT and RT treatments and DNA damage induced by HT and RT
- Occasional meetings within hyperboost community

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

HYPERBOOST

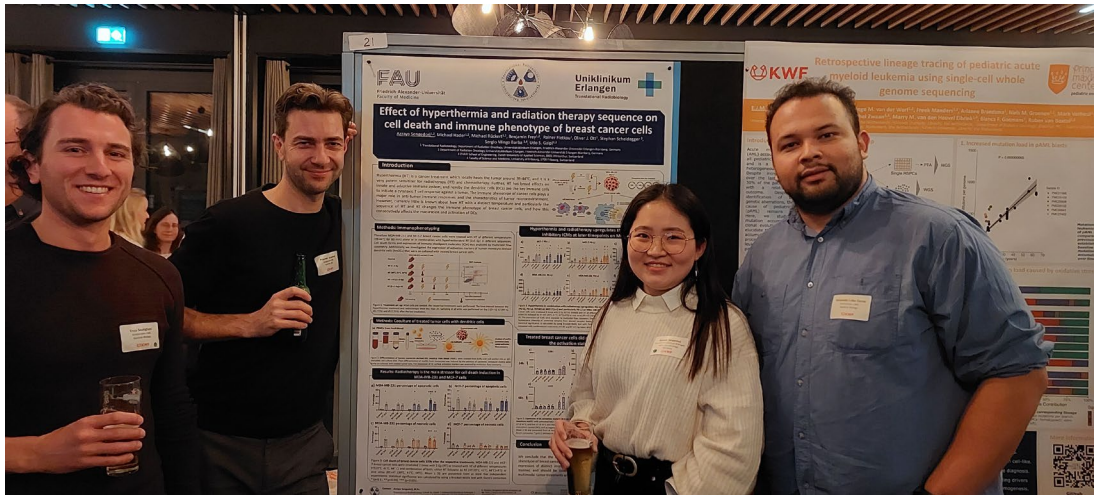
Amsterdam UMC

Universitätsklinikum Erlangen

Thank you for your attention

Translational Radiobiology
Prof. Udo Gaipl

Medical Biology, Amsterdam UMC
Dr. Przemek Krawczyk



@translatradbio

www.strahlenklinik.uk-erlangen.de

Azzaya.Sengedorj@uk-erlangen.de
Udo.Gaipl@uk-erlangen.de

Amsterdam UMC

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HYPERBOOST

Boosting the effect of Radiotherapy

The use of survival dose-rate dependencies as theoretical discrimination criteria for in-silico dynamic radiobiological models

ESR: Sergio Mingo Barba
PI: Prof. Dr. Stephan Scheidegger

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 955625. This website reflects only the author's view and the European Commission is not responsible for any use that may be made of the information it contains

Objectives of the project

WP4 goal: Develop a biological Treatment Planning System (TPS) for RT+HT.

ESR5 contribution: Radiobiological models

Model-based data analysis of tumor response to RT+HT (focus on cellular level, but with MHR model that can be linked to the cell population model → tissue / tumour ecosystem dynamics!)

↓

Identification of key processes observed by preclinical and clinical results as well as in silico studies on different scales (**cellular**, tissue, immune system).

↓

Evaluating and establish a mathematical model which can be integrated into a RT+HT biological Treatment Planning System .

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Boosting the effect of Radiotherapy

Aim of radiobiological models

	Predictive (survival)	Systems Biology Approach
Aim	Only interested in the end-point	Understand biological effects evolution
Dynamical models	No	Yes
Study scenarios out of the calibration range	No	Yes (NOT prediction, but helps to understand!)
Complexity	Simplified	More complex
Computation speed	Fast	Slow

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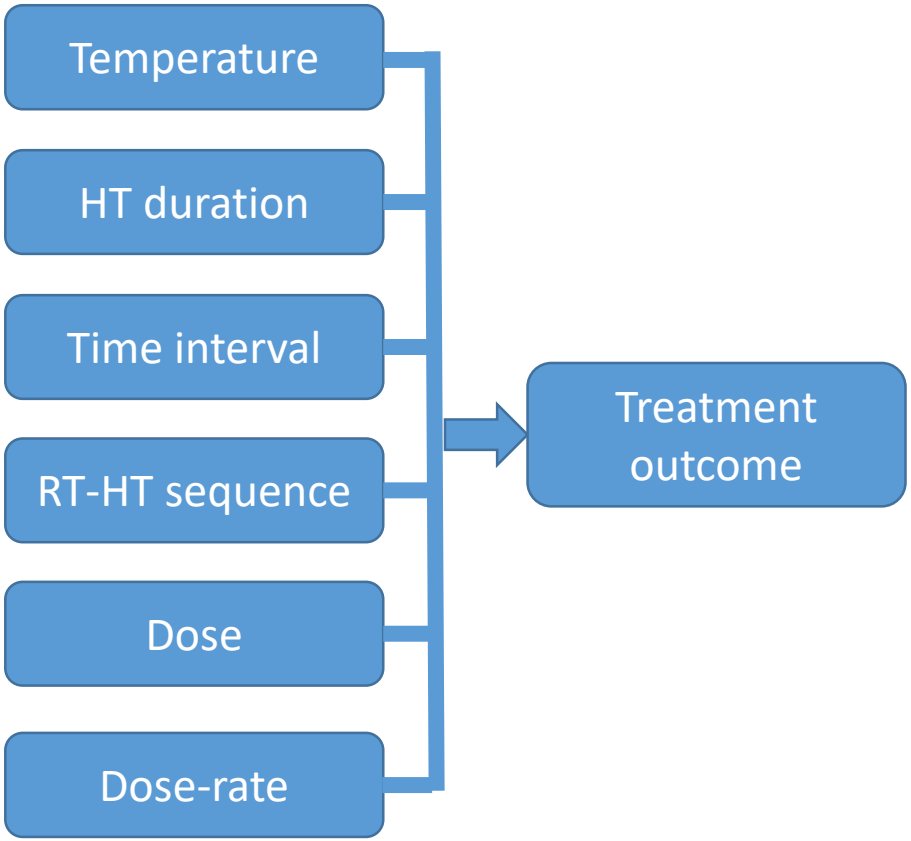
Why do we need in-silico models?



Treatment optimization (schedule, dose, etc.)

↓

Understand the effect of each variable

↓

Radiobiological models

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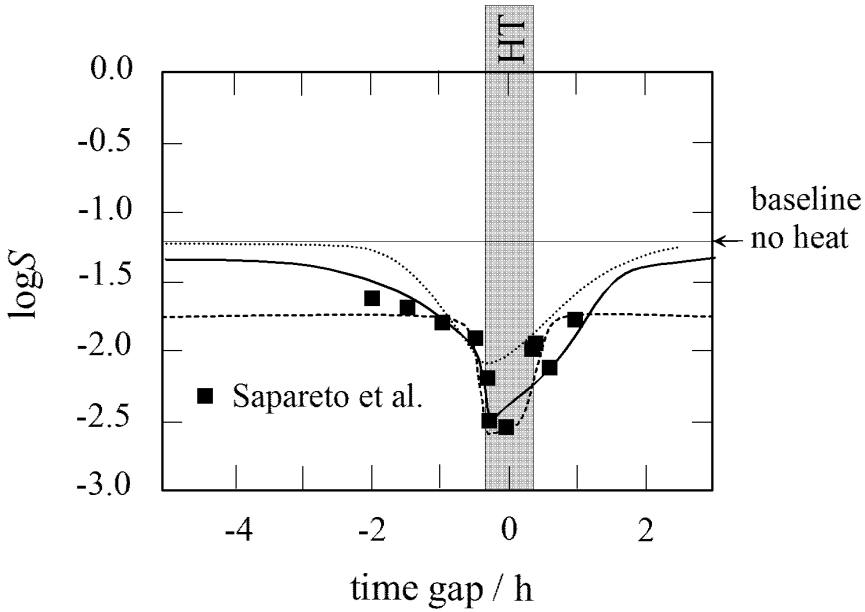
Why do we need dynamical models?

- For synergistic effects of HT and RT, repair speed is essential.
- Reported repair speeds in literature show a wide spread.
- Problem: Repair is a result of complex competing processes, dependent on a large number of parameters including dose, dose rate.
- We have to **understand** repair speeds (as a dynamical process), not only to know them!



Fit of experimental data (redrawn) from (Sapareto et Al., 1978). Chinese hamster cells were irradiated with 5 Gy prior (negative time gap) or after heat (positive time gap). Heat (HT) is applied during 40 min (±20 min of point 0 on the time gap axis). Temperature T during heating was 42.5°C.

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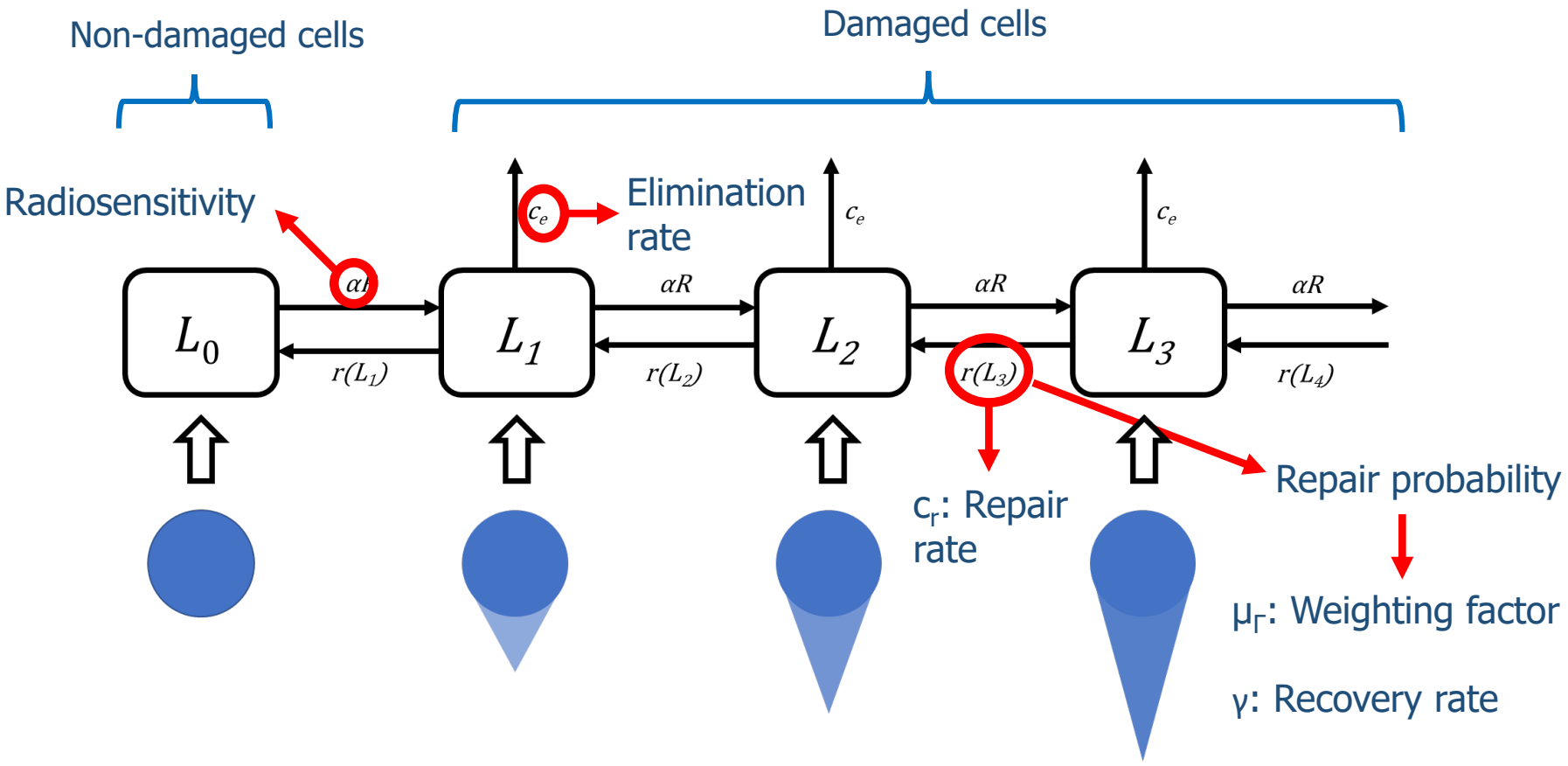
S. A. Sapareto, L. Hopwood, and W. Dewey, "Combined effects of x-irradiation and hyperthermia on CHO cells for various temperatures and orders of application," Radiation Research, vol. 44, pp. 221–233, 1978.

The Multi-Hit Repair (MHR) model



- Chain structure needed to explain LQ survival and dose-rate effects and to compare with comet data.

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Scheidegger, S.; Fuchs, H.U.; Zaugg, K.; Bodis, S.; Füchslin, R.M. Using state variables to model the response of tumour cells to radiation and heat: A novel multi-hit-repair approach. Comput. Math. Methods Med. 2013, 2013, doi:10.1155/2013/587543.

Experimental data and model calibration

- Canine osteosarcoma Abrams cells (6 Gy/min).

Survival: Clonogenic assay

- Doses: 3 and 6 Gy.

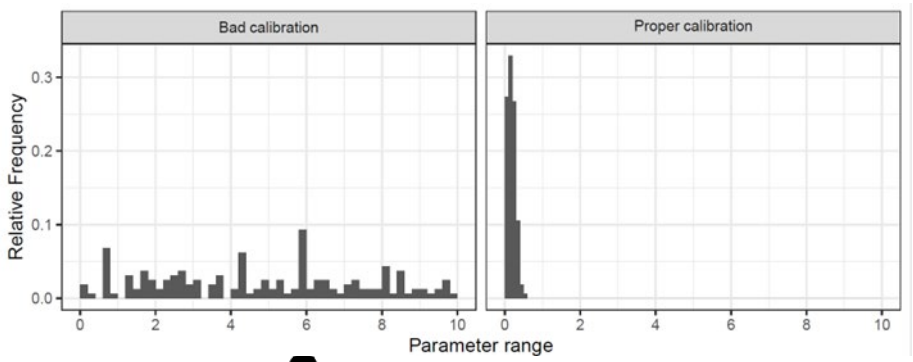
DNA-damage: Time-resolved comet assay

- Dose: 6 Gy.
- Times: 15 mins- 6 hours.

- Combined objective function:

$$\varepsilon_{combined} = \varepsilon_{clonogenic} + \xi \varepsilon_{comet}$$

- Approximate Bayesian Computational (ABC) method → **Probability distributions** of parameters are obtained!



Example of a model parameter calibration not properly calibrated (left) and a properly calibrated one (right).

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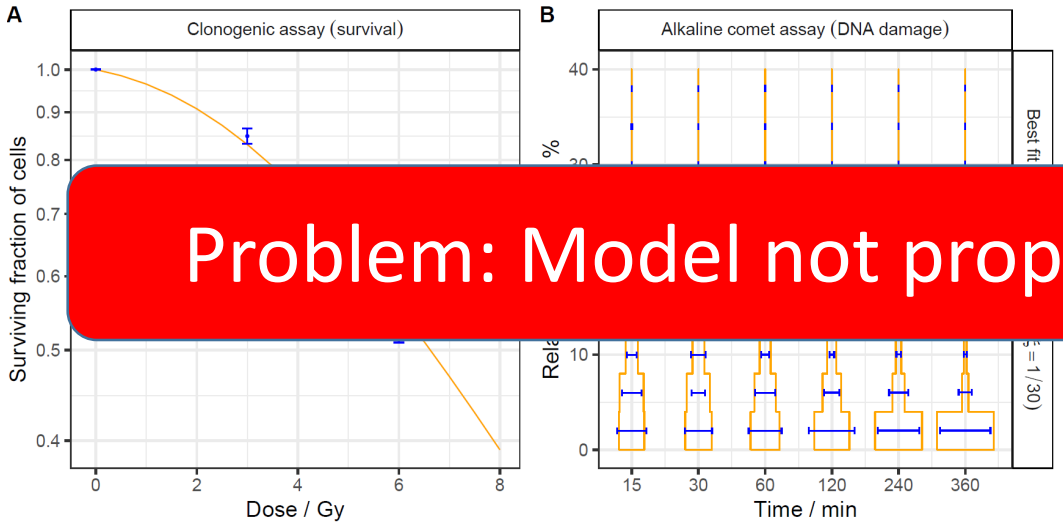
Weyland, M.S.; Thumser-Henner, P.; Nytko, K.J.; Rohrer Bley, C.; Ulzega, S.; Petri-Fink, A.; Lattuada, M.; Füchslin, R.M.; Scheidegger, S. Holistic View on Cell Survival and DNA Damage: How Model-Based Data Analysis Supports Exploration of Dynamics in Biological Systems. Comput. Math. Methods Med. 2020, 2020, doi:10.1155/2020/5972594.

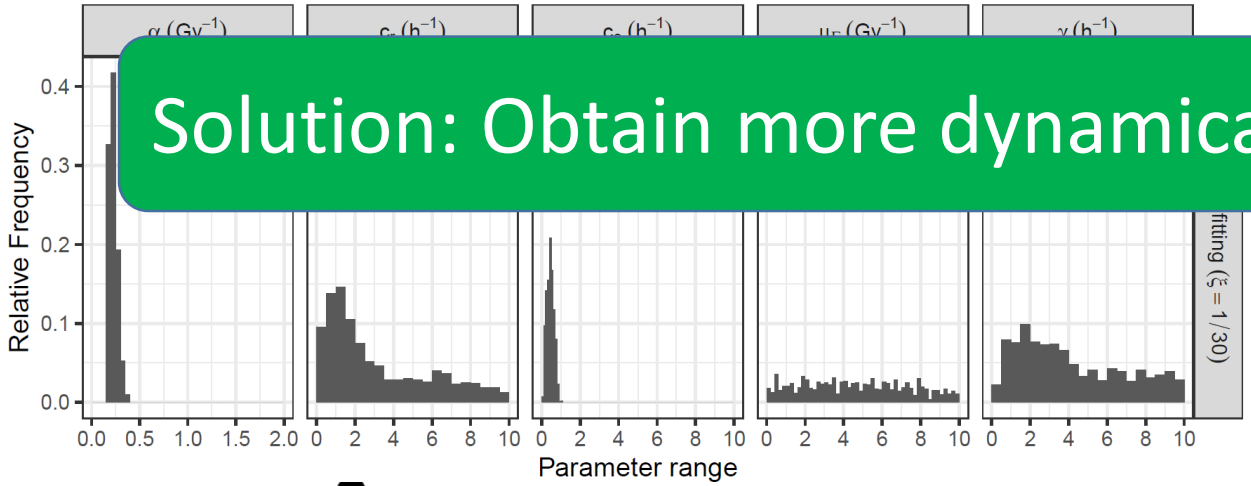
Model calibration results



Cell survival (A) and comet distributions (B) with tions the

Problem: Model not properly calibrated!

Radiosensitivity | Repair speed | Elimination | Repair inactivation | Recovery of repair



Solution: Obtain more dynamical information

HR the combined fitting with a weighted factor ξ=1/30 (middle).

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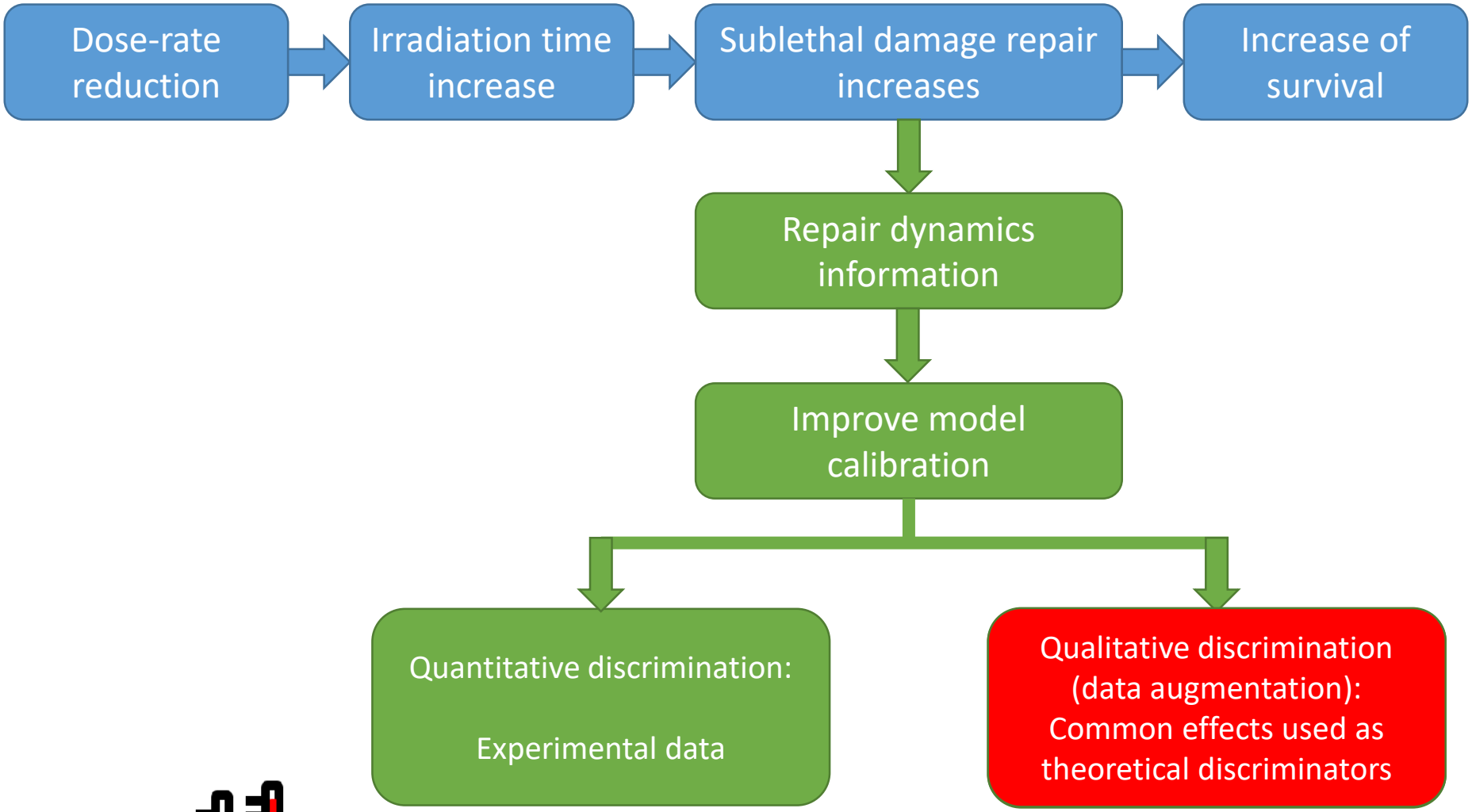
Dose-rate effect



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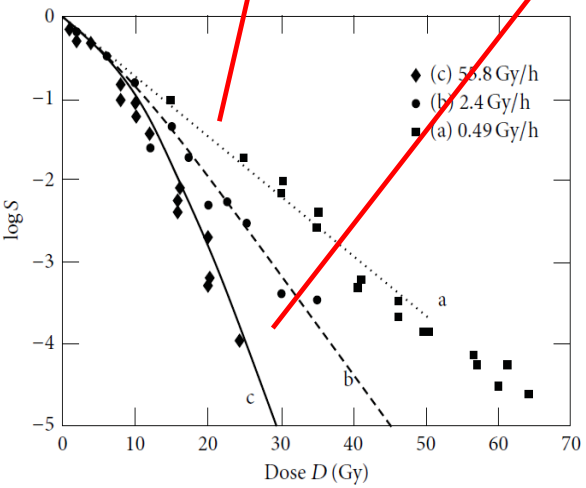
Theoretical dose-rate discriminators

Low dose-rate

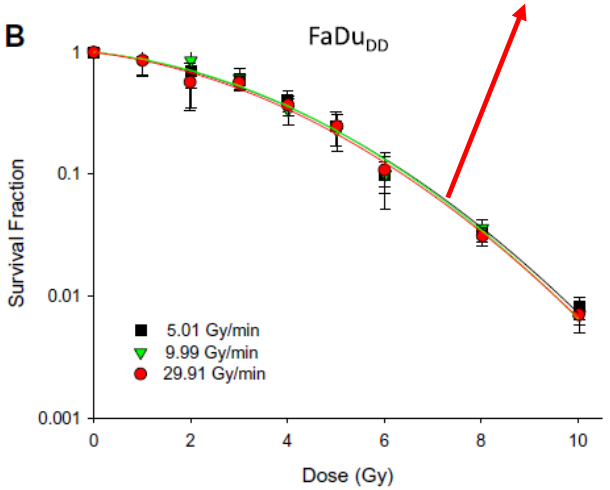
ln SF(0.01 Gy/min) = -αD



Different dose-rates

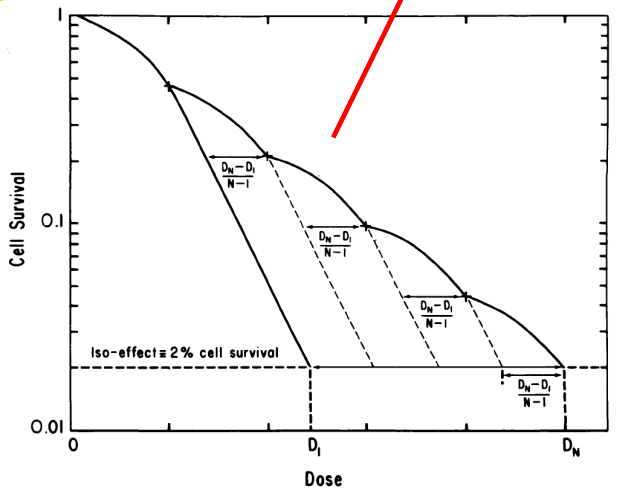
SF(0.1 Gy/min) > SF(2 Gy/min)
Differences increase with D

SF(2 Gy/min) ≥ SF(20 Gy/min)



Fractionation

SF(3 Gy+ 2h+3Gy) > SF(6 Gy)



Left: Fit of experimental data form (Wells and Bedford, 1983) of C3H10T1/2 cells irradiated at different dose rates. Image taken from (Scheidegger et al., 2013). **Middle:** FaDu$_{DD}$ cells at 5, 10 and 30 Gy/min from (Sørensen et al., 2011). **Right:** Theoretical survival curves illustrating a method for quantitating recovery between dose fractions. A dose D_N in N fractions or D_i as a single exposure produces the same effect (Withers, 1975).

R. L. Wells and J. S. Bedford, "Dose-rate effects in mammalian cells. IV. Repairable and nonrepairable damage in noncycling C3H10T1/2 cells", Radiation Research, vol. 94, no. 1, pp. 105–134, 1983.

Scheidegger, S.; Fuchs, H.U.; Zaugg, K.; Bodis, S.; Füchslin, R.M. Using state variables to model the response of tumour cells to radiation and heat: A novel multi-hit-repair approach. Comput. Math. Methods Med. 2013, 2013, doi:10.1155/2013/587543.

Withers, H.R. The Four R's of Radiotherapy; ACADEMIC PRESS, INC., 1975; Vol. 5; pages 241-271; doi: 10.1016/B978-0-12-035405-4.50012-8.

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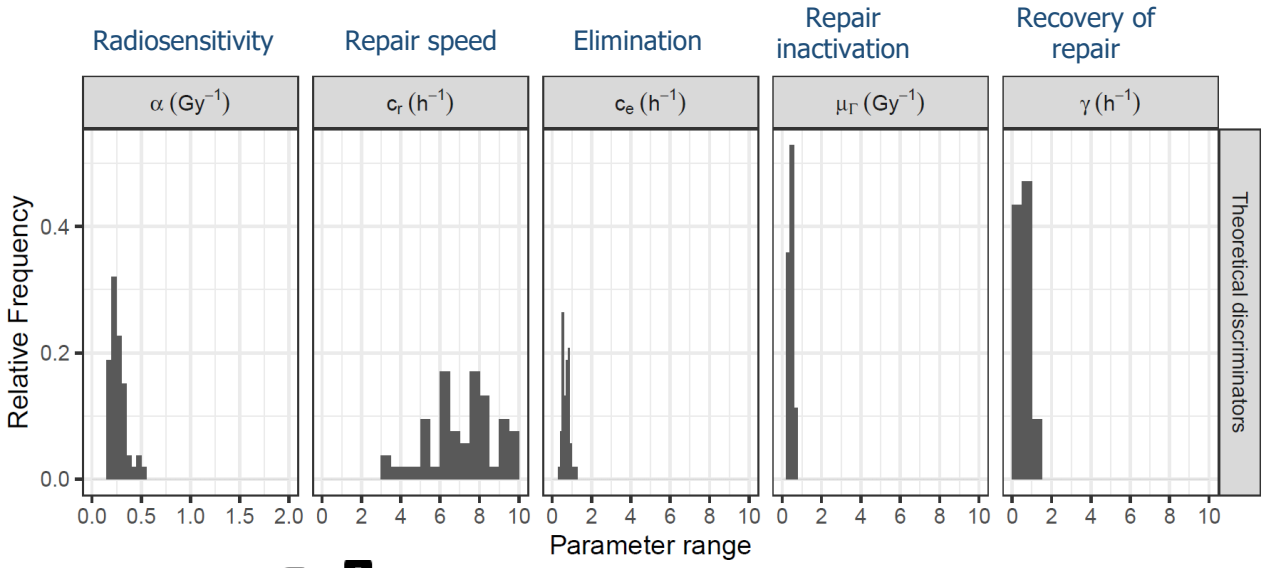
Results

Fitting	Clonogenic	Comet	Combined (ξ=1)	Combined (ξ=1/30)
Different dose-rates	9.3 %	0.1 %	0.2 %	3.4 %
Low dose-rate	94.6 %	75.1 %	80.4 %	90.7 %
Fractionation	99.5 %	57.5 %	56.5 %	54.4 %
Additional	0.2 %	0.1 %	0.3 %	0.4 %
All	0.2 %	0 %	0 %	0.4 %

Number of parameter sets accepted after applying the different discriminators. The model was fitted using different objective functions to obtain 1.000 parameter sets per fitting which were filtered by the described theoretical discriminators.



Probability distributions of the MHR parameters after applying the theoretical dose-rate discriminators.

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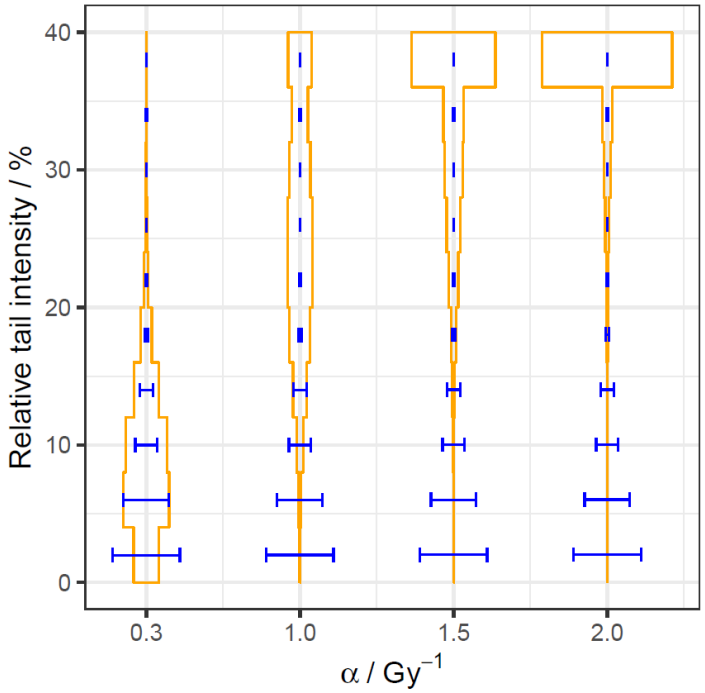
Discussion: Synthetic comets



Simulated comet distributions after 6 Gy irradiation for different radiosensitivity α values. The simulated results (orange) are compared with the experimental comet data (blue).

- α values of 1-2 Gy^{-1}, expected from apoptotic tissues and baseline repair during mitosis.

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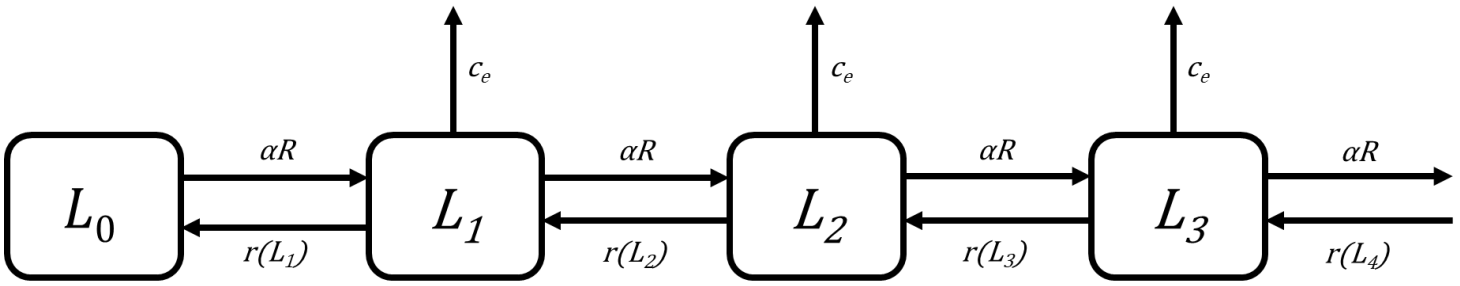
Discussion: Biological interpretation of a hit



Assumption: Hits are indipendent damage

↓

Expected to be repaired simultaneously

↓

Step-by-step repair not representing the biology

↓

Hypothesis: Population characterized by clusters of n hits

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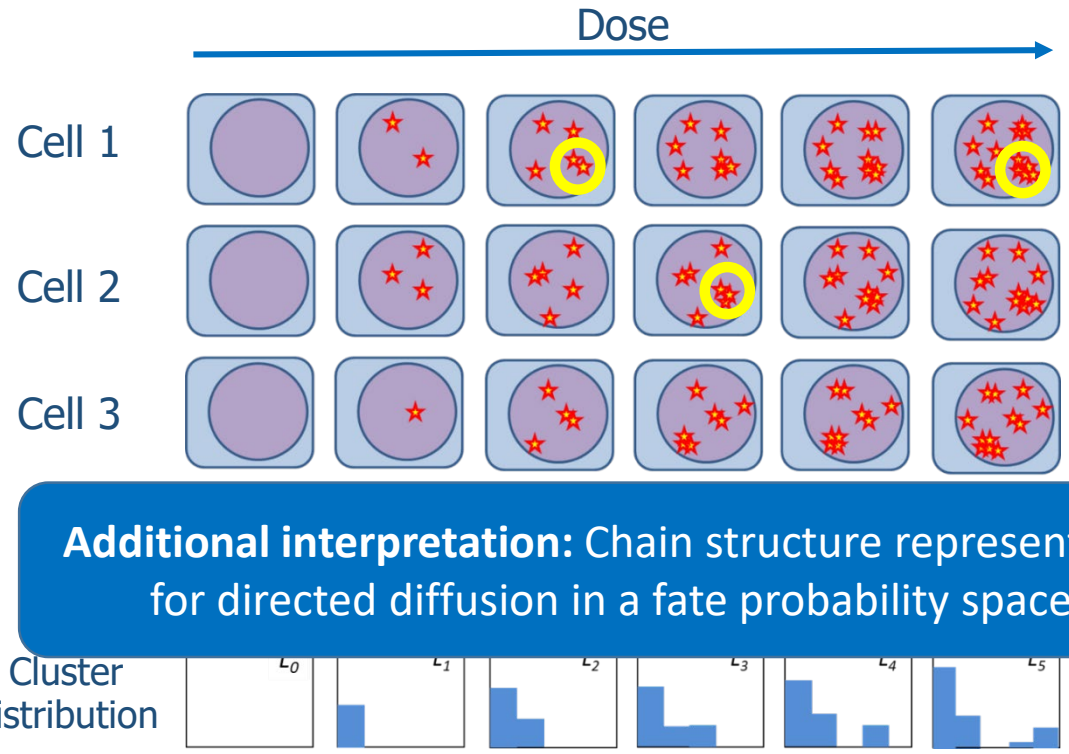
Discussion: Clustered hits

- More complex DNA-damages have longer repair times → Represented by a process chain.



The probability p of cluster formation can be calculated

↓

$$\alpha R L_k \rightarrow \alpha \boldsymbol{p^k} R L_k$$

↓

Less accumulation of damage

comet

Additional interpretation: Chain structure representing Fokker-Planck equation for directed diffusion in a fate probability space (see Alemani A, 2020).

Schematic illustration of the hit distributions in the different populations considered by the MHR model. The population L_0 are cells without radiation-induced hits, in the population L_k, cells have at least one cluster with k hits (yellow stars with red rim = hit). Each row corresponds to one cell with statistically varying number of hits acquired by irradiation with increasing dose (from left to right). The last row shows the histogram for the average number of hits for the depicted four cells.

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Alemany A. Cell differentiation unravelled by single-cell RNA sequencing. Europhys News. 2020;51: 31–34. doi:10.1051/epn/2020505

Conclusions

- A combination of different experiments *in-vitro* and *in-silico* is probably the best approach to study cell repair dynamics.
- 99% of the parameters sets are filtered by the dose-rate theoretical discriminators.
- Dose rate discriminators and combined fitting of different assays are a powerful tool to avoid model falsification!
- MHR model calibration is improved (but not yet completed, also due to model adaption)
- More dynamical information is required for a proper model calibration (**in progress**):
  - Analysis of survival dose-rate experimental data.
  - Inclusion of HT survival data.
  - DNA damage time-resolved assays, e.g. comet assay or γH2AX.
- Variants of the MHR model (e.g., the implementation of clustered hits) should be considered.

Acknowledgments

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- Prof. Stephan Scheidegger (PI)
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- Adela Ademaj (ESR 14)
- Dietmar Marder (Mentor)

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- Prof. Dr. rer. nat. habil. Udo S. Gaipl (PI)
- Azzaya Sengedorj (ESR 4)

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Appendixes

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Model calibration

- Combined error function:

$$\varepsilon_{total} = \varepsilon_{survival} + \xi \cdot \varepsilon_{comet}$$

where ξ is a weighting factor.

$$\varepsilon_{clonogenic} = \sum_{D} \left(log_{10}(S_D) - log_{10}(\hat{S_D}) \right)^2$$

where S_D and $\hat{S}_D$ are the experimental and simulated survival fractions at a dose D, respectively.

$$\varepsilon_{comet} = \sum_{t>0} \sum_{i=0}^{K_{max}} \left(\tilde{l}_i(t) - \tilde{L}_i(t) \right)^2$$

where $\tilde{l}_i(t)$ is the normalized experimental proportion of cells in the population *i* at a time t and $\tilde{L}_i(t)$ is the simulated value.

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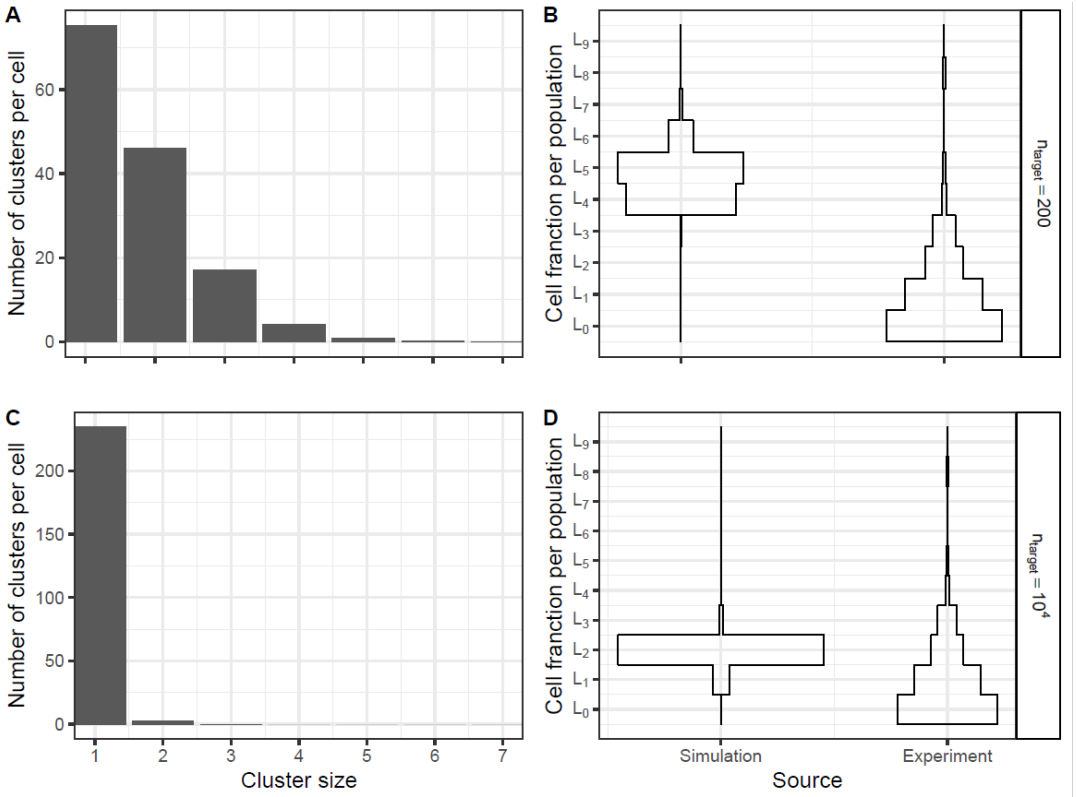
Chain for Fate Probability?



Distributions of clusters with k hits in a cell (A, C) and distributions of the number of cells in the different populations L_k (B,D) for a similar dose (6 Gy) as used for comet data fitting. The calculations were carried out in steps of 0.5 Gy and applying a linear relationship to the dose.

- Probability of cluster formation depends on target size / target numbers.
- For photons small probability for larger DNA damage clusters.
- In alkaline Comets, DSB DNA fragment distribution covered by SSB's!
- Chain structure representing Fokker-Planck equation for directed diffusion in a fate probability space (see Alemani A, 2020).

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Alemany A. Cell differentiation unravelled by single-cell RNA sequencing. Europhys News. 2020;51: 31–34. doi:10.1051/epn/2020505

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Tumor Control Probability (TCP) calculation to theoretically study the impact of different treatment conditions

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 955625. This website reflects only the author's view and the European Commission is not responsible for any use that may be made of the information it contains

Introduction

- **Aim:** To obtain biological information from patient data treated with HT.

- **Problems:**
  - Small number of patients.
  - Heterogeneous treatment conditions (temperatures, thermal/radiation dose, tumor type, etc).
  - Patient complexity.
  - «Logistically» challenging to get the data.

- **Proposed strategy:** Use existing biological models to calculate the expected TCP under diverse conditions → What can we expect to find from the patient data?

(van Leeuwen et al., 2017) model: Radiosensitisation

- Modified LQ model used **to fit** clonogenic data heated during 1 h with different temperatures and time-gaps.

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

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

where $\alpha_{37} = \alpha(37,0)$, $\alpha_{41} = \alpha(41,0)$, $\beta_{37} = \beta(37,0)$, $\beta_{41} = \beta(41,0)$, μ (h^{-1}) is the rate at which the radiosensitising effect of hyperthermia disappears, t_{int} (h) is the time interval between radiotherapy and hyperthermia and D (Gy) is the total radiation dose.

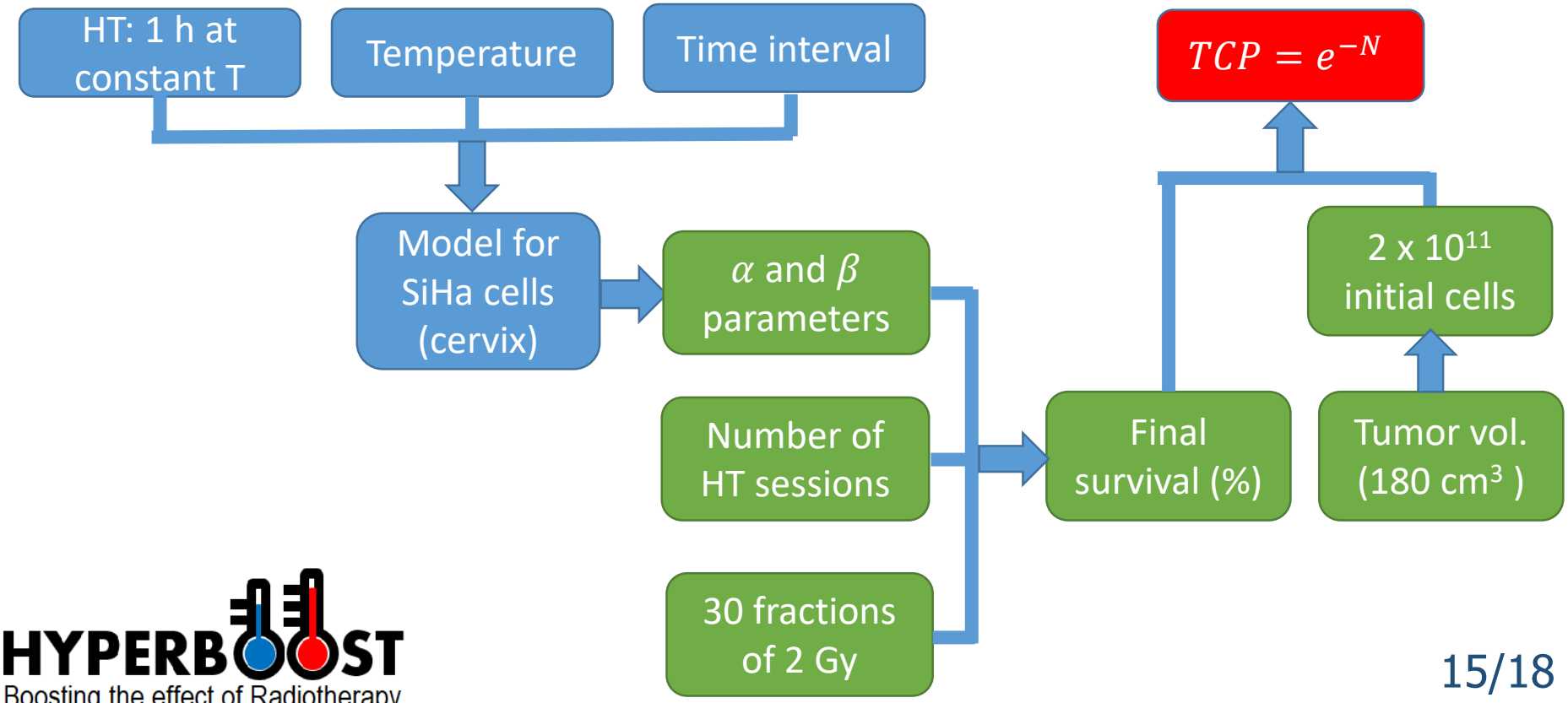
van Leeuwen, C.M.; Oei, A.L.; ten Cate, R.; Franken, N.A.P.; Bel, A.; Stalpers, L.J.A.; Crezee, J.; Kok, H.P. Measurement and analysis of the impact of time-interval, temperature and radiation dose on tumour cell survival and its application in thermoradiotherapy plan evaluation. Int. J. Hyperth. 2017, 34, 30–38, doi:10.1080/02656736.2017.1320812.

Simulated treatment conditions

- Thermal characteristics margins based on patient data.

Number of HT sessions	HT achieved temperatures	Time-gap between HT and RT
3-6	39-43 °C	8-60 min

Margins established for the thermal treatments based on the available patient data at KSA.



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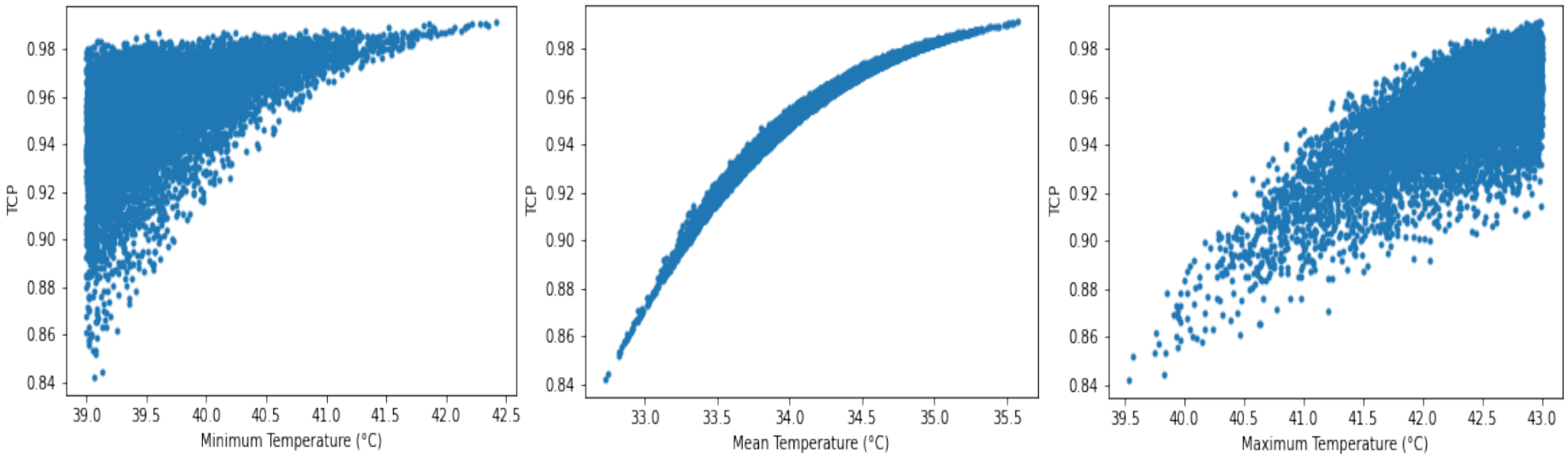
Results: Temperature dependence

5 HT sessions with 10 mins of time-gap and random temperature for each sessions



Obtained TCP values for 10^4 dummy patients after 5 HT sessions with 10 minutes of time-gap achieving a temperature randomly selected for each HT session. The dependence on the mean achieved temperature (left) and the mean time-gap (right) are plotted when direct cell killing is considered (low row) or not (up row). For these simulations, a decay constant of $\mu=1.0\ h^{-1}$ is considered.

Overall treatment seems more important than single HT session.

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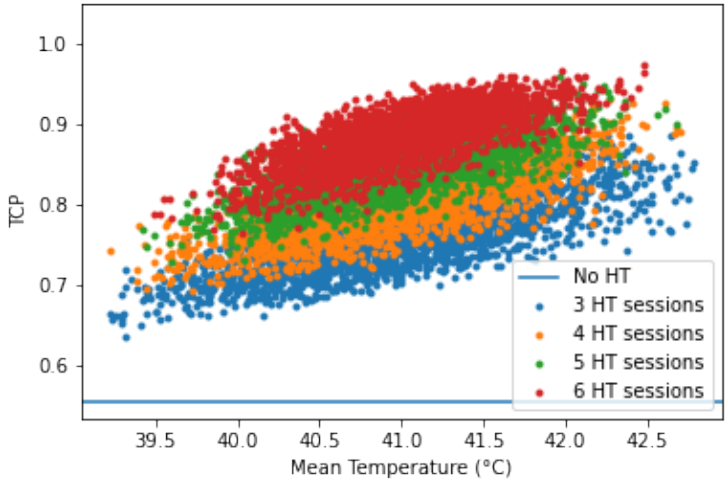
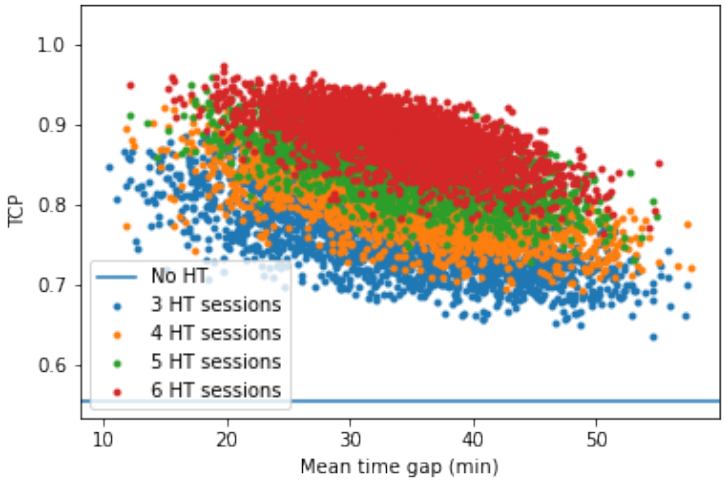
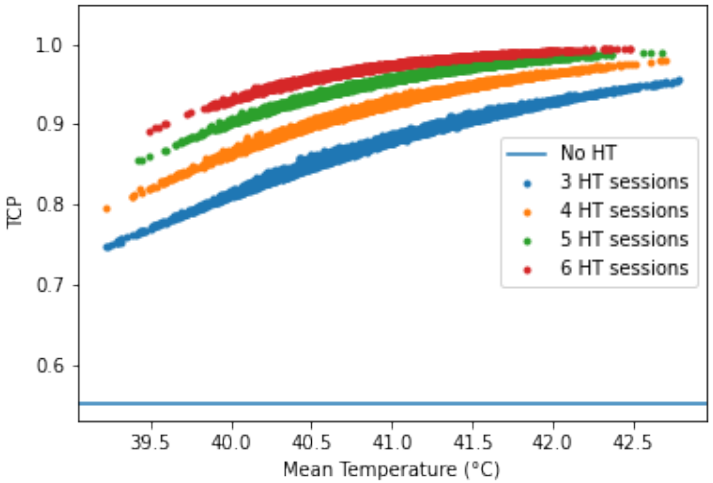
Results: Random conditions

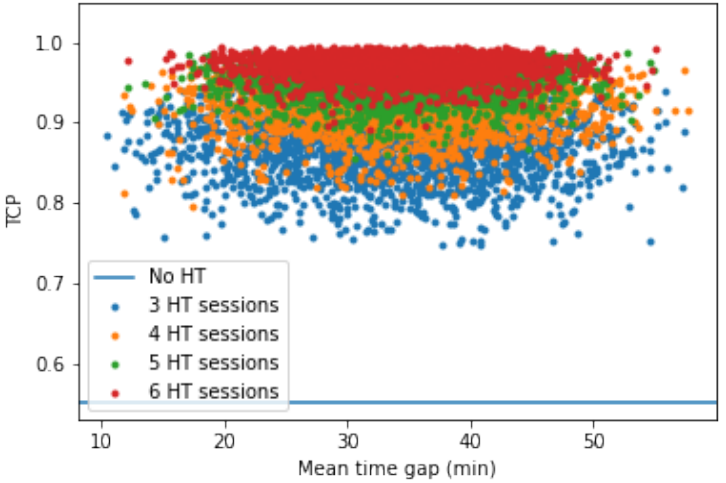
t_{int} important:
μ=1.0 h^{-1}





t_{int} NOT important:
μ=0.027 h^{-1}





Obtained TCP values for 10^4 dummy patients with number of HT sessions, time-gaps and achieved temperature randomly selected for each HT session. The dependence on the mean achieved temperature (left) and the mean time-gap (right) are plotted when a decay constant of μ=1.0 h^{-1} (up row) or μ=0.027 h^{-1} (low row) is considered.

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Conclusions

- Cellular radiobiological models can be used to theoretically have an idea of the clinical results which might be expected.

- The treatment outcome (from the cell radiosensitisation point of view) is more related to the overall treatment than to a single HT session.

- The time-gap importance could be deduced from the temperature dependence.

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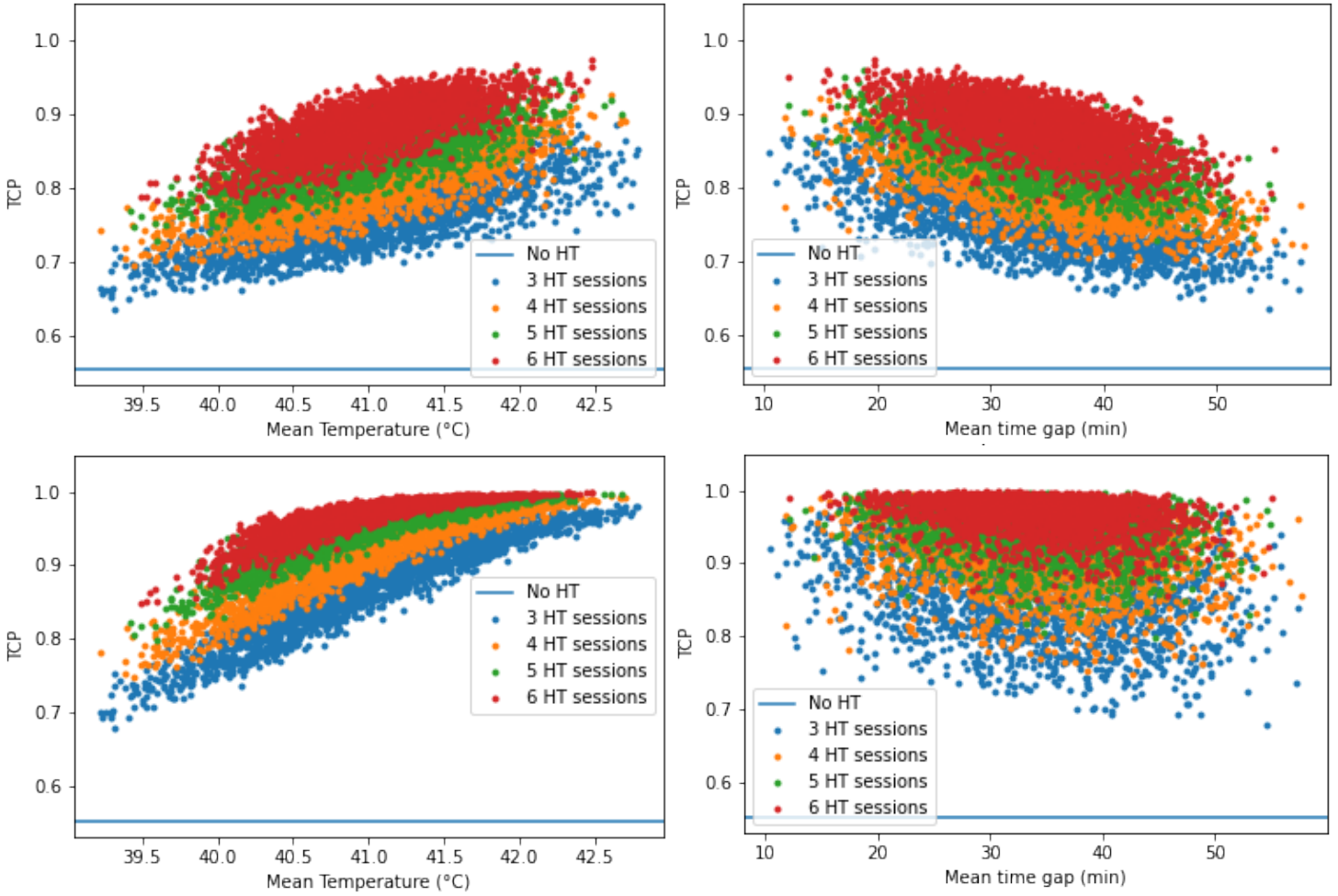
Results: Random conditions (μ=1.0 h^{-1})

No direct cell HT killing

Direct cell HT killing



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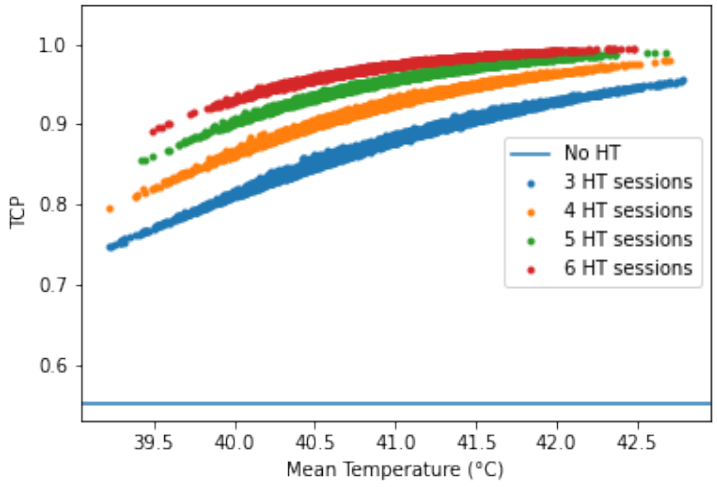
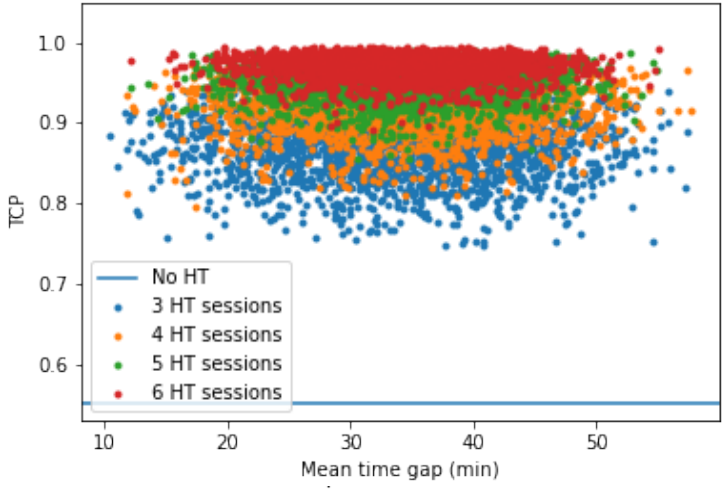
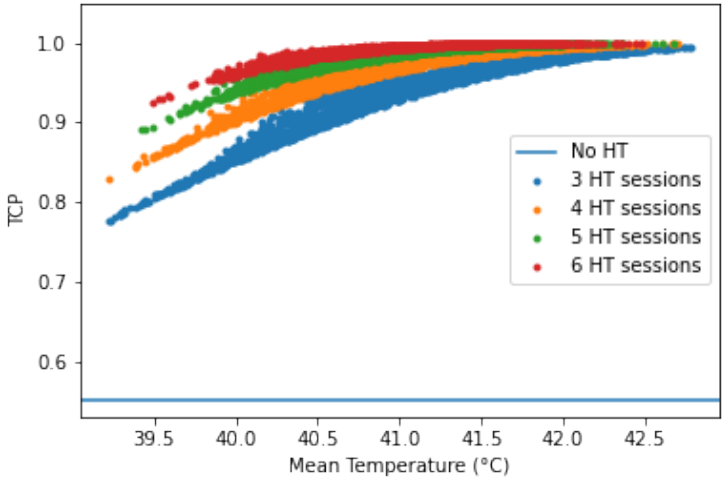
Results: Random conditions (μ=0.027 h^{-1})

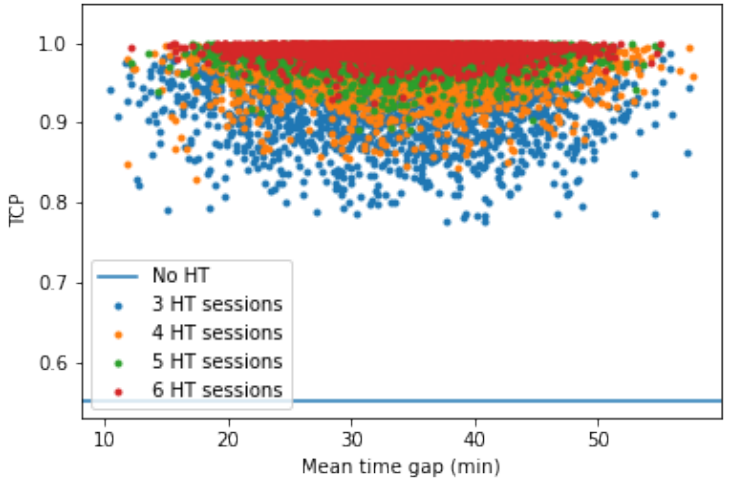
No direct cell HT killing





Direct cell HT killing





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(van Leeuwen et al., 2017) model: Direct HT killing

- Hyperthermic cytotoxicity survival (SF_{HT}) given by

$$SF_{HT}(T,t) = exp[-k(T) \cdot t]$$

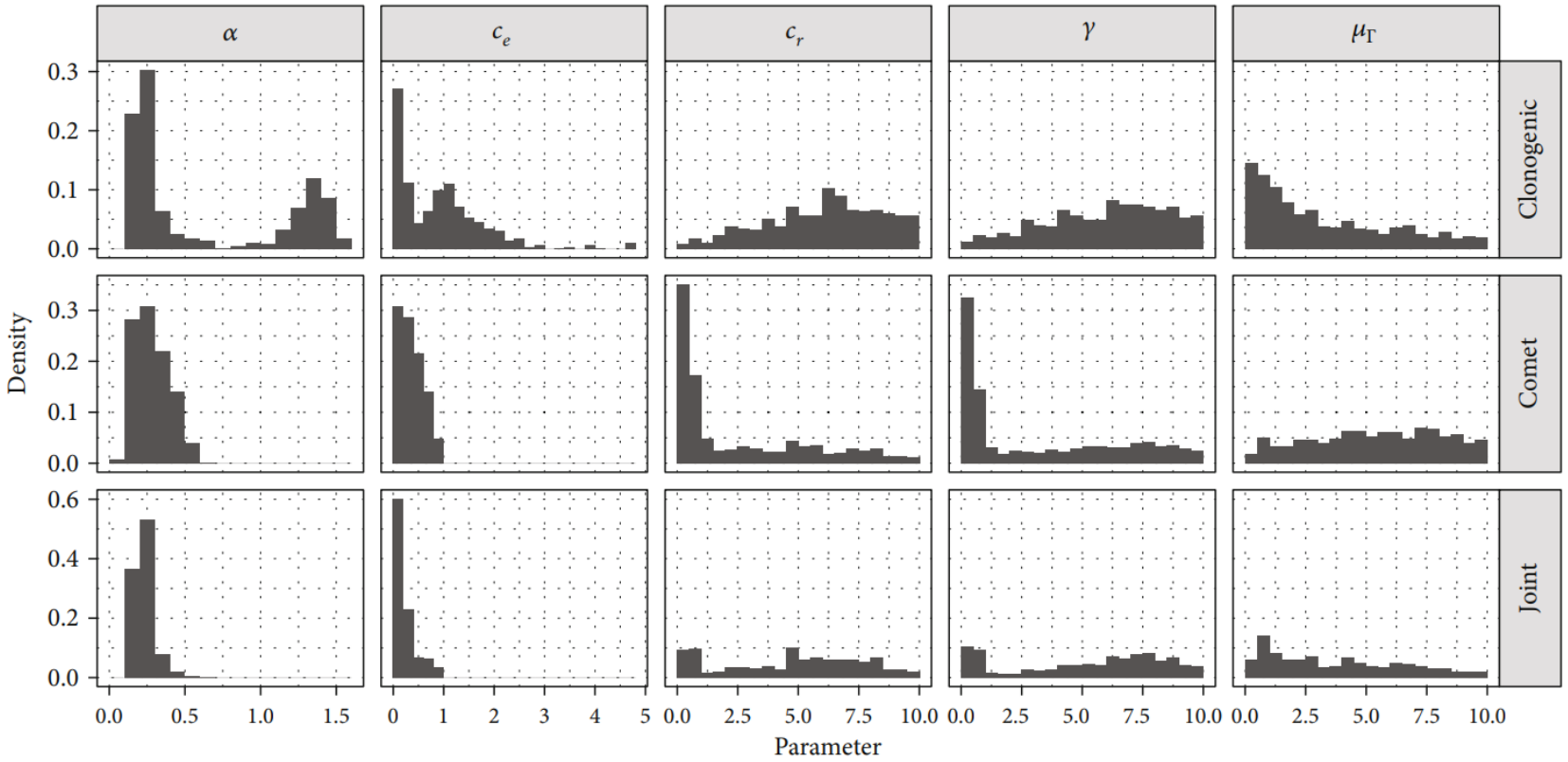
with t (s), the heating time and k the reaction rate as a function of the temperature T (°C), given by

$$k(T) = 2.05 \cdot 10^{10} \cdot (T + 273.15) \cdot exp\left[\frac{\Delta S}{2} - \frac{\Delta H}{2 \cdot (T + 273.15)}\right]$$

where ΔS (cal/°C/mol) is the entropy of inactivation and ΔH (cal/mol) is the inactivation energy of the critical rate-limiting molecules that cause cell lethality.

van Leeuwen, C.M.; Oei, A.L.; ten Cate, R.; Franken, N.A.P.; Bel, A.; Stalpers, L.J.A.; Crezee, J.; Kok, H.P. Measurement and analysis of the impact of time-interval, temperature and radiation dose on tumour cell survival and its application in thermoradiotherapy plan evaluation. Int. J. Hyperth. 2017, 34, 30–38, doi:10.1080/02656736.2017.1320812.

(Weyland et al., 2020) results combination



Histograms of parameter values after calibration with the software set to different modes, and at the bottom, the joint distribution obtained by combining the two posterior sets is shown.

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Weyland, M.S.; Thumser-Henner, P.; Nytko, K.J.; Rohrer Bley, C.; Ulzega, S.; Petri-Fink, A.; Lattuada, M.; Füchslin, R.M.; Scheidegger, S. Holistic View on Cell Survival and DNA Damage: How Model-Based Data Analysis Supports Exploration of Dynamics in Biological Systems. Comput. Math. Methods Med. 2020, 2020, doi:10.1155/2020/5972594.

Model calibration

- Approximate Bayesian Computational (ABC) method:
  - Iterative perturbative method used to minimize an error function.
  - Provides several final parameters sets → The model parameters distributions can be studied.

- Feeding of data for model calibration:
  - **Clonogenic:** Final number of undamaged cells.
  - **Comet:** Comet tail intensity ↔ Model population.

- Combined error function:

$$\varepsilon_{total} = \varepsilon_{survival} + \xi \cdot \varepsilon_{comet}$$

where ξ is a weighting factor.

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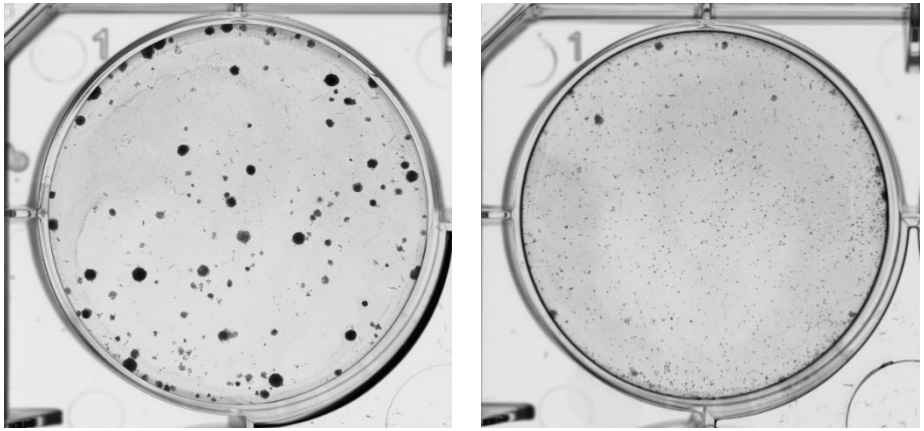
Experimental data: Clonogenic assay

- Canine osteosarcoma Abrams cells.
- Irradiation dose-rate: 6 Gy/min.
- Doses: 3 and 6 Gy.



Example of colonies formation in the clonogenic assay for SiHa cancer cells after.

$$Survival = \frac{Final\ \#\ colonies}{Initial\ \#\ cells}$$

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Procedure

1. Make dilutions to obtain the desired initial number of cells.
2. Plate the cells and leave then incubation during 4 h.
3. Treat the cells.
4. Leave the cells incubating and growing during two weeks.
5. Throw the medium and treat the cells with crystal violet to make the colonies visible.
6. Count the number of colonies (≥50 cells).

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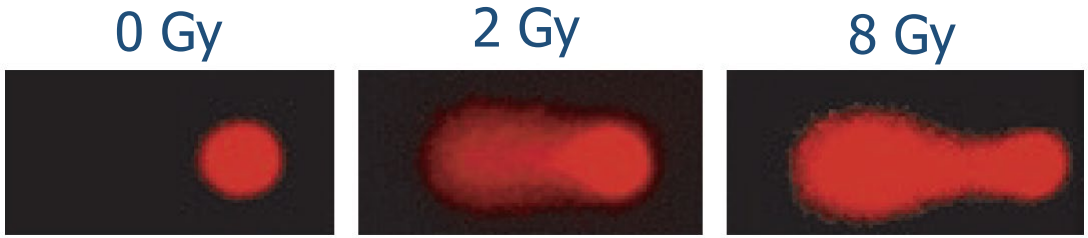
Experimental data: Comet assay

- Canine osteosarcoma Abrams cells.
- Irradiation dose-rate: 6 Gy/min.
- Dose: 6 Gy.
- Times: 15 mins-1 hour.



Example of alkaline comet assay in WIL2NS human lymphoblast cells from controls (left), after 2 Gy (middle), and after 8 Gy (right). Figure obtained from (Olive and Banáth, 2006).

- $$Relative\ tail\ intensity = \frac{\sum_{x,y \in tail} I(x,y)}{\sum_{x,y \in head} I(x,y) + \sum_{x,y \in tail} I(x,y)}$$

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P. L. Olive and J. P. Banáth, "The comet assay: A method to measure DNA damage in individual cells," Nat. Protoc., vol. 1, no. 1, pp. 23–29, 2006, doi: 10.1038/nprot.2006.5.

The Multi-Hit Repair (MHR) model

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Main ideas

- Use a chain of cell populations characterize by the number of radiation induced damages (hits).
- Lethality → Removal from the mitotic cycle.
- Use state variables for a simplistic description of the impact of heat and radiation upon repair proteins.

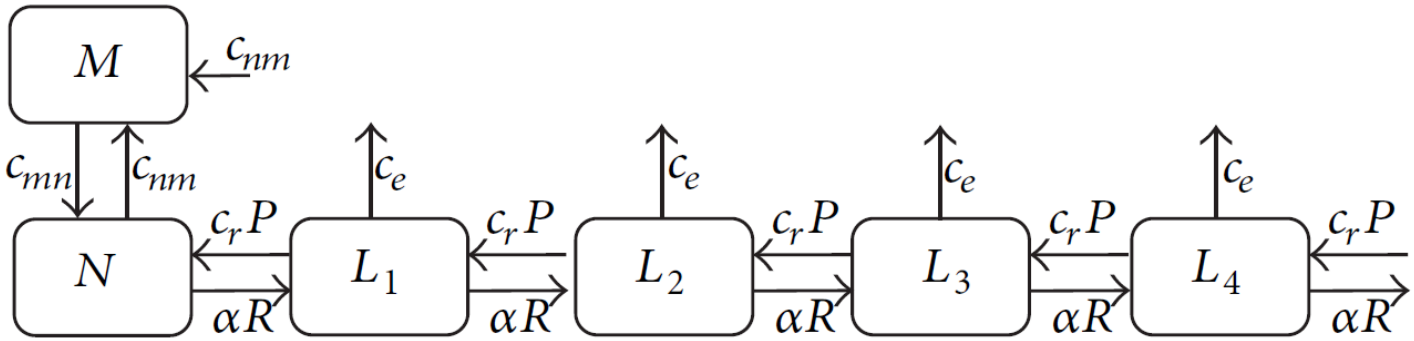

Illustration of the population model.

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Radiation Induced Protein-Related Damage (Γ-LQ model)

- Dose equivalent Γ → Transient dose (Repair proteins)

$$\frac{d\Gamma}{dt} = R - f(\Gamma)$$

R=Dose rate

f(Γ)=Kinetics of protein-related damage repair function

- In this paper: $f(\Gamma) = \gamma\Gamma$

$$\lim_{t\to\infty}\left[\int_{-\infty}^{t} f(\Gamma(\tau))d\tau\right] = \lim_{t\to\infty}[D(t)] = D_{tot}$$

D_{tot}=Total cumulative dose

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Heat-Induced Protein-Related Damage

$$\frac{d\Upsilon}{dt} = -k_1\Upsilon + k_2\Lambda$$

$$\frac{d\Lambda}{dt} = k_1\Upsilon - k_2\Lambda$$

Υ/ Λ = Proportion of functional/non-functional repair proteins

k_1/k_2 = Thermal degradation/repair of proteins constants

$$k_1 = a \cdot 10^{-3} \cdot e^{\frac{E_a}{R(273{,}15+37℃)} - \frac{E_a}{R(273{,}15+T(℃))}}$$

E_a = Activation energy

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Calculation of Repair Probability

- Monotonically decrease with Λ and Γ:

$$\left[\frac{\partial P}{\partial \Lambda}\right]_{\Gamma=const.} = -\mu_\Lambda P \quad \rightarrow P(\Lambda) = e^{-\mu_\Lambda \Lambda}$$

$$\left[\frac{\partial P}{\partial \Gamma}\right]_{\Lambda=const.} = -\mu_\Gamma P \quad \rightarrow P(\Gamma) = e^{-\mu_\Gamma \Gamma}$$

- Statistically independent:

$$P = P(\Lambda, \Gamma) = P(\Lambda) \cdot P(\Gamma) = e^{-\left(\mu_\Gamma \Gamma + \mu_\Lambda \Lambda\right)}$$

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Multi-Hit Repair and Population Model

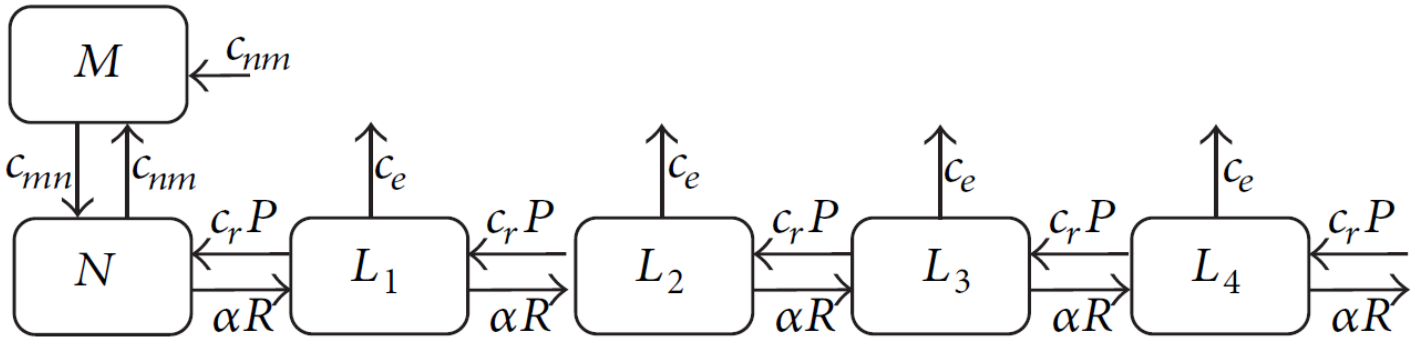

Illustration of the population model.

$$\frac{dN}{dt} = -\alpha RN + r(L_1) = -\alpha RN + c_r e^{-\left(\mu_\Gamma \Gamma + \mu_\Lambda \Lambda\right) L_1}$$

$$\frac{dL_k}{dt} = \alpha R L_{k-1} - \alpha R L_k - r(L_k) + r(L_{k+1})$$

- Apoptotic cell death $\rightarrow -c_e L_k$
- HT cytotoxicity $\rightarrow -a_k \cdot 10^{10}\left(273{,}15 + T(°\mathrm{C})\right) \cdot e^{\frac{\Delta S}{R} - \frac{\Delta H}{R\left(273{,}15 + T(°\mathrm{C})\right)} L_k}$

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University Medical Centers

Robust optimization and evaluation of radiotherapy combined with hyperthermia based on equivalent enhanced radiation dose

Timoteo D. Herrera, Jakob Ödén, Andrea Lorenzo, Hans Crezee, H. Petra Kok

Hyperboost Meeting 2023 - Erlangen

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 955625

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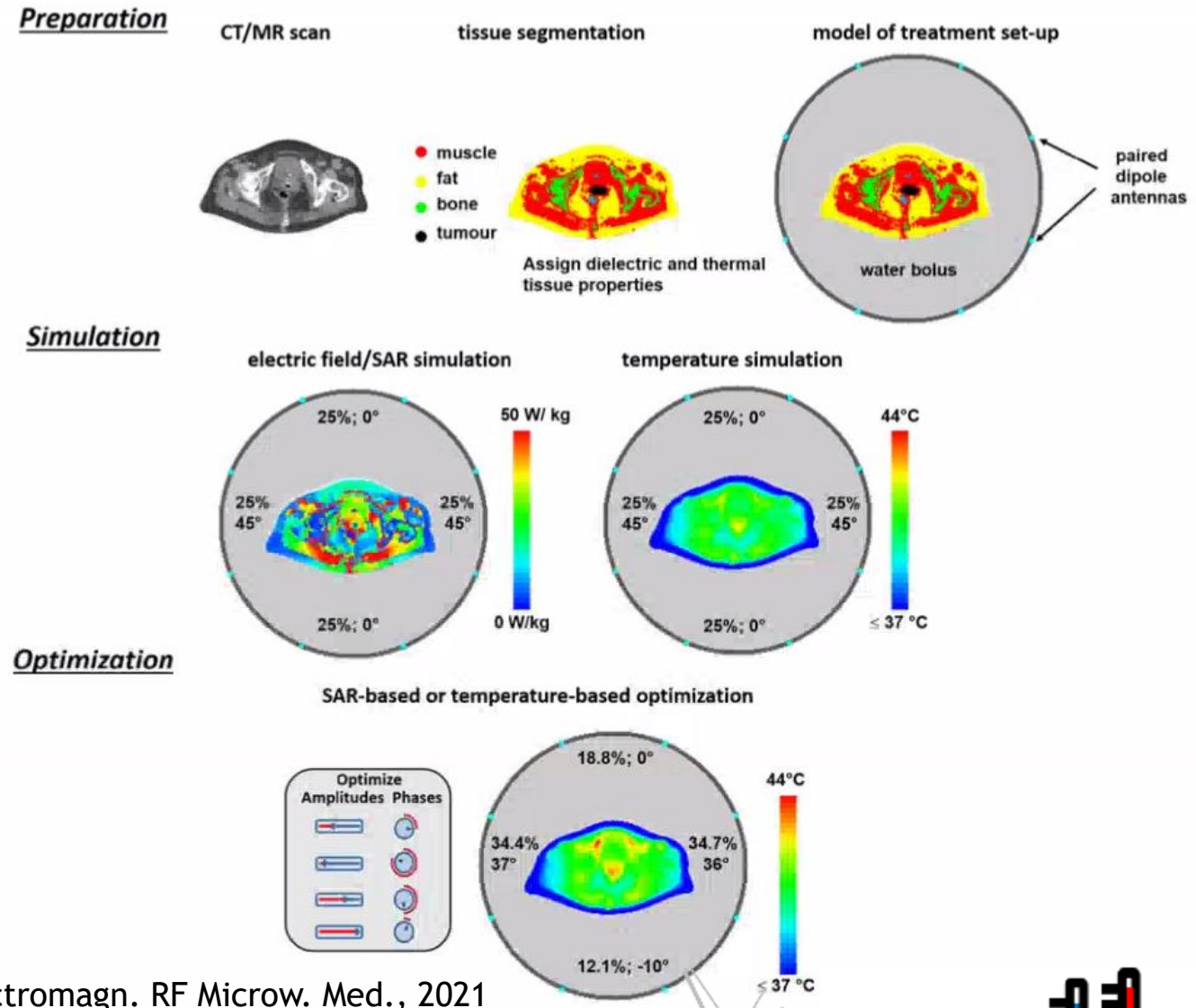
Outline

- Introduction: Hyperthermia in combination with radiotherapy
- Motivation – Hyperboost Project and RaySearch secondment
- Implementation – Robust optimization and evaluation
- Some results
- Summary and future work

Hyperthermia Treatment Planning

- Limited clinical application
  - Device configuration
  - Heating ability evaluation
  - Assistance on-line treatment guidance
- Ongoing research to improve reliability and increase applicability
  - Patient-specific dielectric properties
  - Perfusion and oxygenation modelling
  - Biological modelling of response.



Kok and Crezee, IEEE J. Electromagn. RF Microw. Med., 2021

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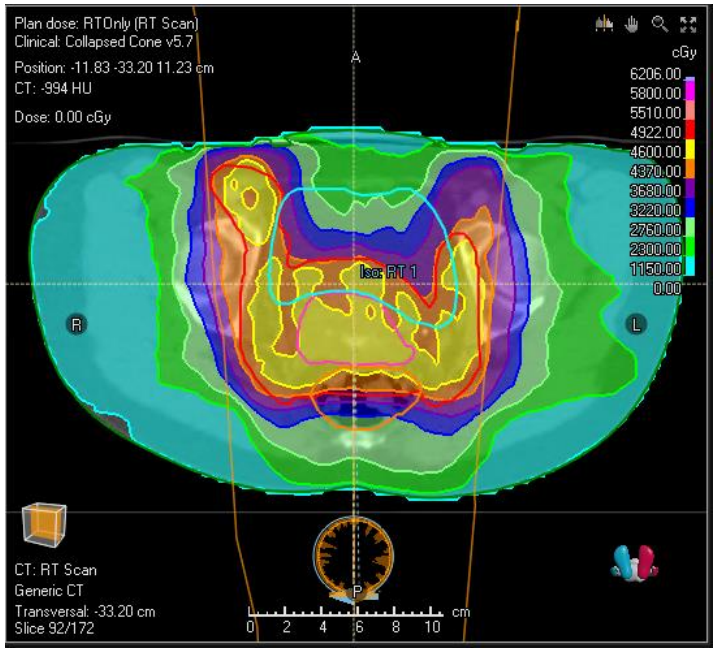
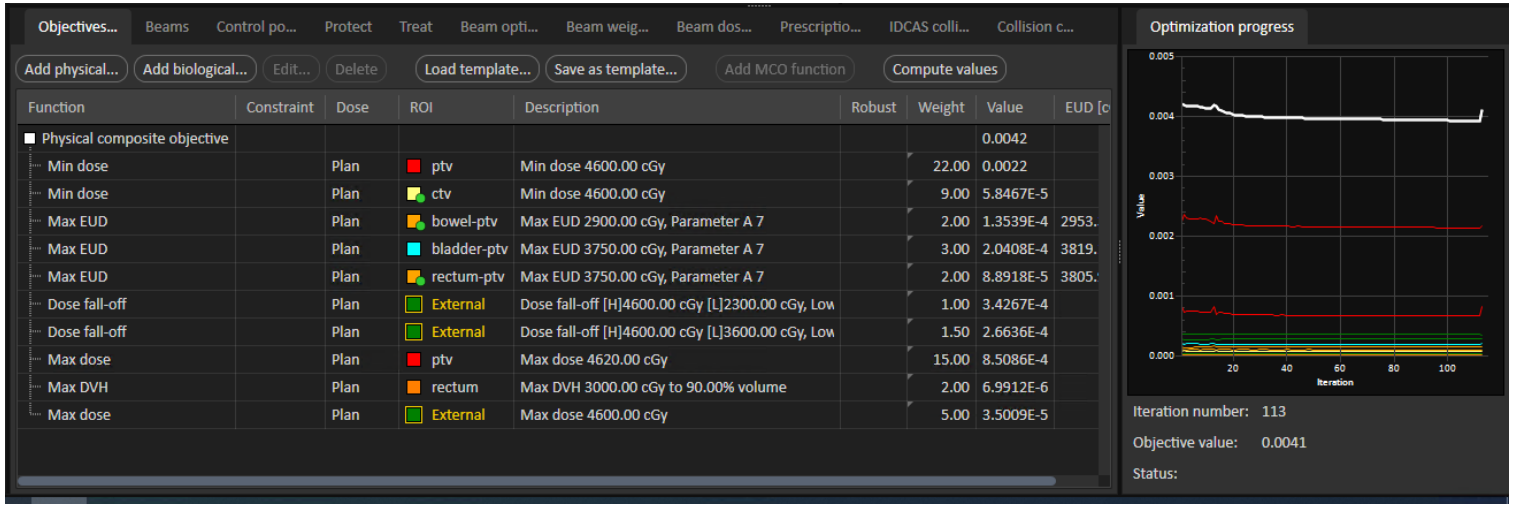
Radiotherapy Treatment Planning

- Standardized prescription for indication, based on results of clinical trials:
  - Dose coverage for treatment volumes: GTV, CTV, PTV
  - Dose limits for organs at risk
- Modulated techniques, optimization of objective functions related to the prescription.
  - Dose distribution is optimized at a voxel level.





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Modeling the combined treatment

- Linear Quadratic Model (LQM):
- Survival fraction

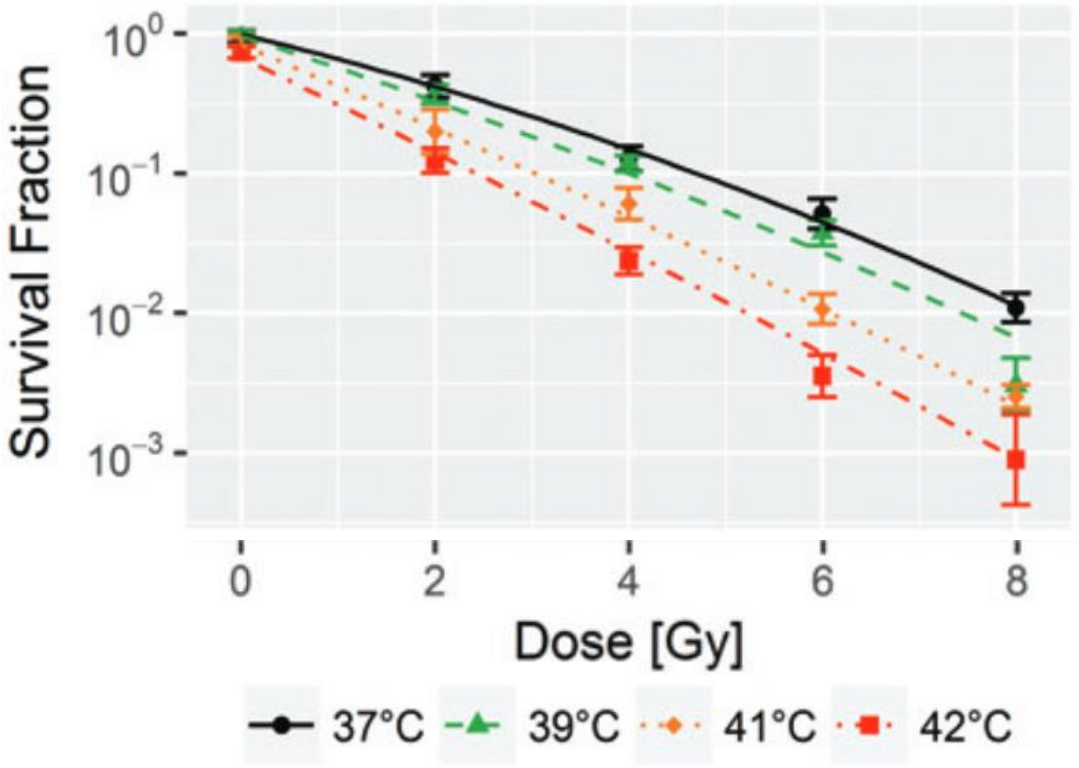
$$SF = e^{-n(\alpha d + \beta d^2)}$$

- α, ß, radiosensitivity parameters
- Comparison of fractionation schemes:

$$EQD_2(d) = \frac{nd(\alpha + \beta d)}{\alpha + 2\beta}$$

With hyperthermia:

- Cell survival assay of RT + HT (no interval between modalities) for a cervical cancer cell line.
- Similar curves for different time intervals of up to 4 h.



Van Leeuwen et al. Int J Hyperth 2018

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Equivalent dose for RT + HT

- α_{37}, β_{37} parameters from linear quadratic model at baseline temperature (37°C)
- α_{41}, β_{41} modified LQ-parameters reflecting the synergistic effect at 41°C
- $T_{1/2}$ time decay of the synergistic effect
- $c(T)$ direct thermal cell kill

- $EQD_{RT}(T, t_{int}, D) = \frac{\alpha(T,t_{int})\cdot D+\beta(T,t_{int})\cdot D^2+c(T)}{\alpha_{37}+2\cdot\beta_{37}}$

- $\alpha(T, t_{int}) = \alpha_{37} \cdot exp\left[\frac{T-37}{41-37} \cdot ln\left(\frac{\alpha_{41}}{\alpha_{37}}\right) \cdot exp\left(\frac{-\ln(2)\cdot|t_{int}|}{T_{1/2}}\right)\right]$

Van Leeuwen et al. Int J Hyperth 2018

- $\beta(T, t_{int}) = \beta_{37} \cdot exp\left[\frac{T-37}{41-37} \cdot ln\left(\frac{\beta_{41}}{\beta_{37}}\right) \cdot exp\left(\frac{-\ln(2)\cdot|t_{int}|}{T_{1/2}}\right)\right]$

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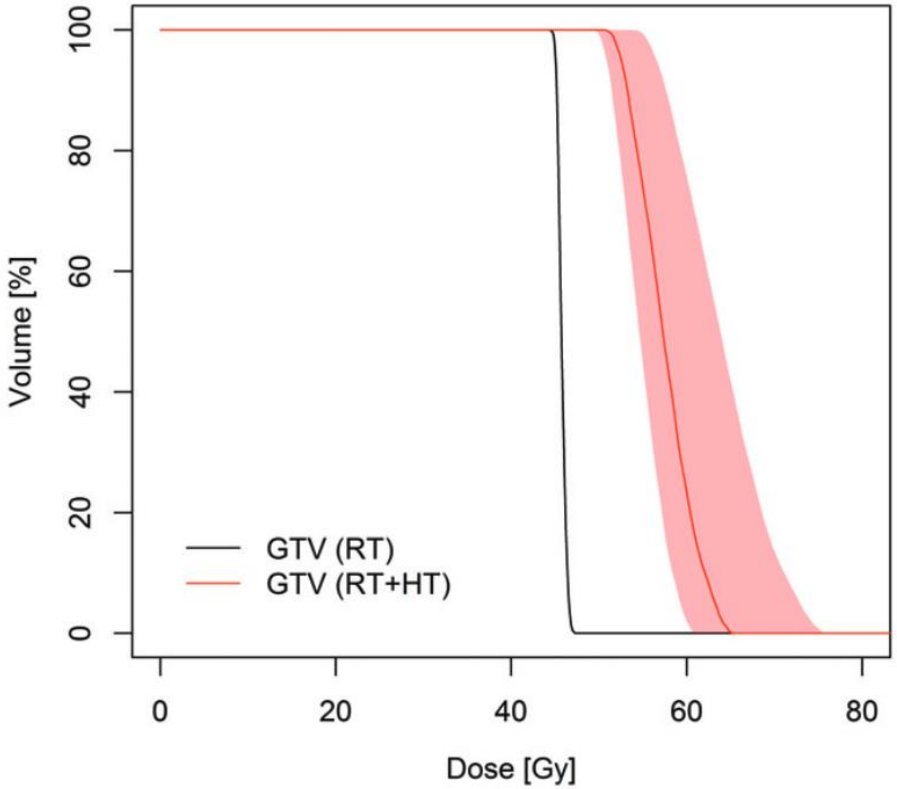
Secondment Project - Motivation

- Optimization (current status):
  - HT is optimized to maximize T90 in the tumor, with normal tissue constraints.
  - RT is optimized independently according to protocol.
  - The resulting EQD_{RT} is heterogeneous, and will depend in the achieved temperature, patient and session dependent.
- Research prototype in RayStation 12A
  - Optimization with temperature as an input using EQD_{RT} model.
  - EQD_{RT} evaluation.

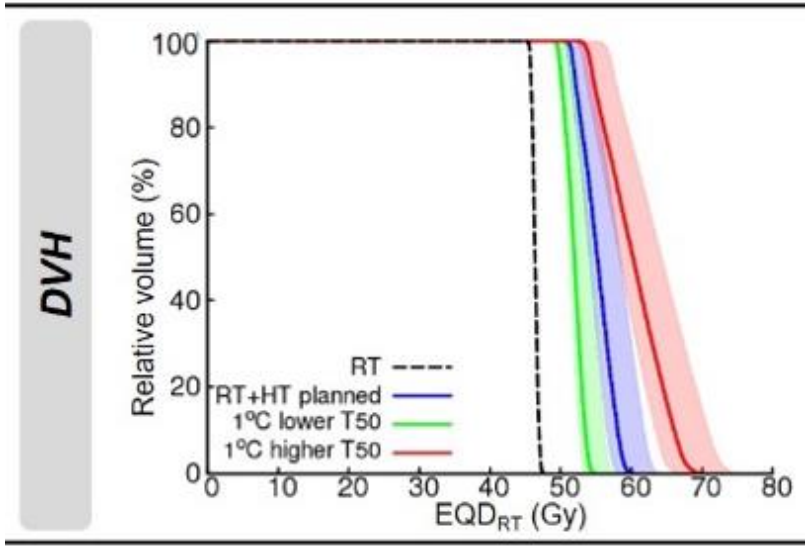


Van Leeuwen et al. Int J Hyperth 2018

Secondment Project - Motivation

- Robustness in deep locoregional hyperthermia:
  - Not many degrees of freedom compared to RT
    - 4 antennas: amplitude and relative phase, total power
  - Steering of amplitude and phase during treatment
    - Focus on the tumor
    - Hot spots/patient complaints (avoid T>45° C)
  - Determinants of the temperature level:
    - Amplitudes and phases
    - Power increase/decrease
    - Changes in perfusion
    - Patient-specific dielectric properties

EQD_{RT} for a cervical cancer patient, effect of scaling of temperature



Kok et al. Int J Radiat Oncol Biol Phys 2022

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Secondment Project

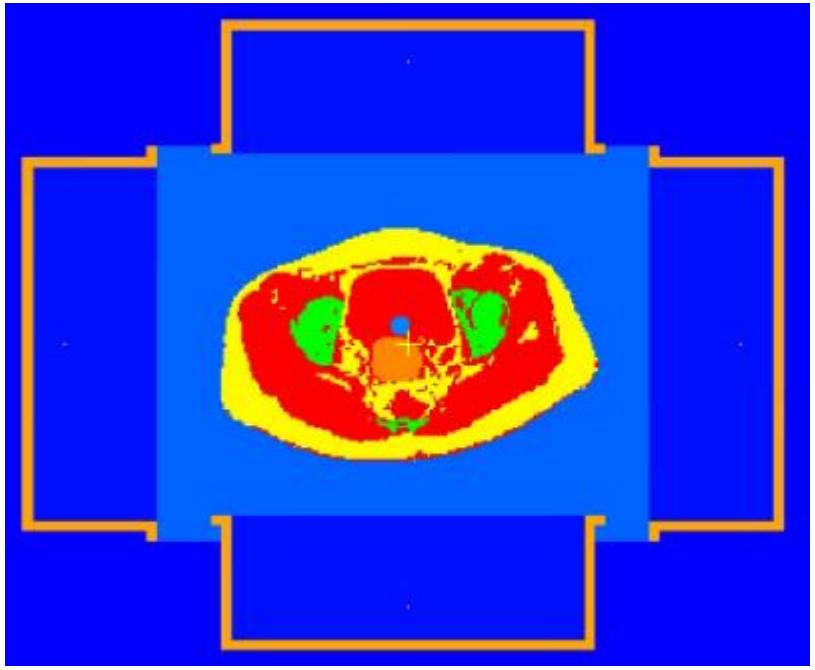
- Objectives:
  - Optimize RT to control level and homogeneity of EQD_{RT}.
  - Robustness evaluation of optimized plans:
    - What happens with level and homogeneity of EQD_{RT} in optimized plans in case of:
      - Phase and amplitude steering
      - Power increase/decrease
      - Increased time interval
  - Robust optimization:
    - Optimized plans for (realistic) alternative scenarios
    - Robustly optimized plan

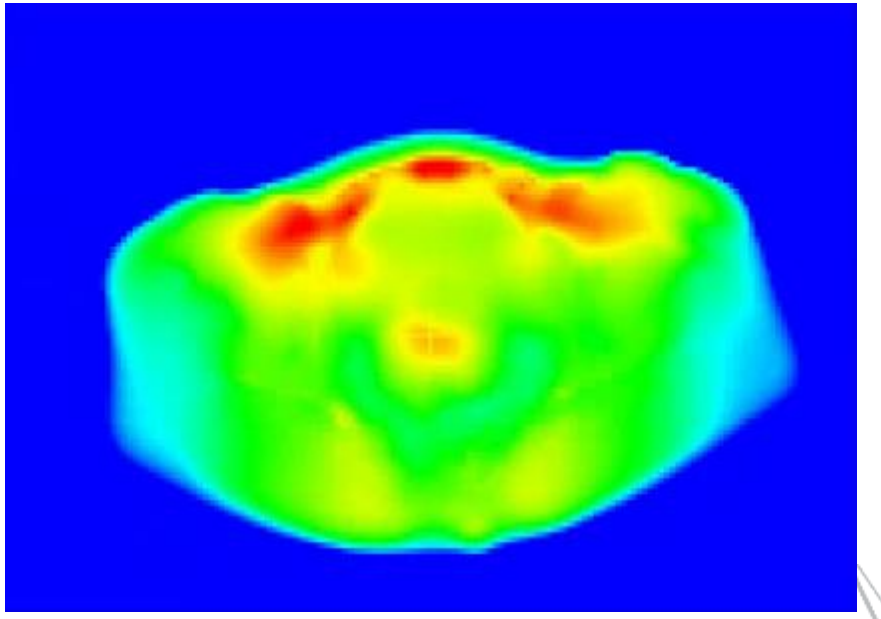
Implementation

Hyperthermia Treatment Planning: research version of Plan2Heat.

- Nominal temperature distribution
  - Maximize T90 in the GTV
  - Hard constraint normal tissue temperature < 45°C
  - Nominal device configuration
    - Total power, amplitudes and phases for each antenna.
- Realistic alternative temperature distributions. Simulate 16 scenarios:
  - Phase-amplitude steering.
  - Power increase/decrease.
  - Change in time interval.

Patient model: segmented tissue types, water bolus and antennas





Temperature distribution

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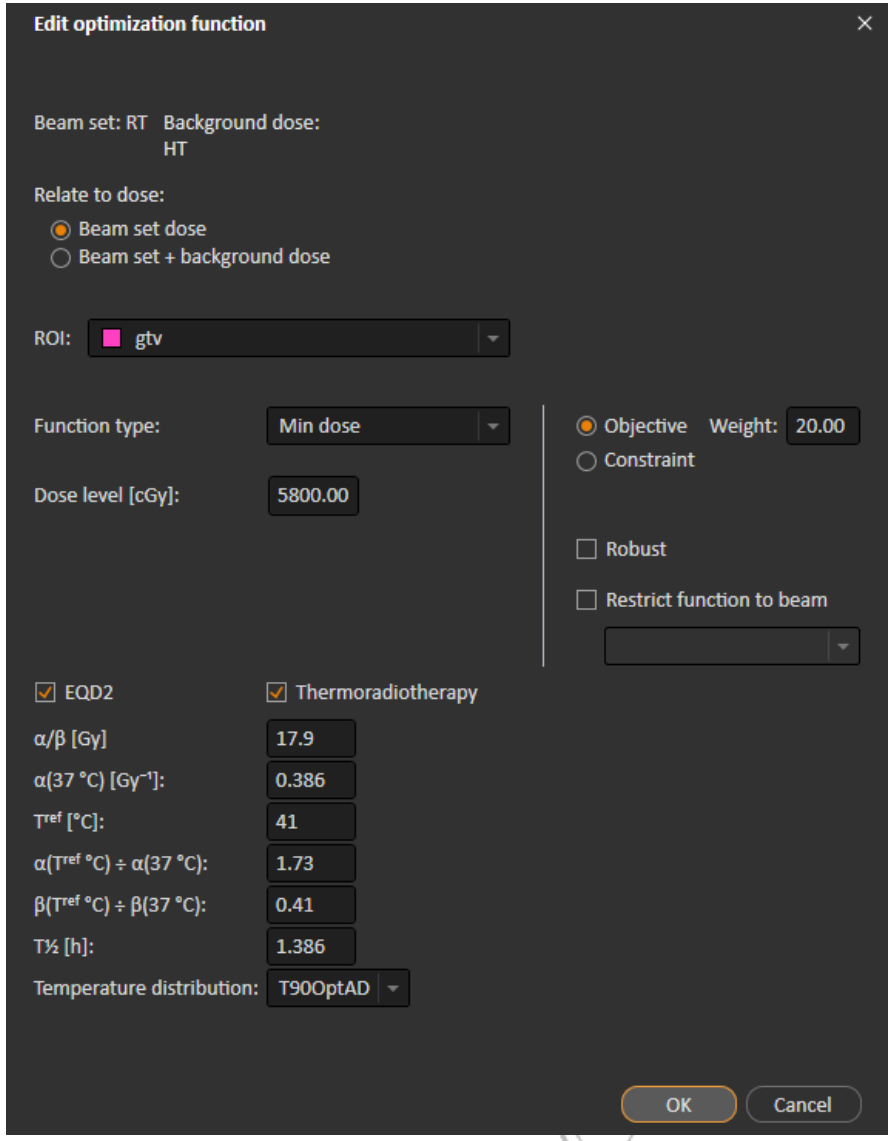
Implementation

- Optimization:
  - Optimization functions will take into account dose of the voxel as the EQD_{RT}.
    - Model parameters
    - Temperature distribution.
  - Strategic goals:
    - Keep dose in OARs and PTV as in the RT only plan
    - Achieve a specific dose level with EQD_{RT} in the GTV (58 Gy)
    - Homogeneous coverage of the GTV.



Implementation

- Robust Optimization:
  - Used for GTV
    - Maintain GTV coverage for lower temperature levels
    - Avoid overdosage for higher temperature levels

Function	Constraint	Dose	ROI	Description	Robust	Weight	Value	EUD [cGy]	α/β [Gy]	Thermoradiotherapy
Physical composite objective										
Max dose		Beam set	bladder	Max dose 5000.00 cGy		3.00	1.2800E-4		3	★
Max DVH		Beam set	bladder-ptv	Max DVH 3000.00 cGy to 80.00% volume		5.00	8.7960E-6			
Max DVH		Beam set	bladder-ptv	Max DVH 4000.00 cGy to 20.00% volume		5.00	5.1133E-4			
Max dose		Beam set	bowel_bag	Max dose 5000.00 cGy		3.00	5.5463E-5		3	★
Max EUD		Beam set	bowel-ptv	Max EUD 2900.00 cGy, Parameter A 7		5.00	1.0438E-4	2929.63		
Dose fall-off		Beam set	External	Dose fall-off [H]4800.00 cGy [L]3600.00 cGy, Low dose distance 2.00 cm		1.50	6.7993E-5			
Dose fall-off		Beam set	External	Dose fall-off [H]4800.00 cGy [L]2300.00 cGy, Low dose distance 4.00 cm		1.00	4.0119E-4			
Min dose		Beam set	gtv	Min dose 5800.00 cGy	★	30.00			17.9	★
Max dose		Beam set	gtv	Max dose 5800.00 cGy		15.00	0.0000			
Max DVH		Beam set	gtv	Max DVH 5950.00 cGy to 0.10% volume	★	15.00			17.9	★
Min dose		Beam set	ptv	Min dose 4600.00 cGy		18.00	0.0035			
Max DVH		Beam set	ptv-gtv	Max DVH 4650.00 cGy to 0.10% volume		12.00	0.0053			
Max dose		Beam set	rectum	Max dose 4900.00 cGy		3.00	7.1314E-4		3	★
Max DVH		Beam set	rectum-ptv	Max DVH 3000.00 cGy to 75.00% volume		2.00	5.4490E-5			
Max DVH		Beam set	rectum-ptv	Max DVH 4000.00 cGy to 30.00% volume		3.00	2.9648E-7			

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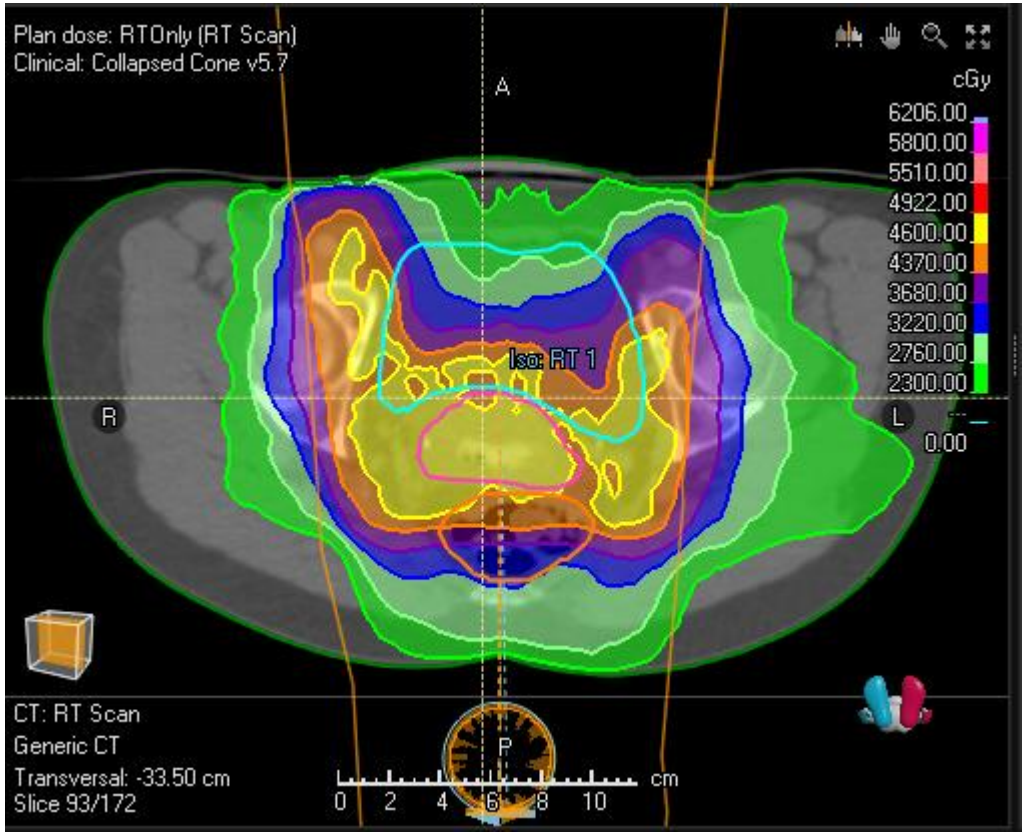
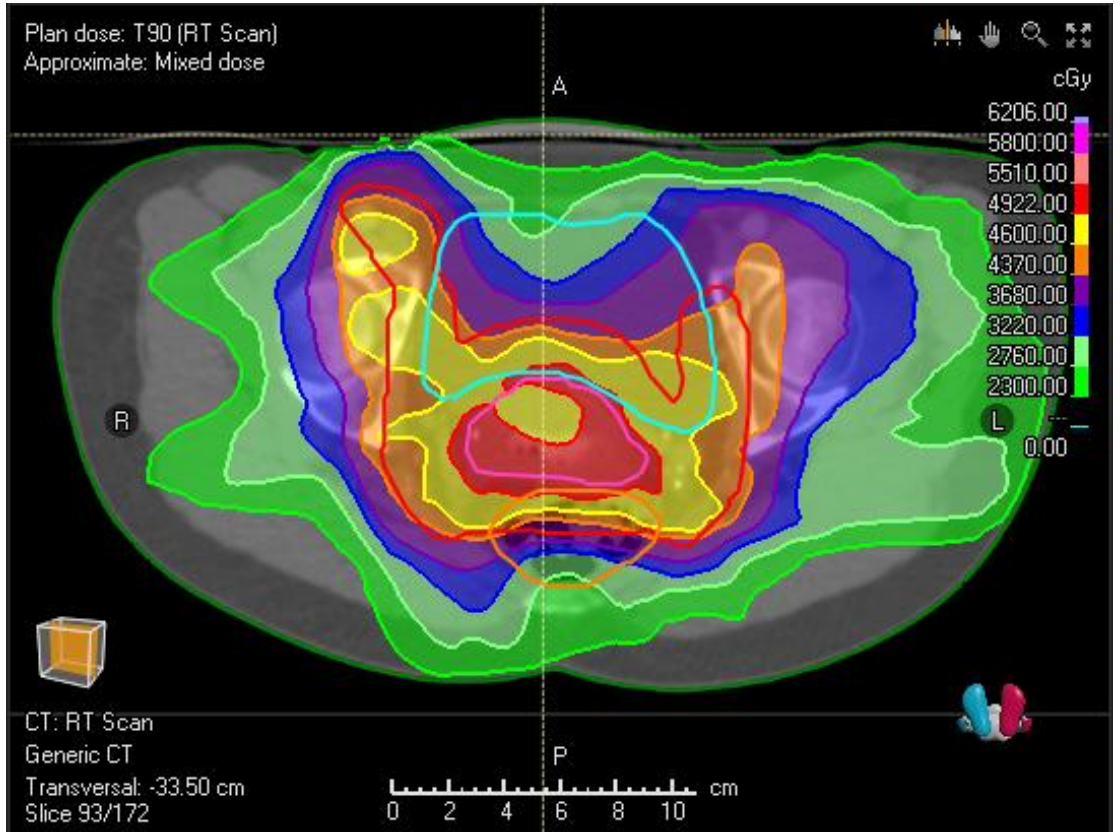
Some Results

EQD_{RT} optimization: increase in EQD_{RT} level and homogeneity with respect to standard planning.



Dose: standard plan



Dose: EQD_{RT} optimized plan

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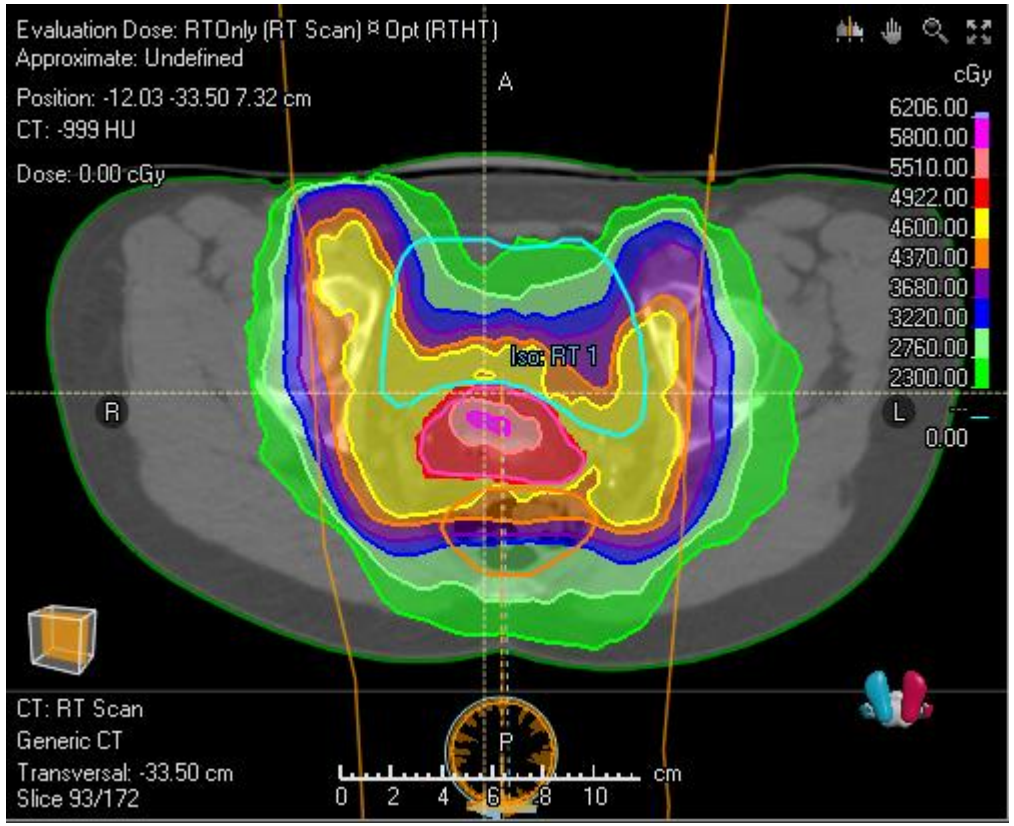
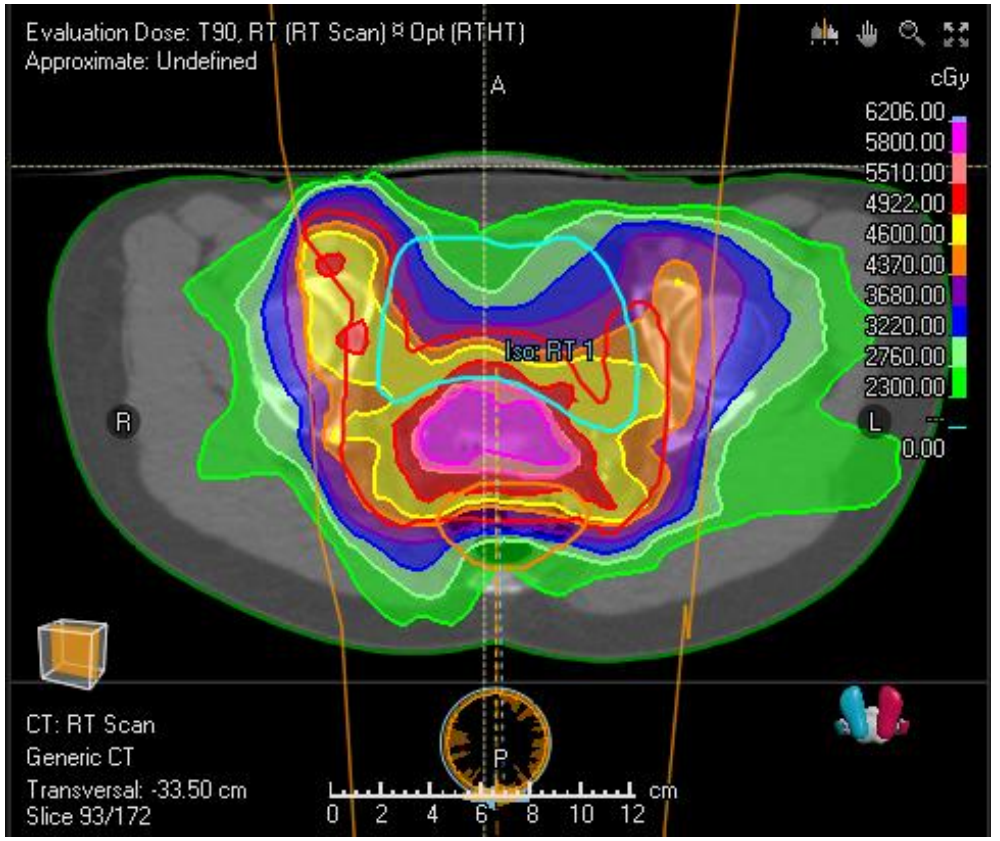
Some Results

EQD_{RT} optimization: increase in EQD_{RT} level and homogeneity with respect to standard planning.



EQD_{RT}: standard plan



EQD_{RT}: EQD_{RT} optimized plan

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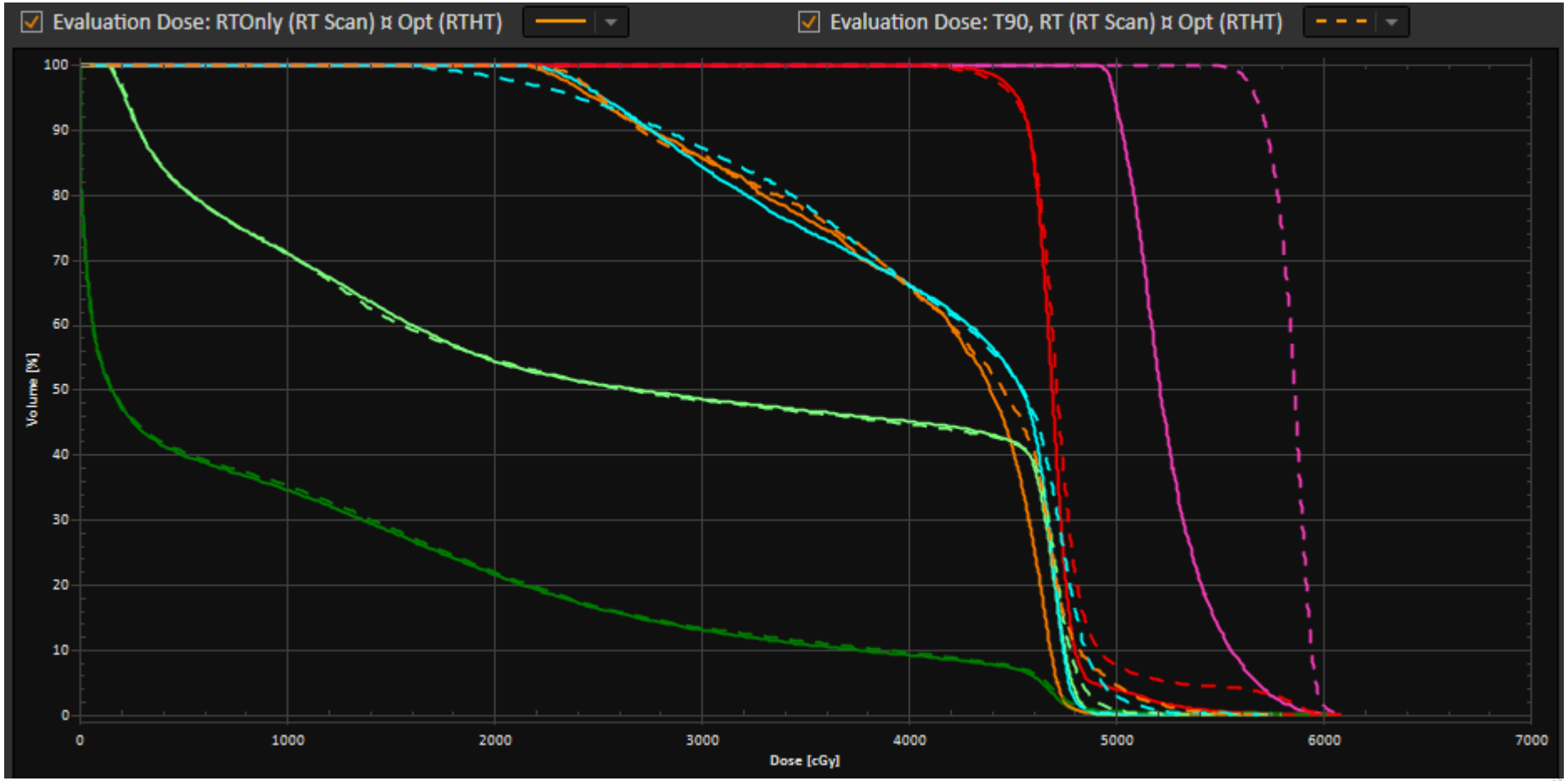
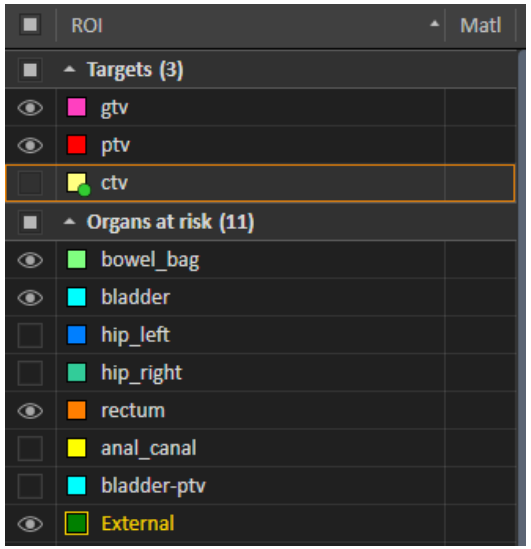
Some Results

EQD_{RT} optimization: increase in EQD_{RT} level and homogeneity with respect to standard planning.





EQD_{RT}: EQD_{RT} optimized plan (dashed) and standard plan (solid)

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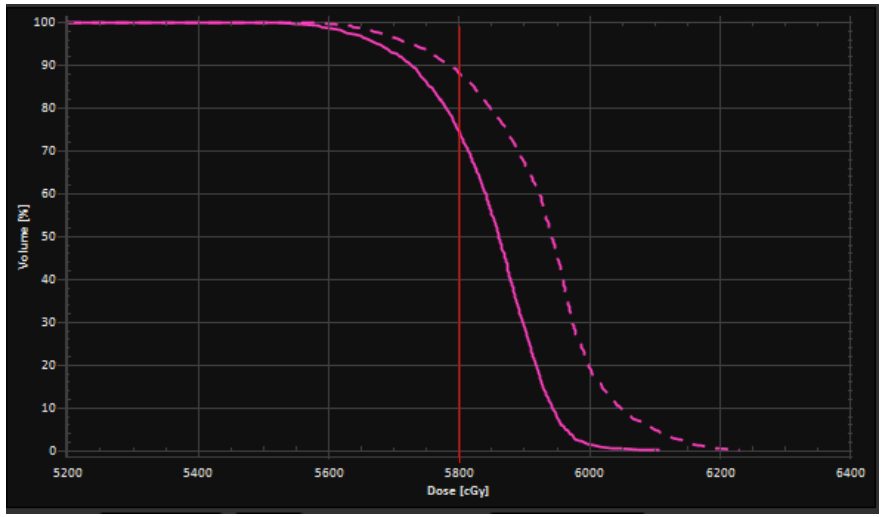
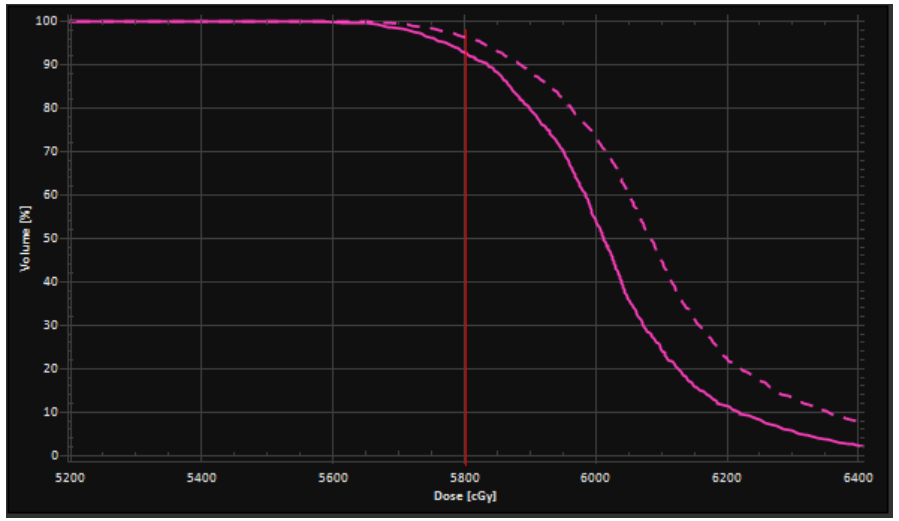
Some Results

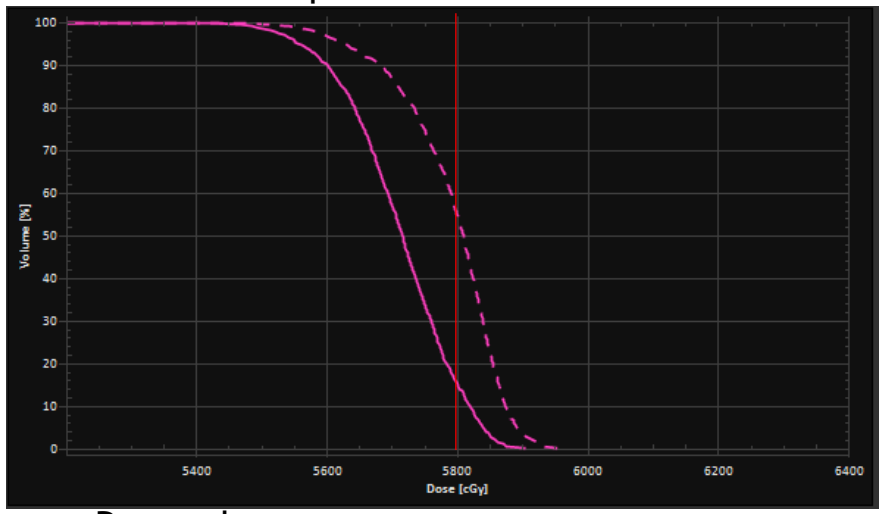
Robust optimization: GTV coverage improves for alternative temperatures at the cost of reduced homogeneity



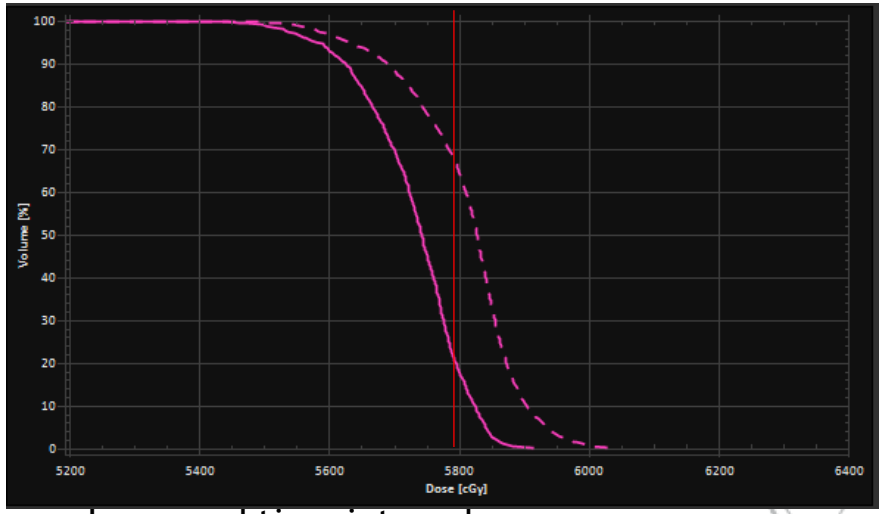
Nominal temperature



Power increase



Power decrease



Increased time interval

EQD_{RT} for the GTV:

— nominal EQD_{RT} optimized plan

– – robust EQD_{RT} optimized plan

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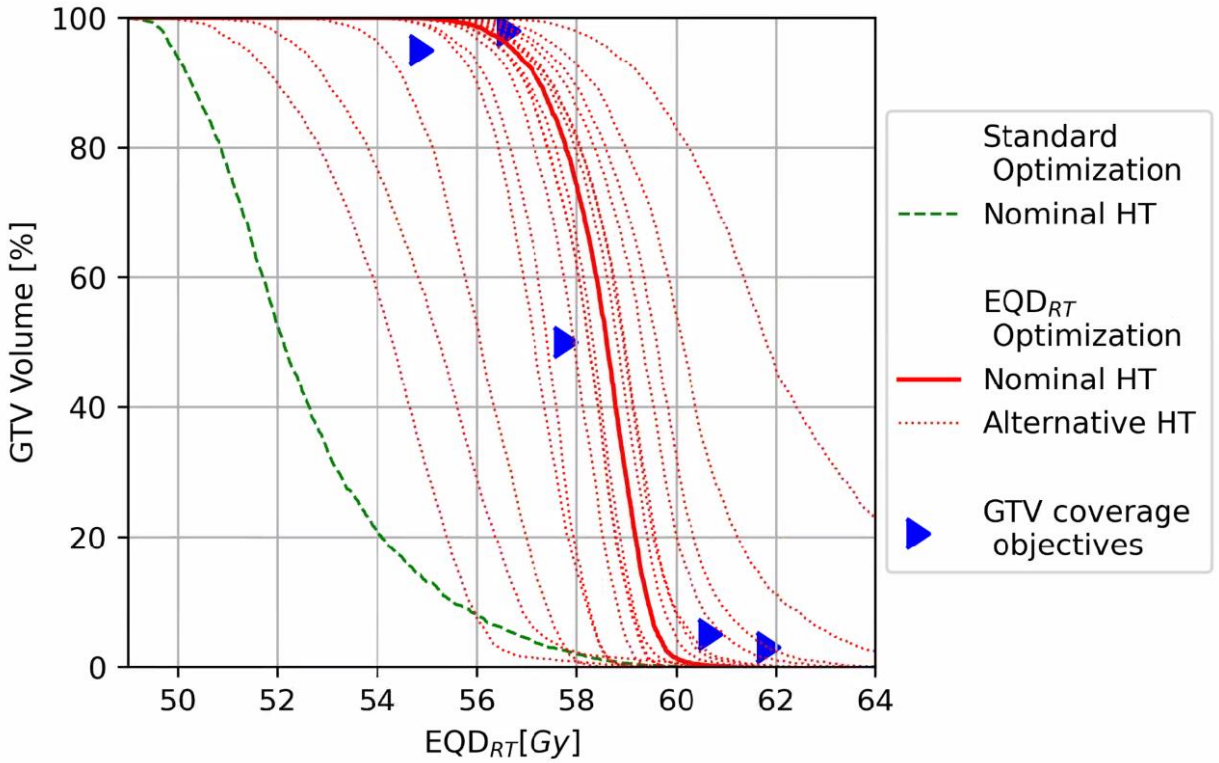
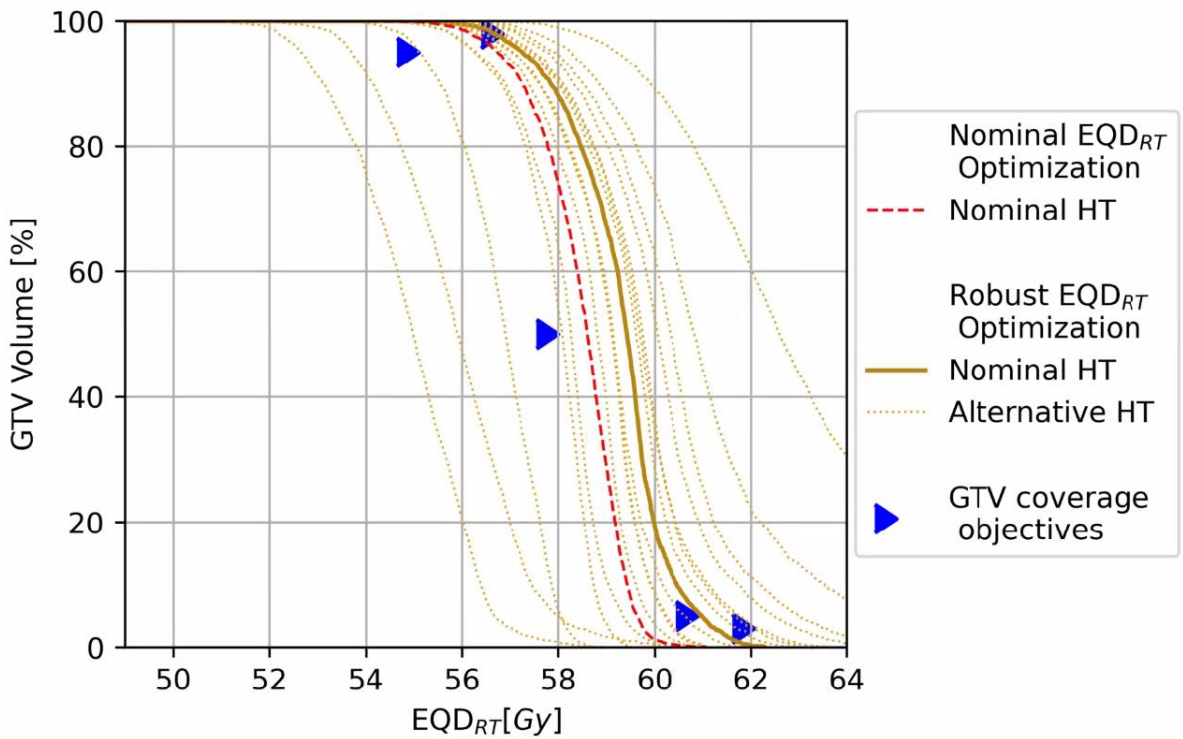
Some Results

Robustness evaluation for the nominal and 16 alternative temperature scenarios



Nominal EQD_{RT} optimized plan



Robust EQD_{RT} optimized plan

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Some Results

Comparison robust vs nominal EQD_{RT} optimized plan:

- Evaluation of clinical goals in the GTV
  - Coverage:
    - EQD_{RT}98%>56.84 Gy
    - EQD_{RT}95%>55.1 Gy
    - EQD_{RT}50%>58 Gy
  - Homogeneity:
    - EQD_{RT}5%<60.9 Gy
    - EQD_{RT}3%<62.06 Gy
    - Homogeneity index at 95% volume > 0.94
- 6 clinical goals evaluated in 17 EQD_{RT} distributions (nominal and 16 alternative) for each plan.

Some Results

Comparison robust vs nominal EQD_{RT} optimized plan:

- Coverage:
  - 53% clinical goals achieved for nominal plan
  - 69% robust
- Homogeneity:
  - 74% clinical goals achieved for nominal plan
  - 55% robust
- GTV coverage improves for alternative temperatures for the robustly optimized plan, at the cost of reduced homogeneity
  - In both the robust and nominal plan, clinical goals are not achieved for some of the alternative scenarios

Summary

- Hyperthermic enhancement of RT dose can be modelled at a voxel level with the linear quadratic model (EQD_{RT}).
- RayStation prototype for (robust) optimization of EQD_{RT} accounts for the temperature distribution and realistic alternative scenarios that could occur as a result of changing device settings in response to hot spots or a change in time interval for logistic reasons.
- EQD_{RT}optimization allows to increase dose level and homogeneity compared to standard planning.
- Robust optimization can increase dose coverage at the cost of reduced homogeneity.

Future work

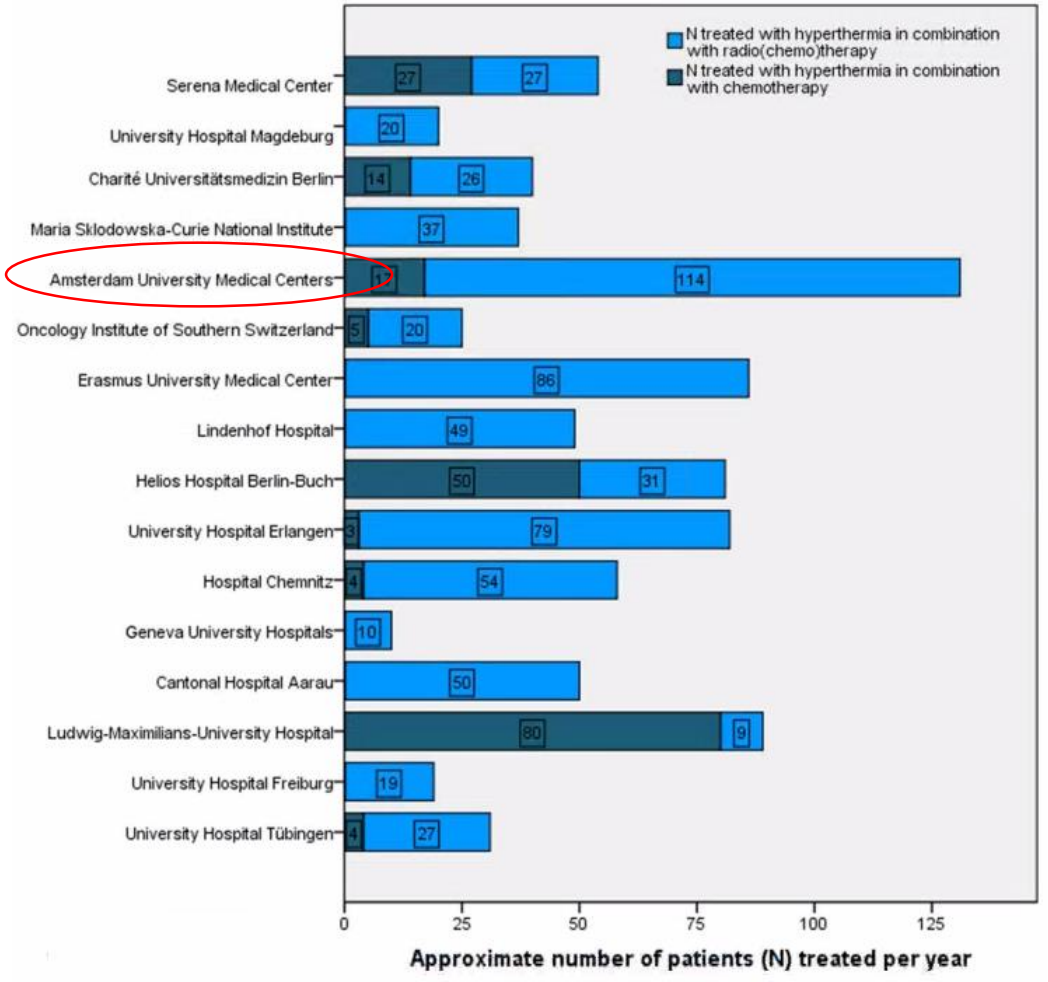
- Poster ESTRO 2023 (EQD_{RT} optimization and robustness evaluation)
  - Plans optimized for alternative scenarios (not shown here)
- Oral presentation STM 2023 for robust optimization.
- Paper in progress (comparison of optimization strategies)
- Further analysis of optimization strategies and influence of treatment schedule.
- Improvements in the model: normal tissue effects, heterogeneities.

Amsterdam UMC
Universitair Medische Centra

Thanks for your attention!
Questions?

Clinical Application of Hyperthermia

- Cervical cancer (Van der Zee, 2002):
  - Increase in OS of ~20% in randomized trial.
  - Radiation toxicity not enhanced by HT
- Amsterdam UMC:
  - HT when contraindication for CT
  - 1 weekly fraction with 5 weekly RT.
- Other indications:
  - Breast (recurrent), head and neck, rectal, bladder, melanoma, NSCLC, glioblastoma, sarcoma and others (Peeken, 2002).
- Reimbursement for some indications



Ademaj et al. Strahlenther Onkol 2022

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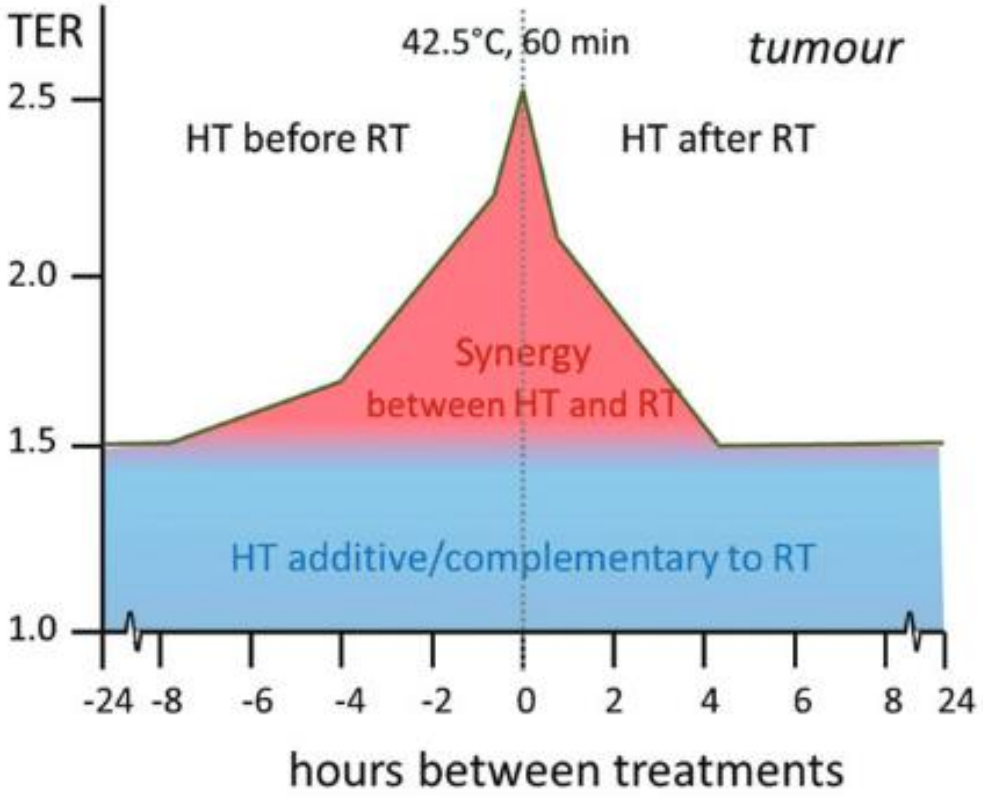
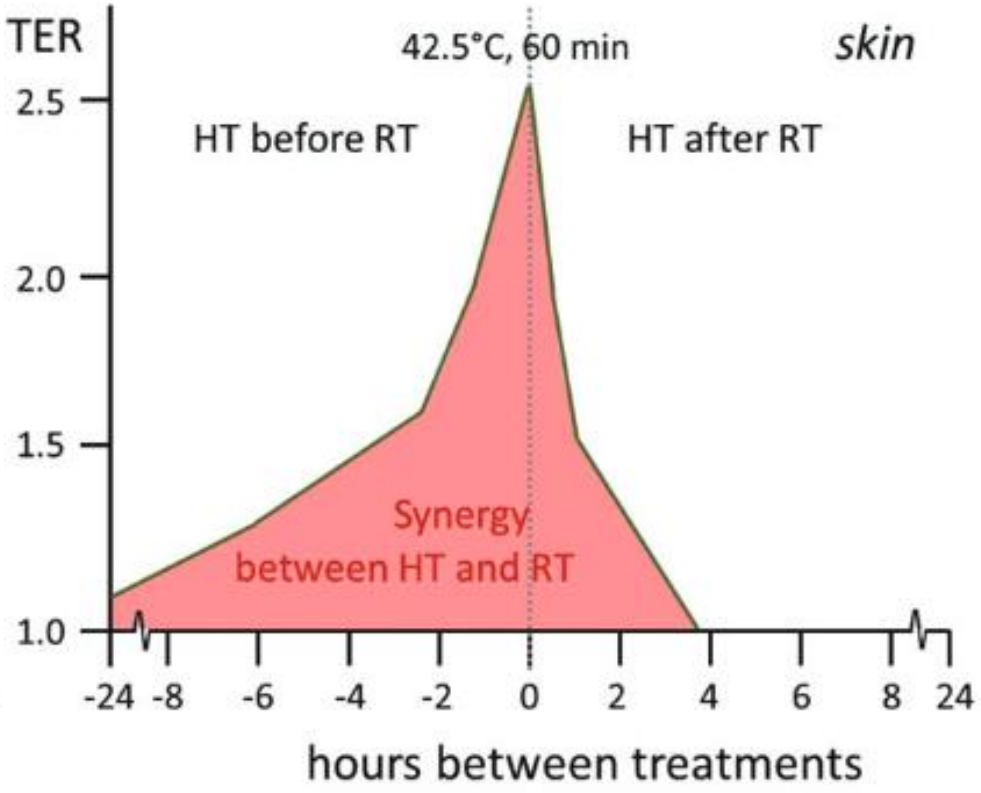
Response to RT + HT treatment

- Thermal Enhancement Ratio (TER): Ratio of the RT dose for RT alone divided by the RT dose for RT + HT with the same cell survival *in vitro*.
- Radiosensitization is tumor sensitive, and time interval is relevant.

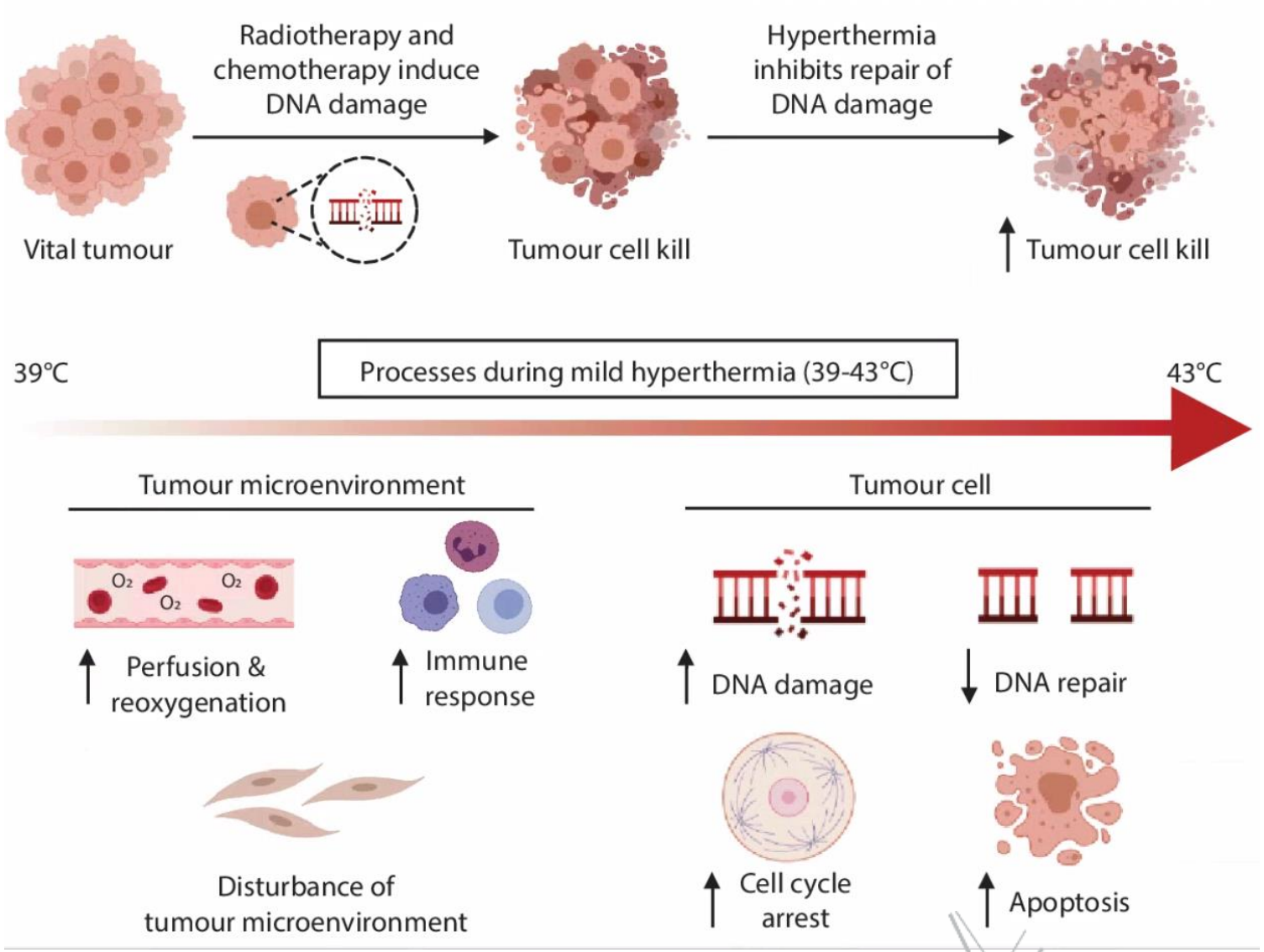




Crezee et al. Int J Hyperth 2016, data from Overgaard, Int J Radiat Oncol Biol Phys 1980

Response to RT + HT treatment

- Complex interaction with cell mechanisms (especially DNA repair) and tumor microenvironment.
- Synergistic effects (depend on RT dose, temperature, duration, time interval)
- Additive effects (independent on RT dose).



IJff et al. Int J Gynecol Cancer 2021

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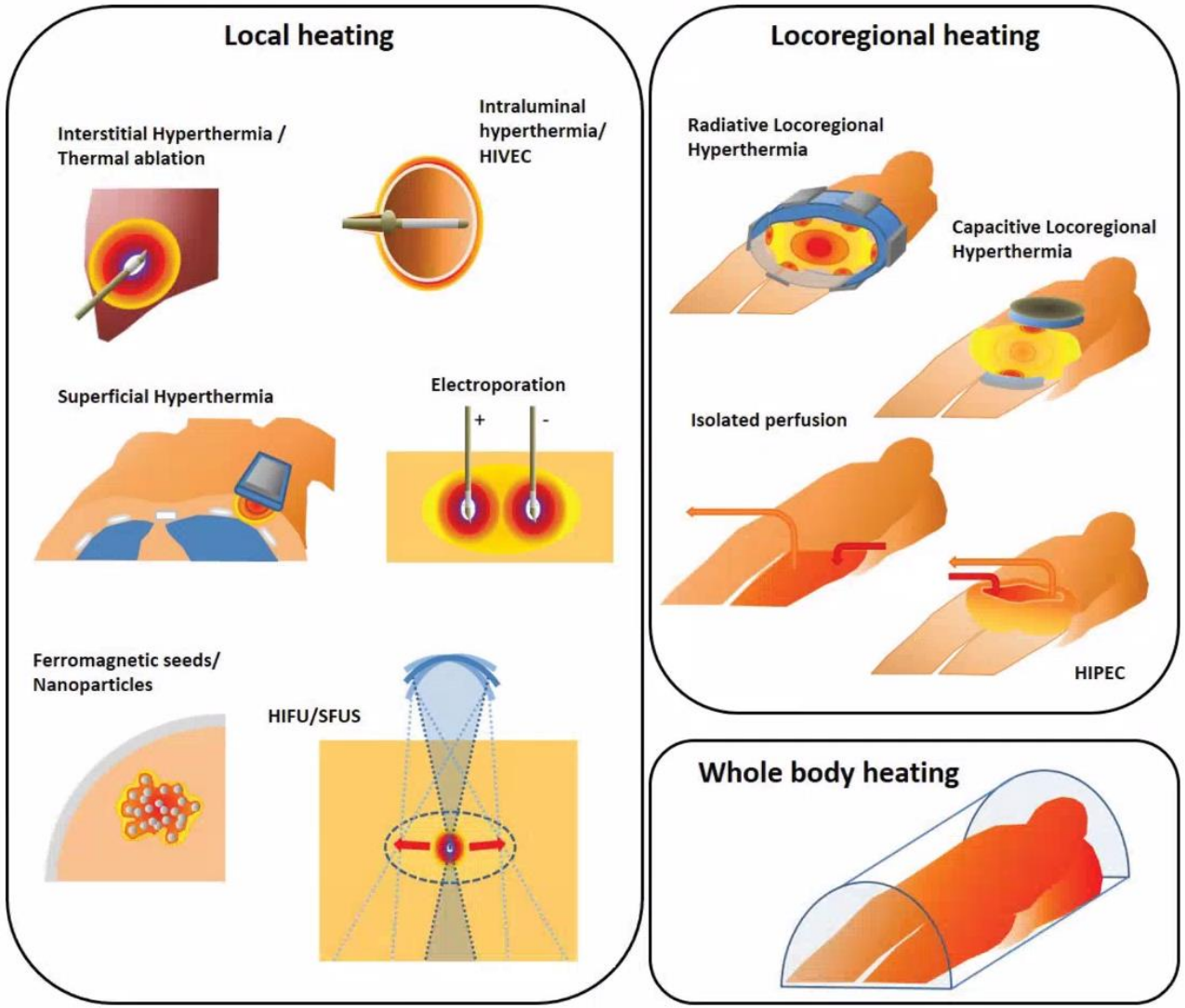
Thermal Therapy in Oncology



Kok et al. Int J Hyperth 2020

- Hyperthermia: Heating to 39-45°C to induce sensitization to radiotherapy and chemotherapy.
- Thermal ablation: temperatures beyond 50°C to destroy tumor cells directly.
- Different heating techniques and extent, depending on application.
  - Focus on deep locoregional radiative hyperthermia.

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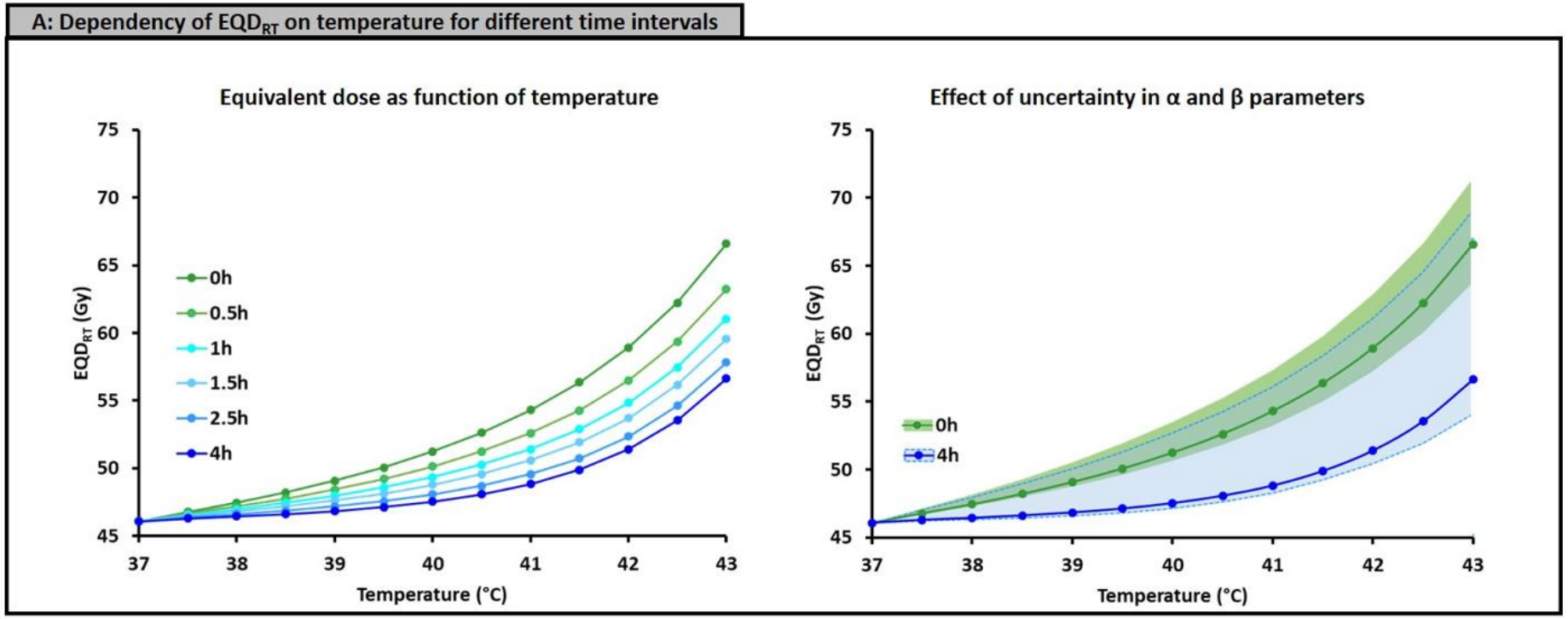
Equivalent dose for RT + HT

- EQD_{RT} : Dose needed with radiotherapy to have the same effect than the combined treatment.
- Derived from EQD concept
  - α and ß function of temperature and time Interval between radiotherapy and hyperthermia
- Parameters from cell survival assays.
- Calculation at a voxel level
  - EQD_{RT} distribution, DVHs, etc.
- EQD_{RT} for the whole treatment:
  - Take into account fractions RT + HT, fractions only RT

Modeling the combined treatment

- Model limitations:
  - Tumor homogeneous in sensitivity
    - Not taking into account oxygen levels, vascularization, etc.
  - Mostly DNA repair inhibition (modified LQM parameters) and direct cell kill (temperature dependent term).
  - Normal tissue: No direct cell kill and fastest decay for synergistic effect.



EQD_{RT} for a scheme of 23 fractions of 2 Gy with weekly hyperthermia (homogeneous temperature)

Kok et al. Int J Radiat Oncol Biol Phys 2022

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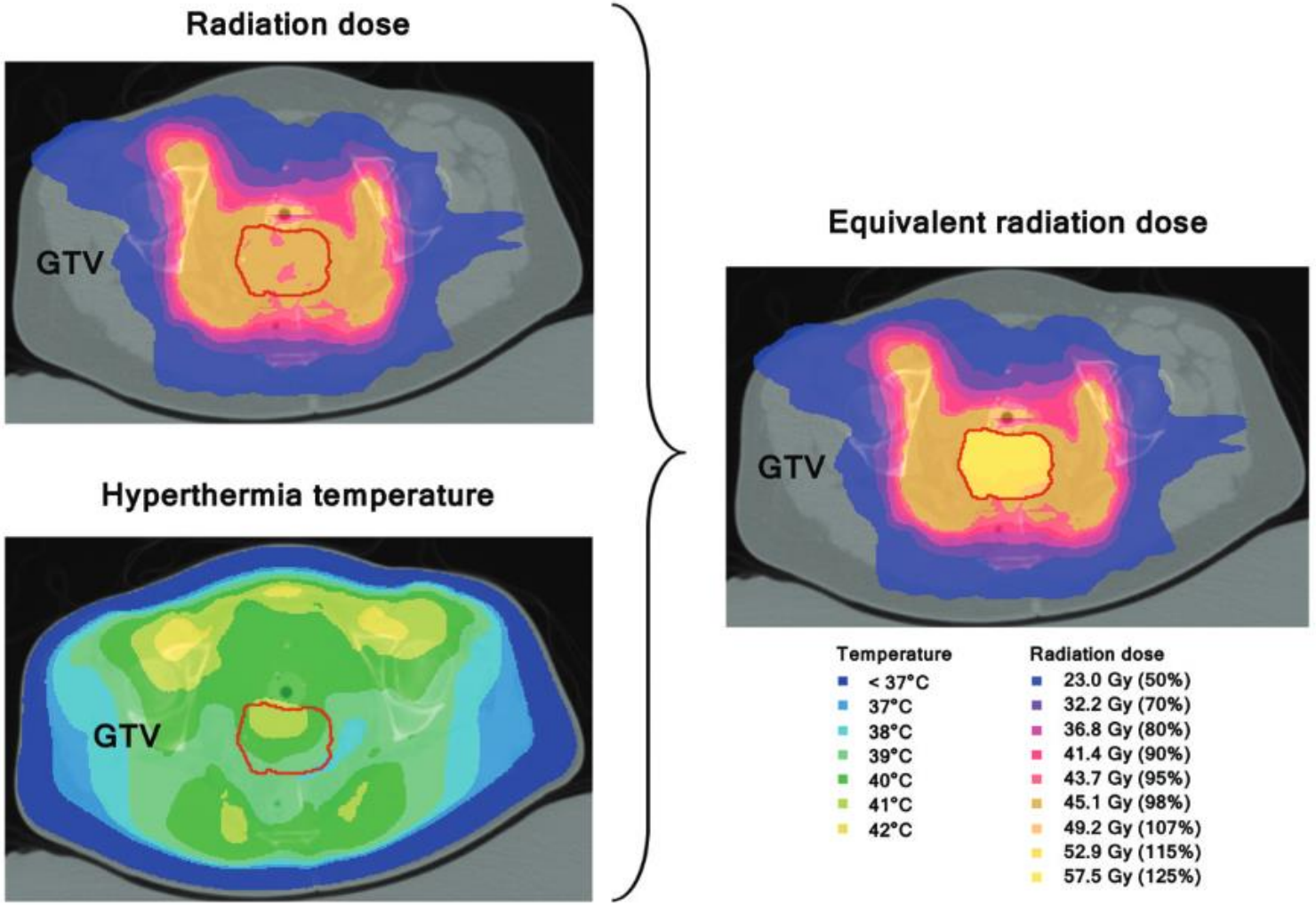
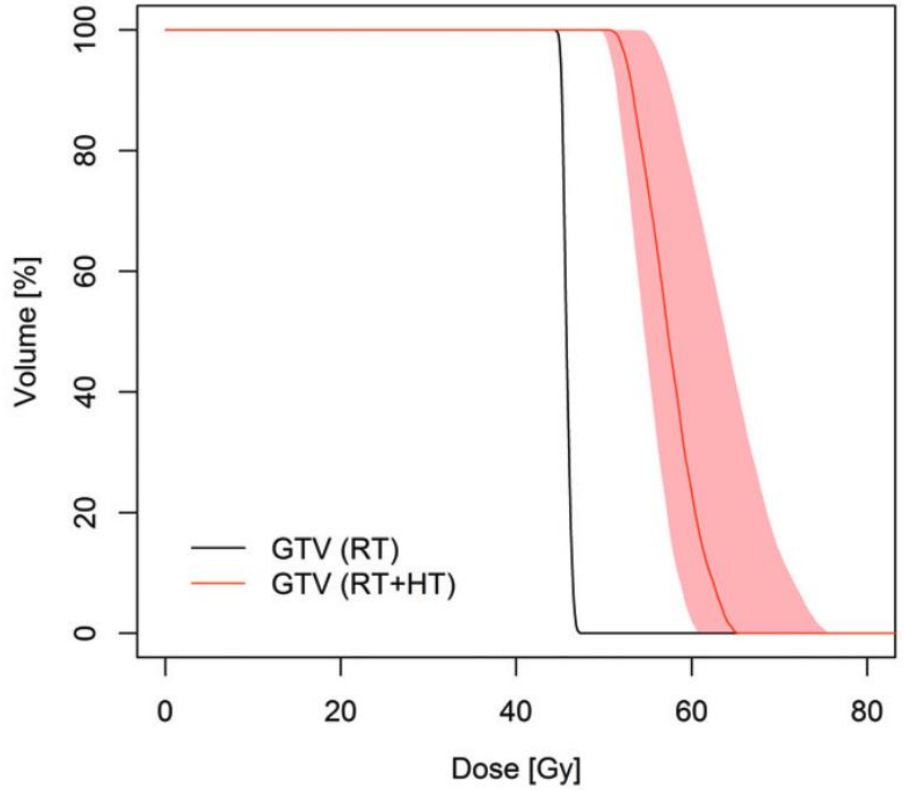
Equivalent dose for RT-HT



- The temperature distribution can be used to calculate an equivalent radiation dose voxel by voxel.



Van Leeuwen et al. Int J Hyperth 2018

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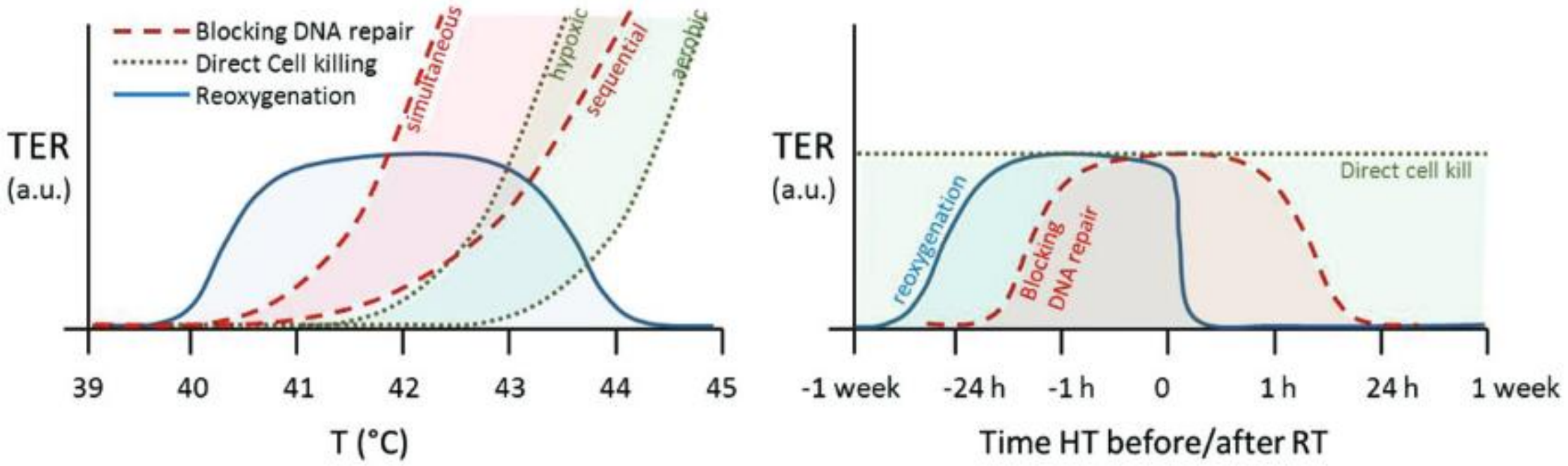
Effects of the combined treatment

- Modeling is not the same for additive and synergistic effects of hyperthermia and radiotherapy.
- Time and spatial dependence (heterogeneity, heat response).



Crezee et al. Int J Hyperth 2016

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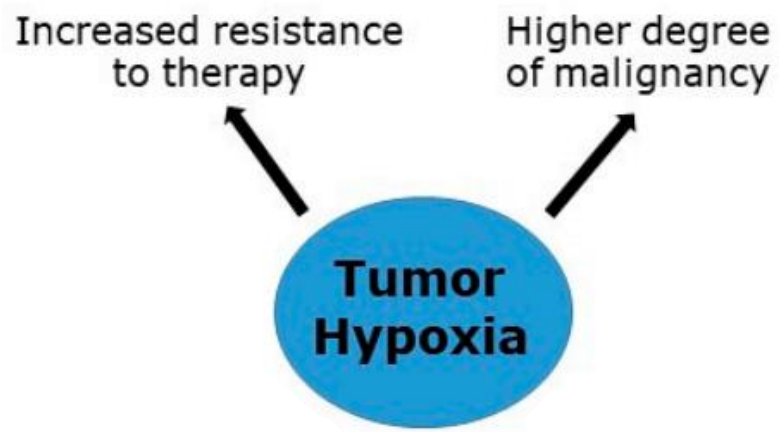
Hypoxia and hyperthermia



Elming et al.,
Cancers (Basel)
2019

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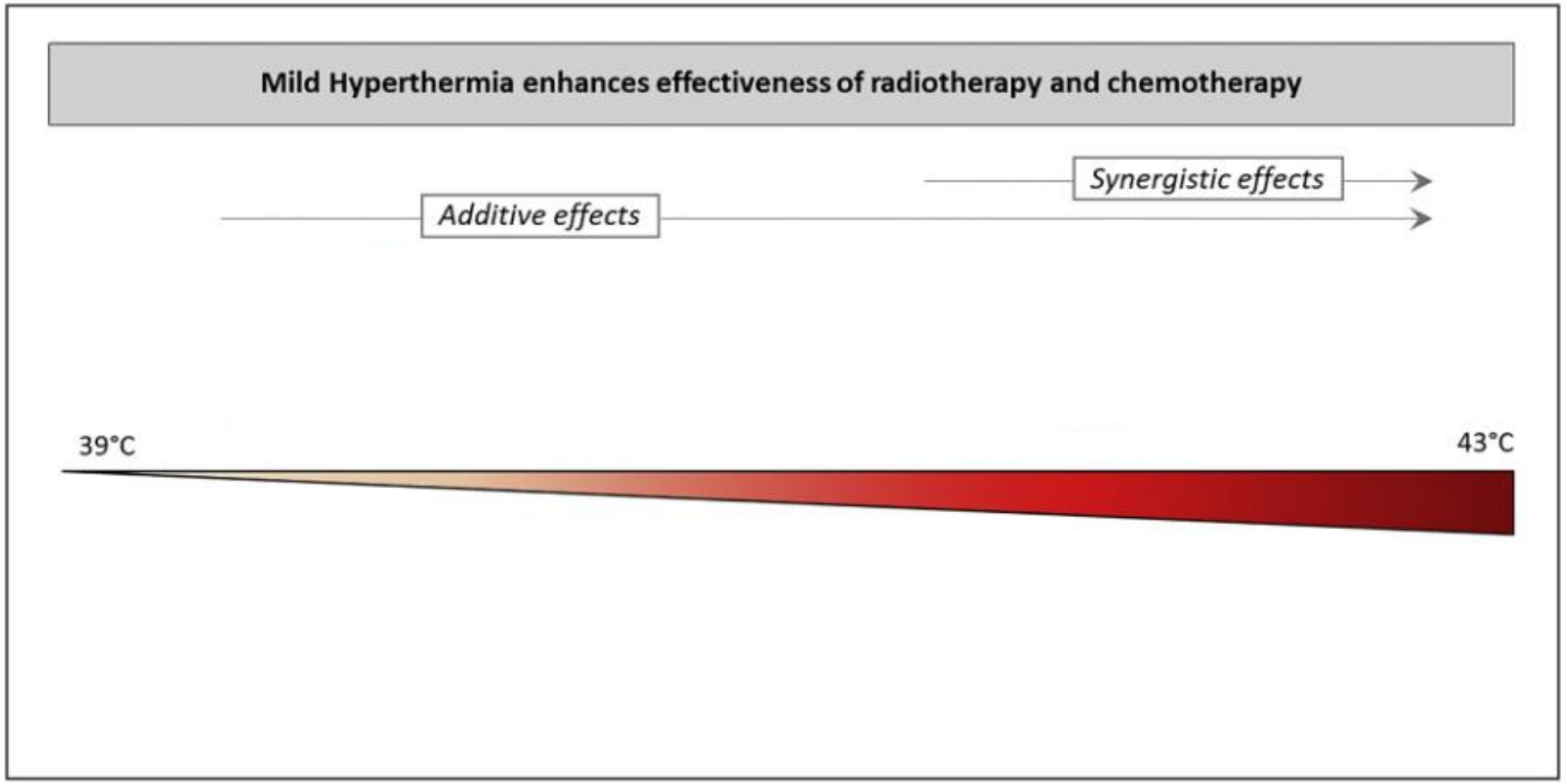
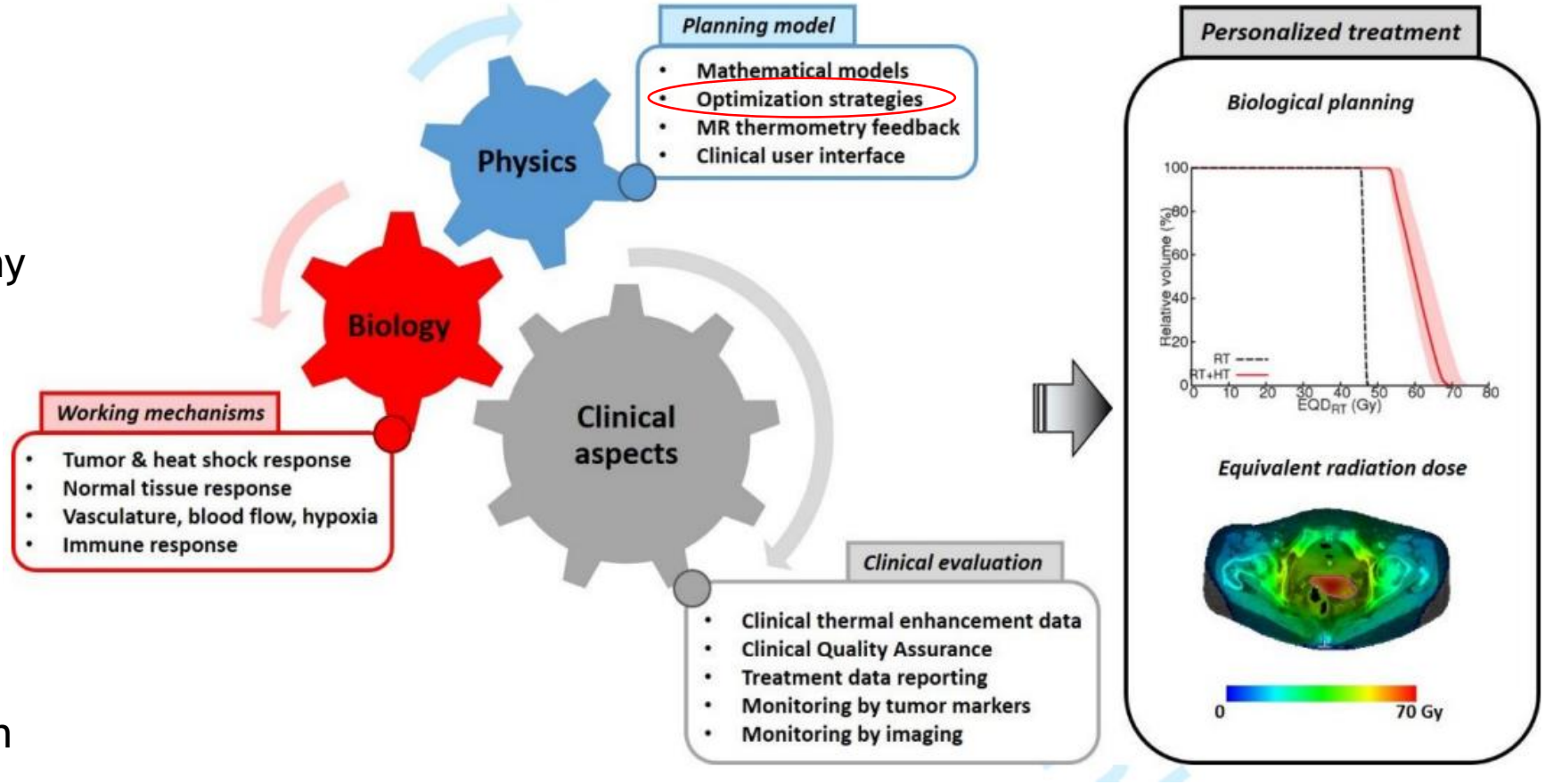
Response to RT + HT treatment



Oei et al. Adv. Drug Deliv. Rev. 2020

Hyperboost Consortium

- EU Horizon 2020 Innovative training network.
- 14 PhD projects, 11 beneficiaries in Netherlands, Sweden, Switzerland, Germany and Italy.
- Amsterdam UMC lead beneficiary, 2 PhD projects.
- RaySearch is a partner organization for the project.
- Secondments for collaboration within the network



Kok et al. Int J Hyperth 2022

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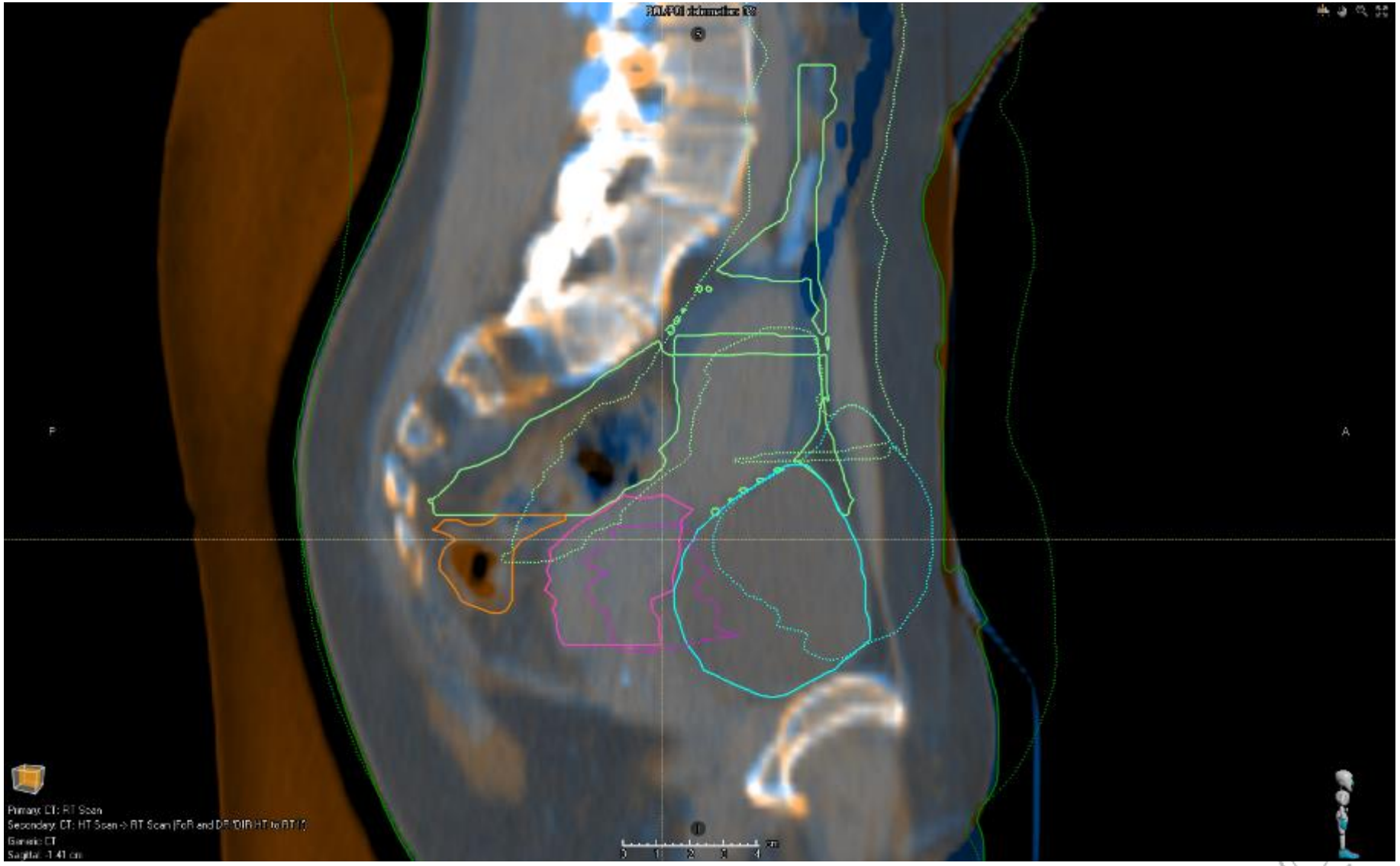
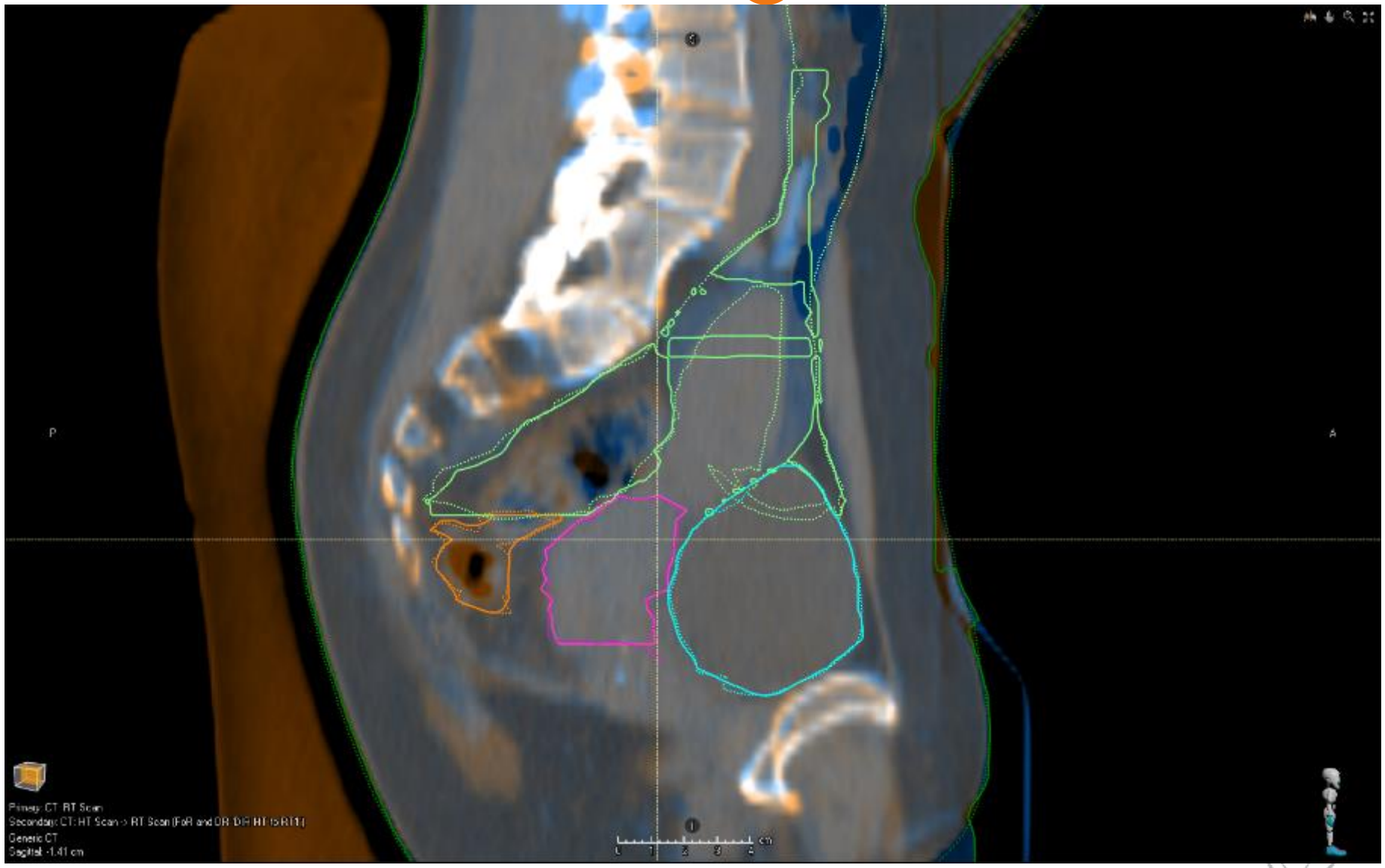
HYPERBOOST
Boosting the effect of Radiotherapy

Implementation in RayStation



Deformed CT,
undeformed ROIs

Implementation in RayStation



Deformed CT,
deformed ROIs

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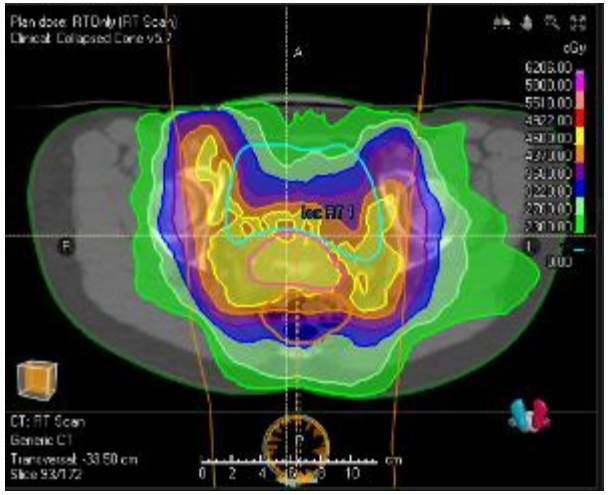
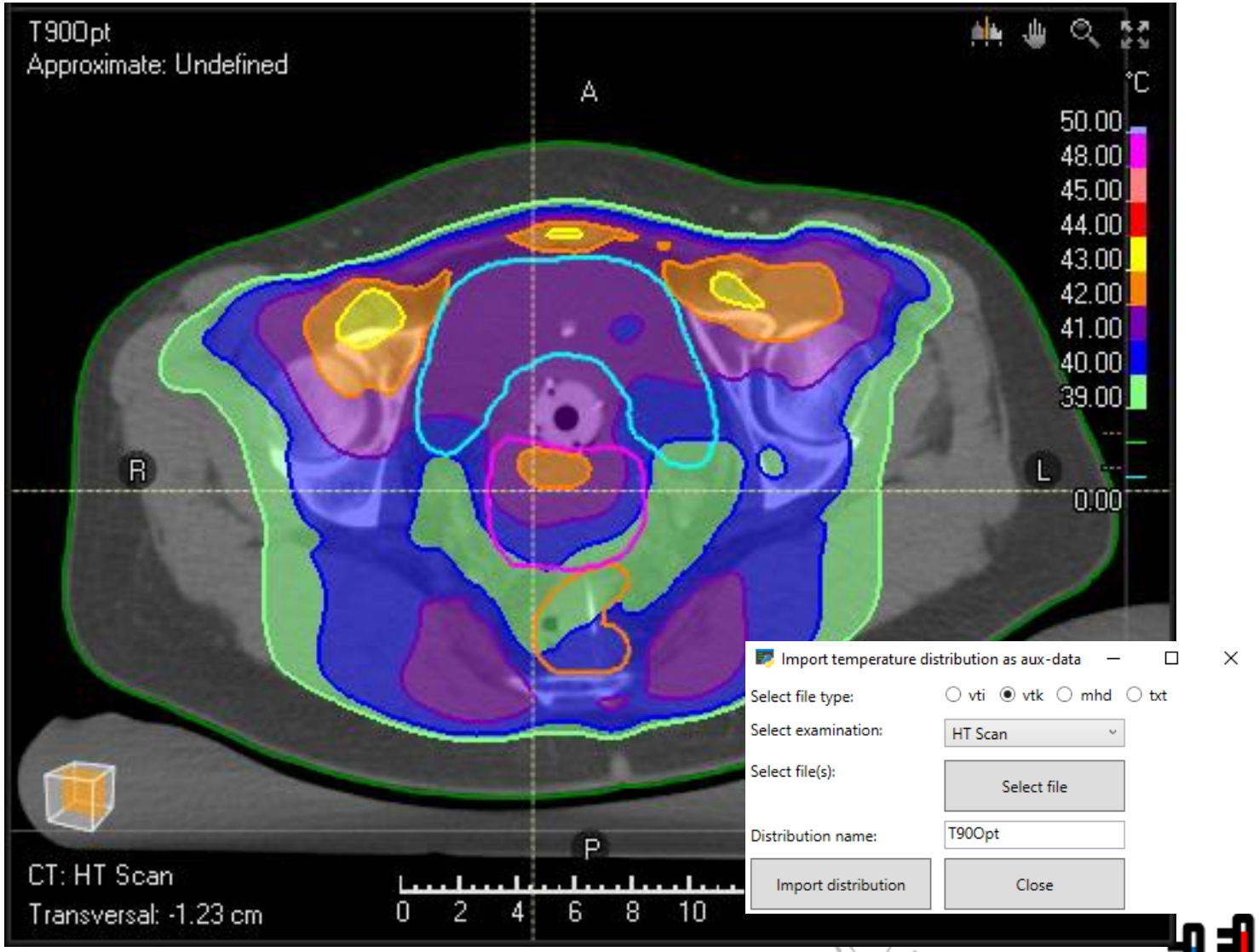
HYPERBOOST
Boosting the effect of Radiotherapy

Implementation

- Nominal and alternative temperature distributions imported to RayStation as .vtk (Python scripting)
  - Auxiliary dose associated to the HT scan.
- Standard VMAT plan
  - 23 fractions of 2 Gy to PTV
  - For comparison and reference of dose to OARs.





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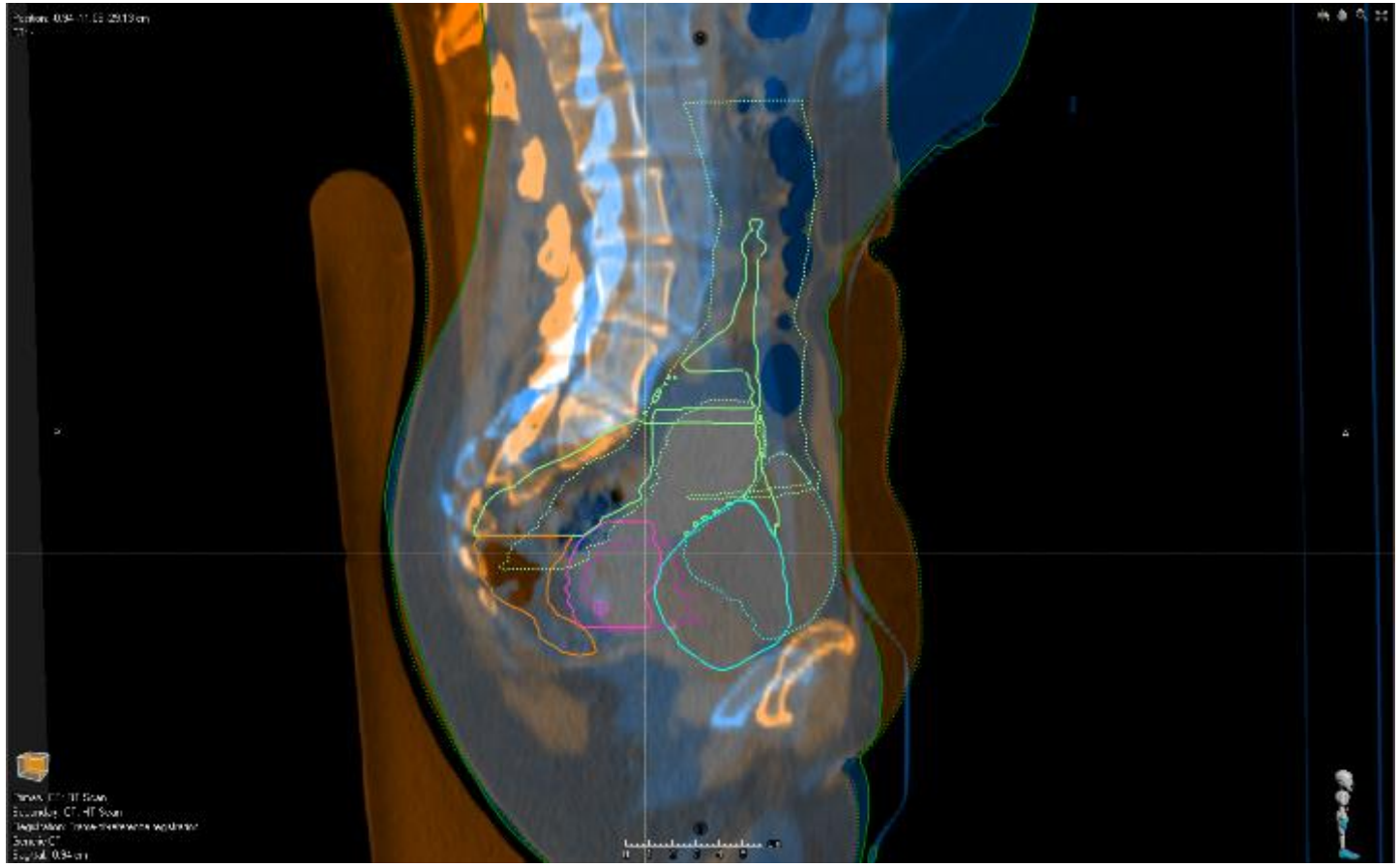
Implementation

- Deformable registration, target HT scan, reference RT scan
  - HT scan supine, RT scan prone
  - HT scan with water bolus, RT scan on flat couch
  - HT scan with empty bladder, RT full bladder.

Reference image set:	CT: RT Scan [20 Aug 2014, 10:44:42 (hr:min:sec)]
Target image set:	CT: HT Scan [12 Sep 2014, 15:16:03 (hr:min:sec)]
Group type:	Hybrid
Discard image information:	No
Deformation strategy:	Default
Similarity measure:	Correlation coefficient
Algorithm:	Hybrid GPU, v3.1
Created on:	15 Nov 2022, 13:21:35 (hr:min:sec)
Default for dose deformation:	No
Approved:	No
Inverted elements:	No

Controlling ROI(s):

Color	Name
	bowel_bag_DIR
	rectum_DIR
	bladder_DIR
	gtv_DIR



Primary RT scan (blue), secondary HT scan (orange)

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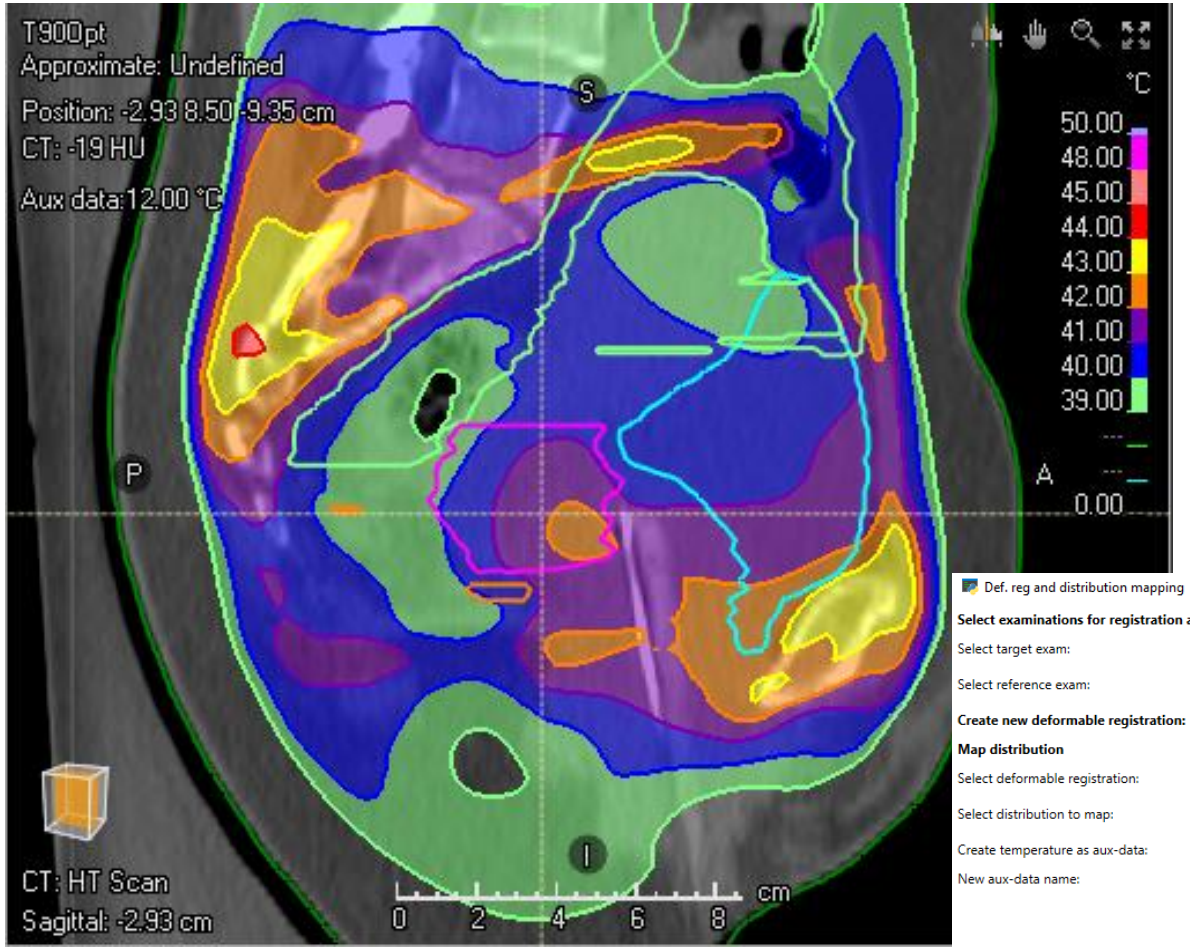
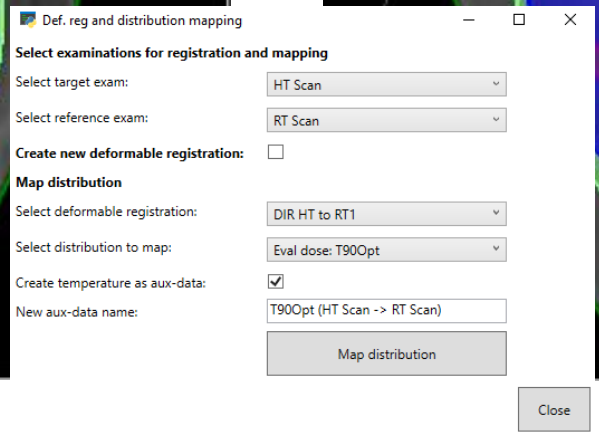
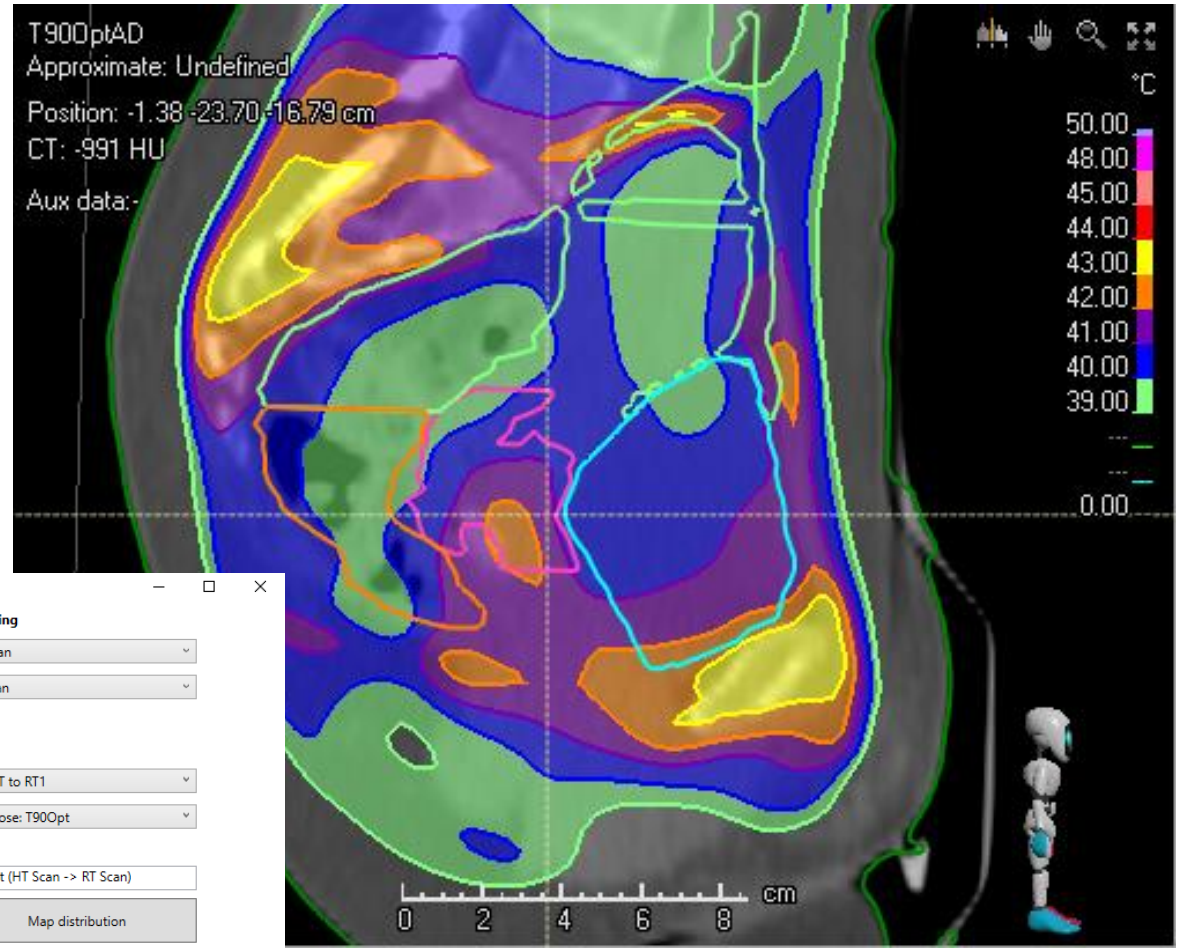
Implementation

- Temperature distribution deformed to RT scan (Python scripting)

RT scan, deformed temperature







HT scan, original temperature

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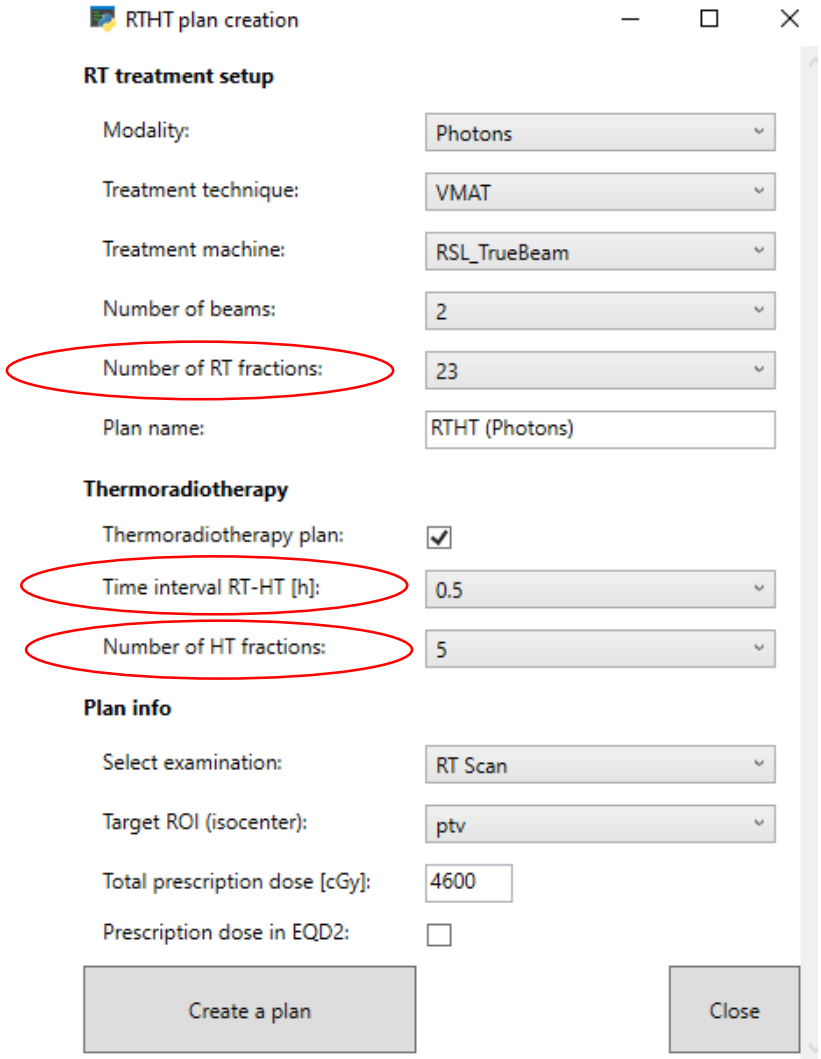
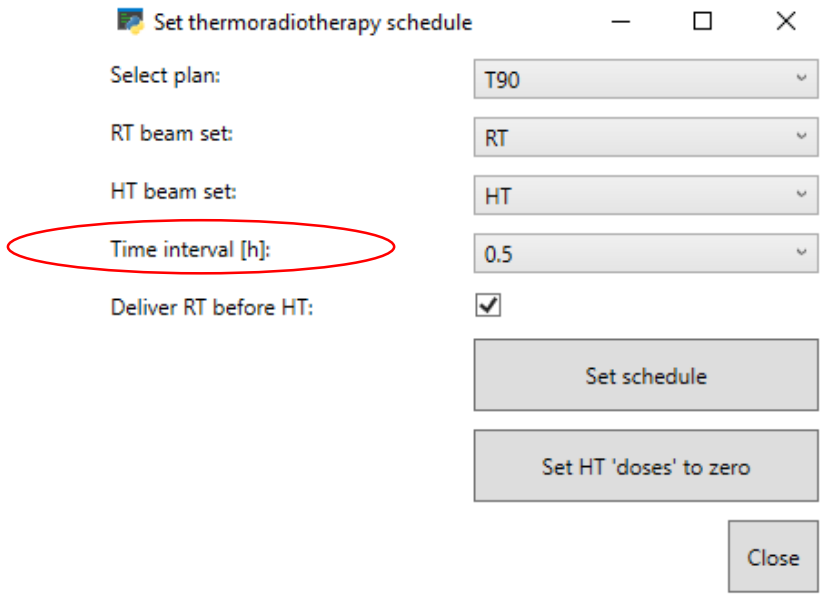
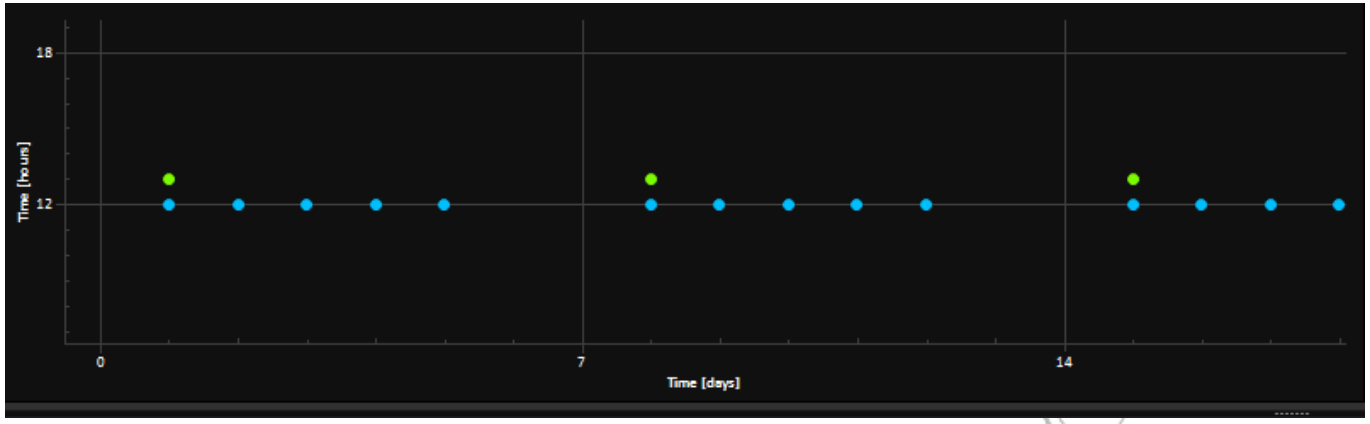
Implementation

- Schedule: HT weekly (mock beam set), time interval with RT is relevant for optimization (Python scripting)







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Implementation

- Optimization: Combination of functions for dose and for EQD_{RT}.

Function	Constraint	Dose	ROI	Description	Robust	Weight	Value	EUD [cGy]	α/β [Gy]	Thermoradiotherapy
Physical composite objective							0.0117			
Max dose		Beam set	bladder	Max dose 5000.00 cGy		3.00	1.1807E-4		3	★
Max DVH		Beam set	bladder-ptv	Max DVH 3000.00 cGy to 80.00% volume		5.00	6.0785E-6			
Max DVH		Beam set	bladder-ptv	Max DVH 4000.00 cGy to 20.00% volume		5.00	3.1120E-4			
Max dose		Beam set	bowel_bag	Max dose 5000.00 cGy		3.00	5.5021E-5		3	★
Max EUD		Beam set	bowel-ptv	Max EUD 2900.00 cGy, Parameter A 7		5.00	5.4064E-5	2921.32		
Dose fall-off		Beam set	External	Dose fall-off [H]4800.00 cGy [L]3600.00 cGy, Low dose distance 2.00 cm		1.50	4.3798E-5			
Dose fall-off		Beam set	External	Dose fall-off [H]4800.00 cGy [L]2300.00 cGy, Low dose distance 4.00 cm		1.00	4.2191E-4			
Min dose		Beam set	gtv	Min dose 5800.00 cGy		20.00	0.0016		17.9	★
Max dose		Beam set	gtv	Max dose 5800.00 cGy		15.00	0.0000			
Max DVH		Beam set	gtv	Max DVH 5900.00 cGy to 0.10% volume		15.00	4.7128E-4		17.9	★
Min dose		Beam set	ptv	Min dose 4600.00 cGy		18.00	0.0029			
Max DVH		Beam set	ptv-gtv	Max DVH 4650.00 cGy to 0.10% volume		12.00	0.0050			
Max dose		Beam set	rectum	Max dose 4900.00 cGy		3.00	6.4211E-4		3	★
Max DVH		Beam set	rectum-ptv	Max DVH 3000.00 cGy to 75.00% volume		2.00	2.9429E-5			
Max DVH		Beam set	rectum-ptv	Max DVH 4000.00 cGy to 30.00% volume		3.00	0.0000			

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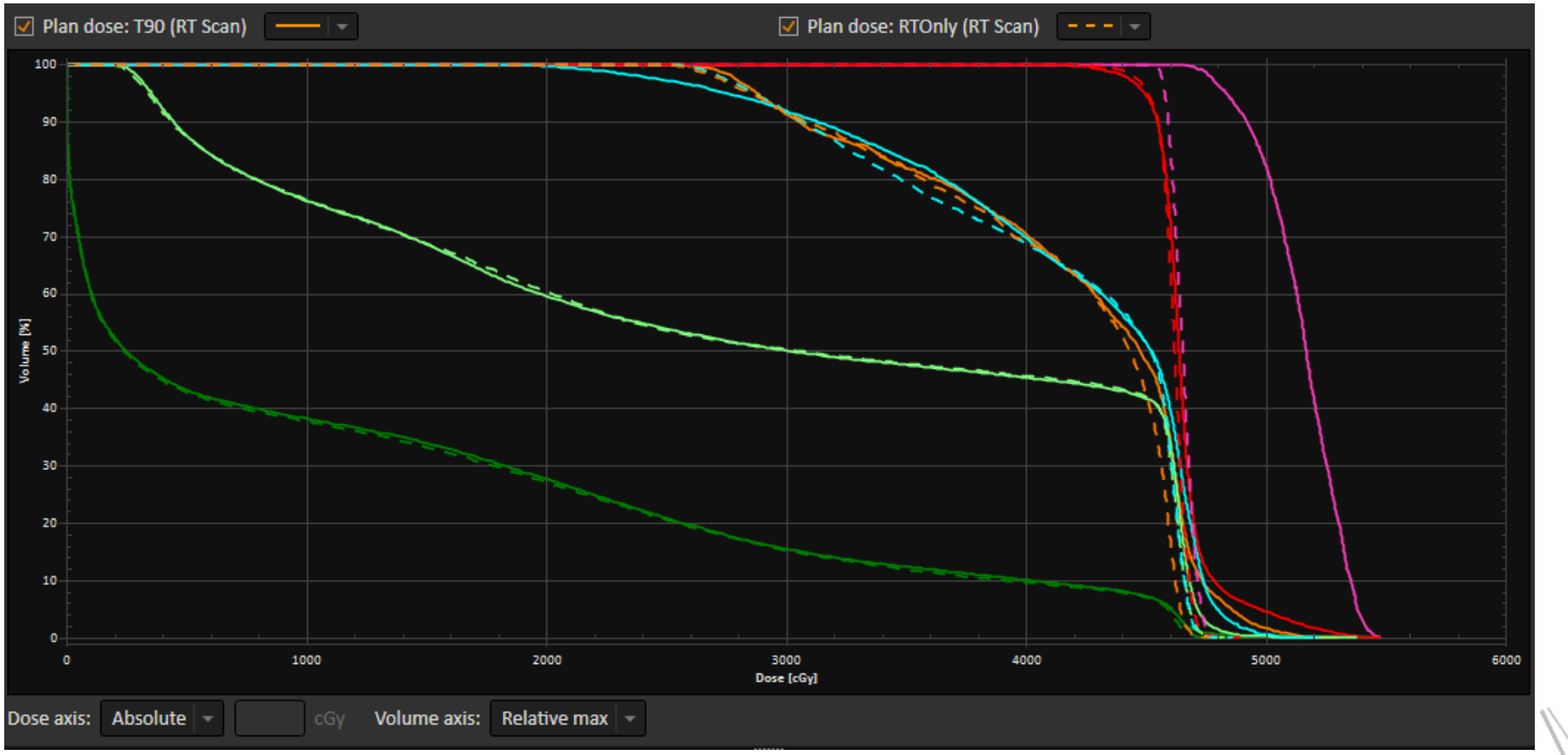
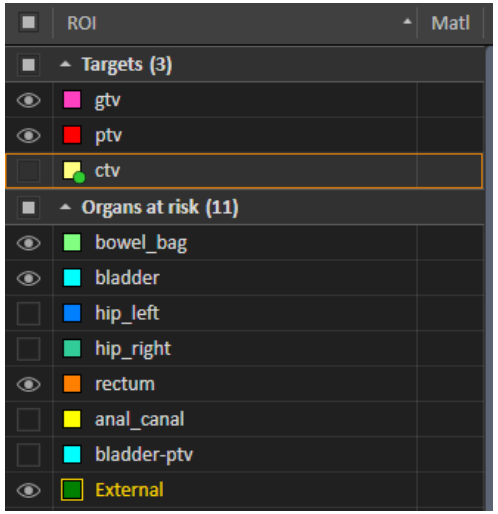
HYPERBOOST
Boosting the effect of Radiotherapy

Implementation

- Optimization:
  - Shape of DVHs for OARs and PTV is kept, but max doses are increased.
  - GTV coverage is heterogeneous.



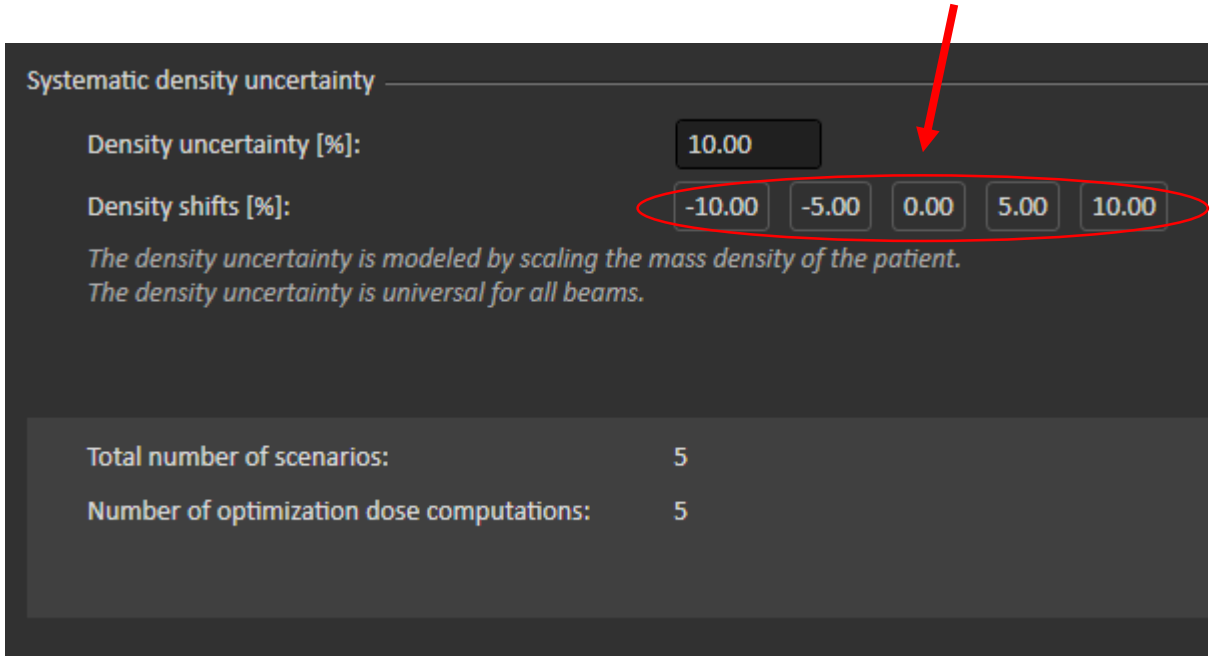


Dose (not EQD_{RT})
EQD_{RT} optimized plan (solid) and standard plan (dashed)

Implementation

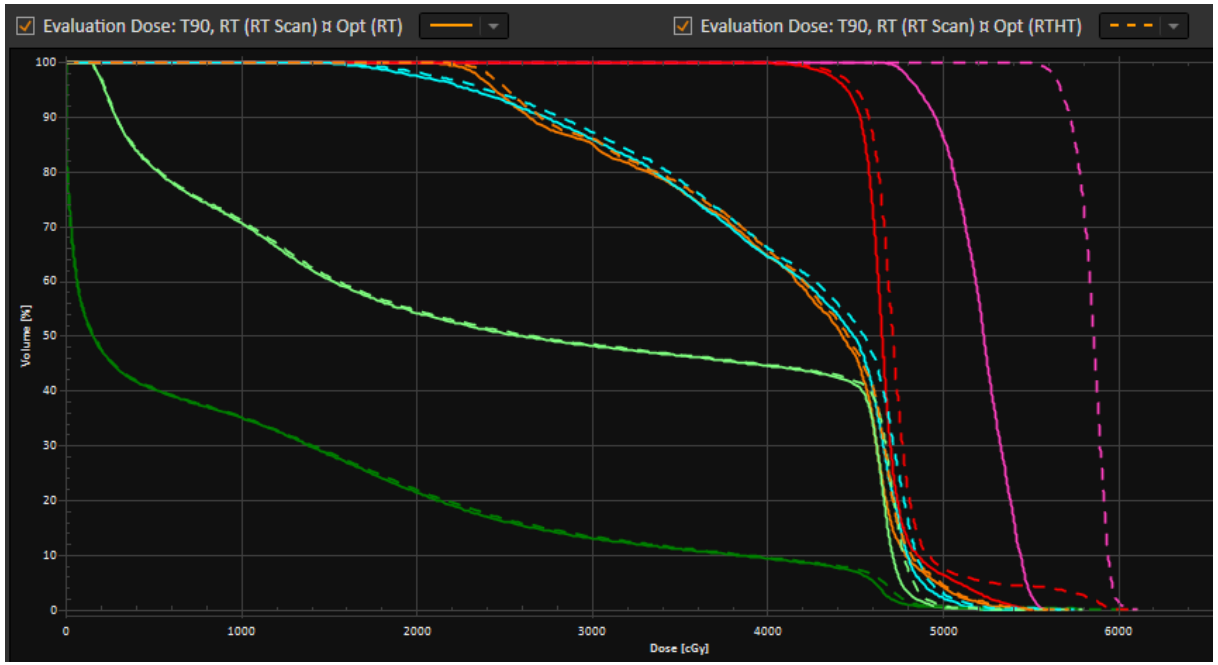
- Robust Optimization:
  - Minimax robust framework in RayStation
    - Alternative temperature scenarios instead of setup/density errors.
  - Alternative temperatures:
    - 16 scenarios created and used for robustness evaluation.
      - Steering adjustment (with constant total power).
      - Power increase/decrease.
      - Increased time interval.
    - 4 of these used in robust optimization

Temperature scenarios

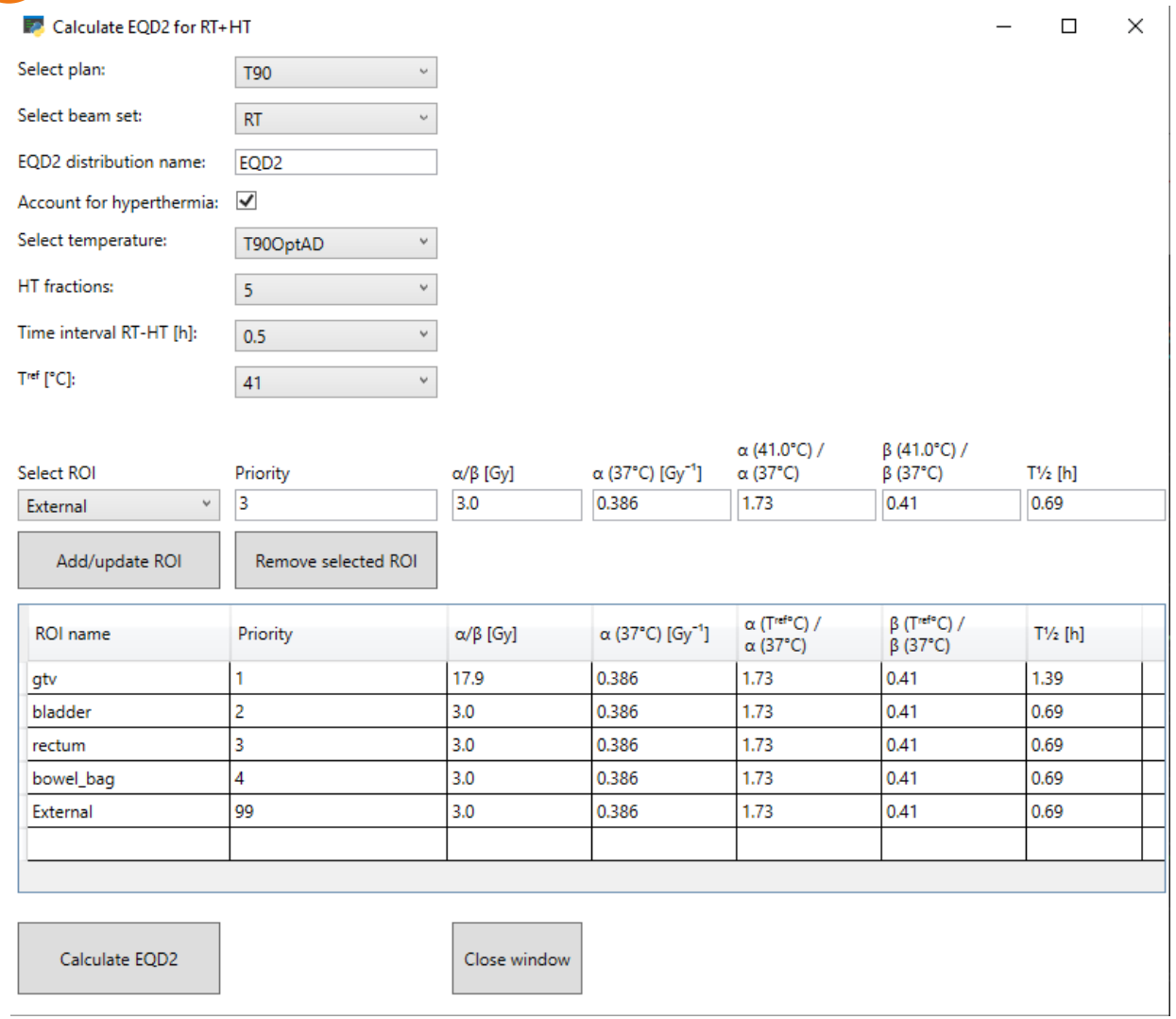


Implementation

- EQD_{RT}: Created as an evaluation dose using Python scripting with ROI specific model parameters.
  - Effect is much larger in GTV than in OARs



EQD_{RT}: EQD_{RT} optimized plan (dashed) and standard plan (solid)



HYPERBOOST
Boosting the effect of Radiotherapy

DR. SENNEWALD
medizintechnik gmbh

C3Te CENTER FOR CARE & CURE TECHNOLOGIES EINDHOVEN

TU/e

Erasmus MC
University Medical Center Rotterdam

LMU KLINIKUM

Hyperboost Presentation_Progress meeting

Spyridon Karkavitsas _ 13/03/2023

Outline

- Introduction of Thermometry & Magnetic Resonance Thermometry (MRT)

- Topic and research goals
- Materials and Methods
- Results_Early
- Future actions

Improvement of local control by Regional Hyperthermia combined with Systemic Chemotherapy (1),(2)

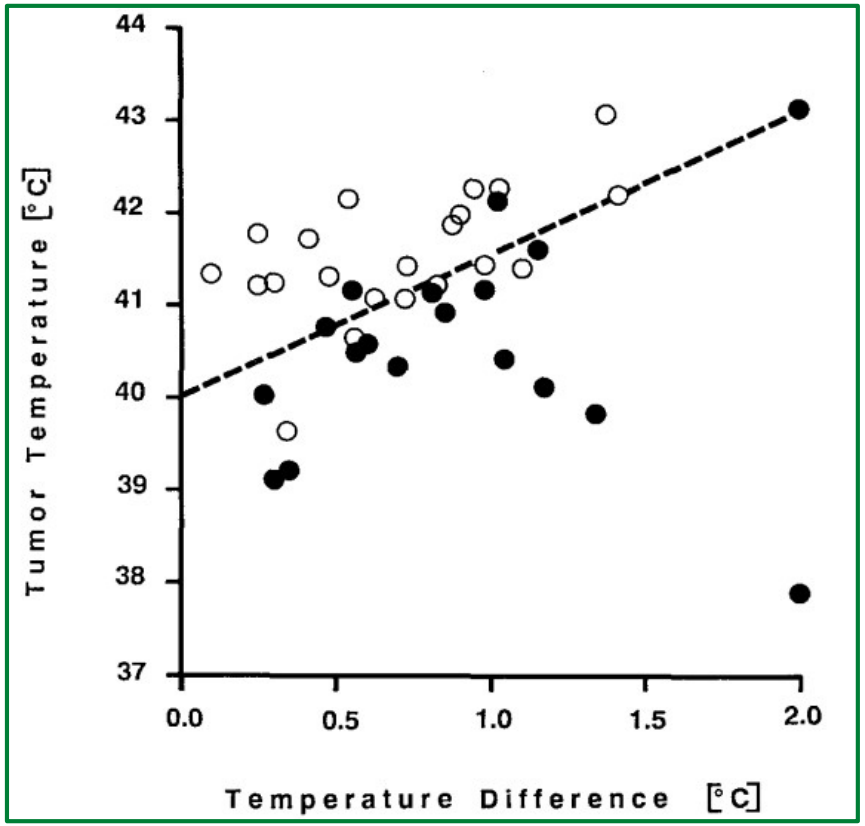
LMU KLINIKUM

- Accurate and Precise Thermometry in Thermochemotherapy

Table 5. Correlation[a] of treatment factors with response

Parameter	*P* (single variable)
Age	0.51
Karnofsky status	0.002*
Tumour volume	0.20
No. of heat treatments	0.0005*
T_{min}	0.007*
T_{max}	0.02
T_{20} (mean)	0.001*
T_{50} (mean)	0.0005*
T_{90} (mean)	0.0001*
TD_{min}	0.0001*
TD_{max}	0.02

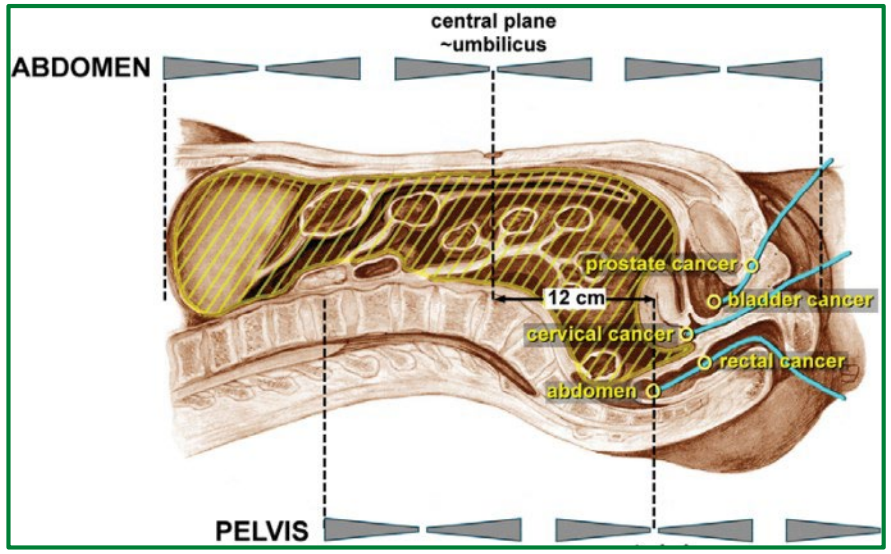
[a] Mann-Whitney non-parametric test
* Statistically significant ($P = < 0.01$)

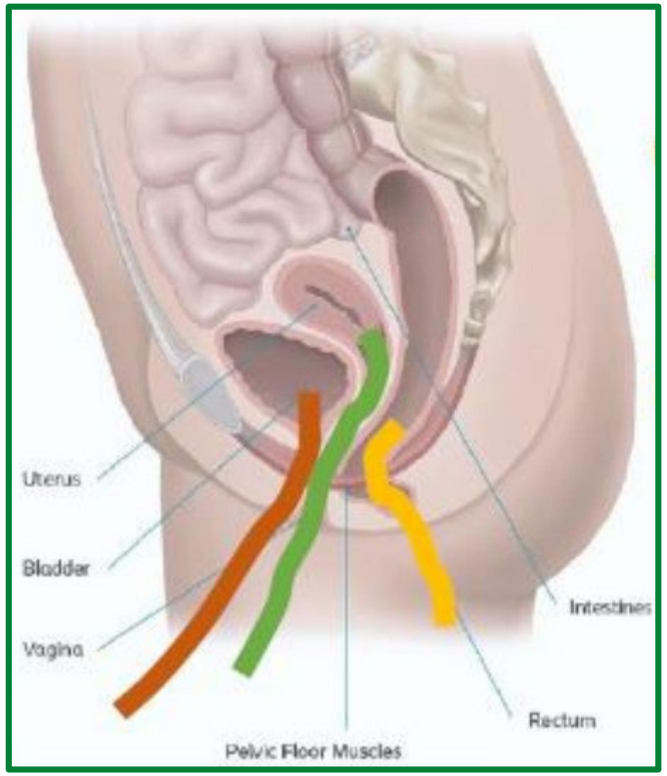


(1): Issels et al., J Cancer Clin Oncol, 1991, (2) : Issels et al., J Cancer Clin Oncol, 1990

Thermal monitoring during deep pelvic-regional Hyperthermia

- Invasive Thermometry
  -Intratumoral
- Min.Invasive
  -Intraluminal
- Tumor-related reference points





- Disadvantages :

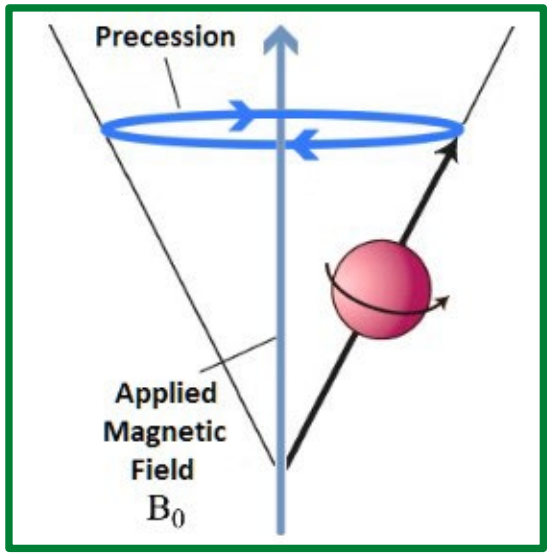
Limited spatial information on temperature distribution + discomfort for the patients (sometimes refusal)[3]

Solution : Magnetic Resonance Imaging or Magnetic Resonance Thermometry (MRT)

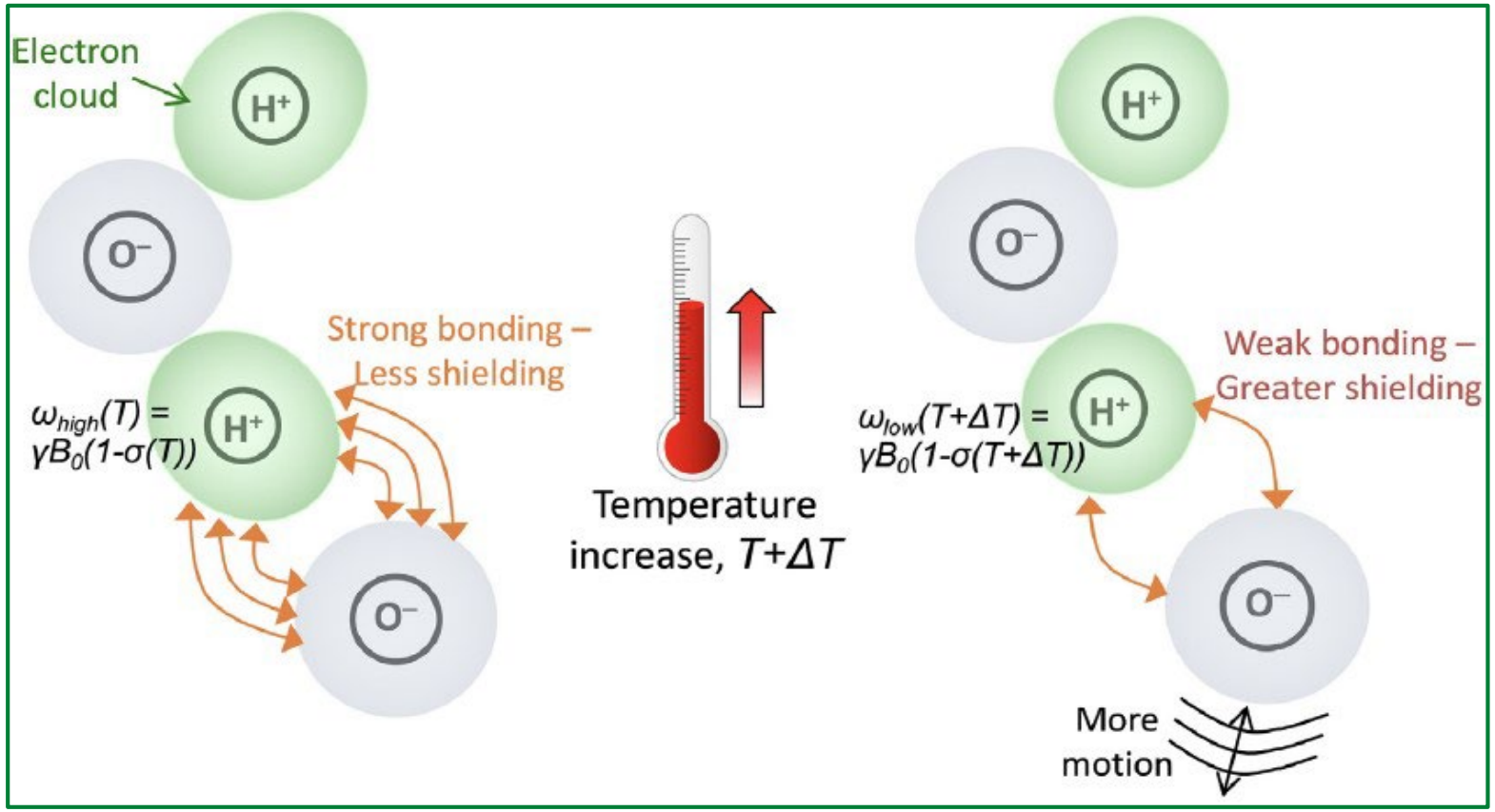
(3): Wust et al., Int.Journal of Hyperthermia,2009

Proton Resonance Frequency(4)

Larmor Frequency

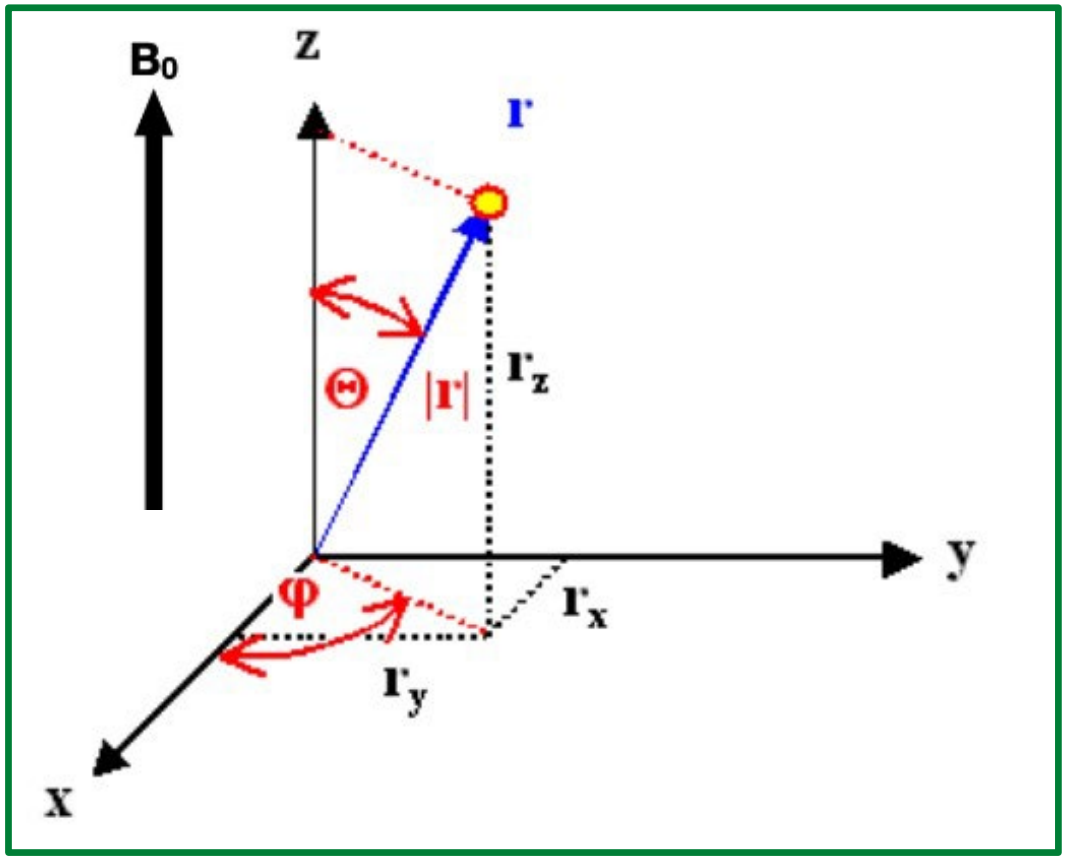


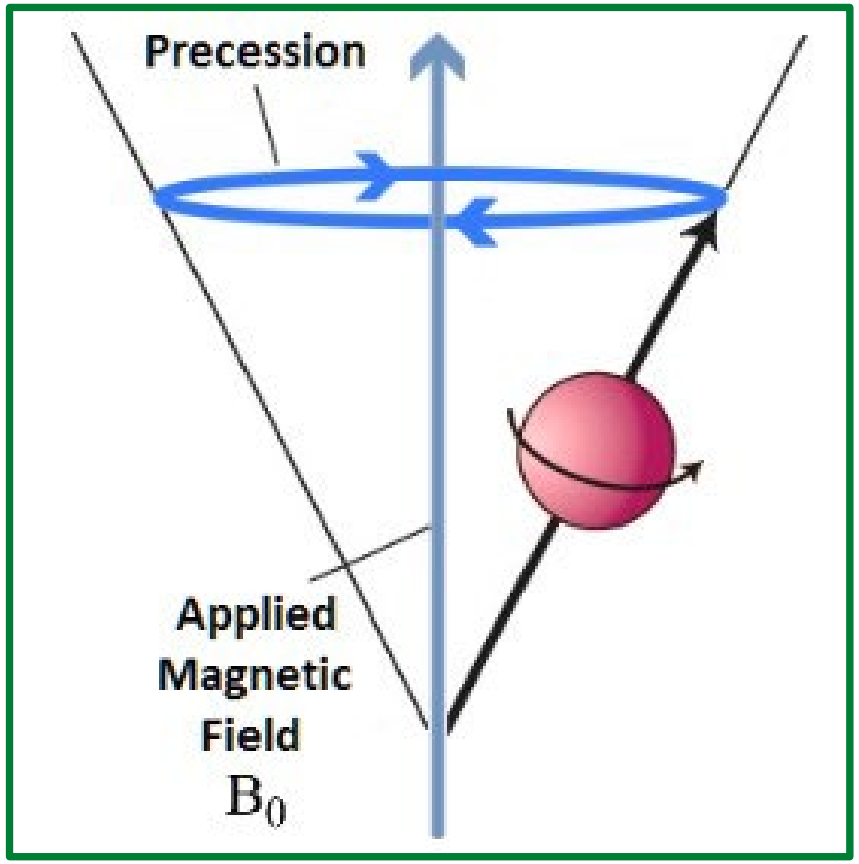
$$\omega_{Larmor} = \frac{d\phi}{dt}$$



(4):H Odeen et al. Prog Nucl Magn Reson Spectrosc.,2019

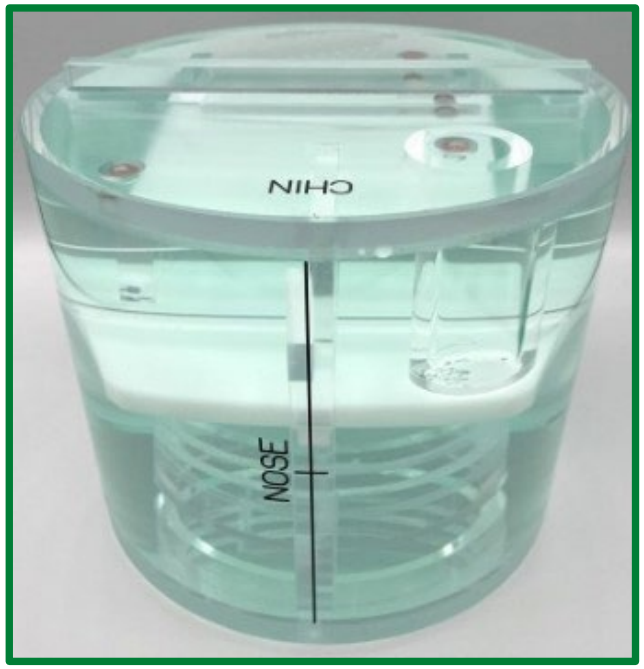
Proton Resonance Frequency_ Phase

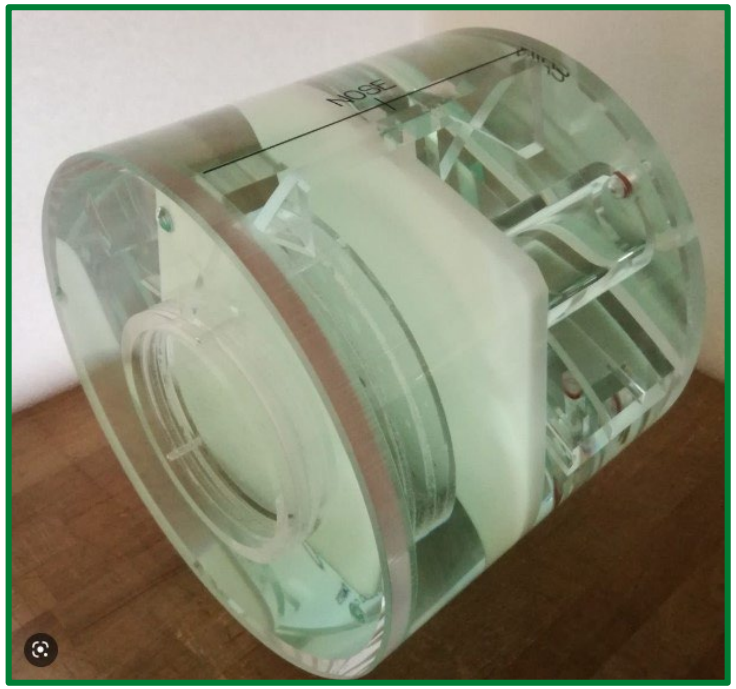


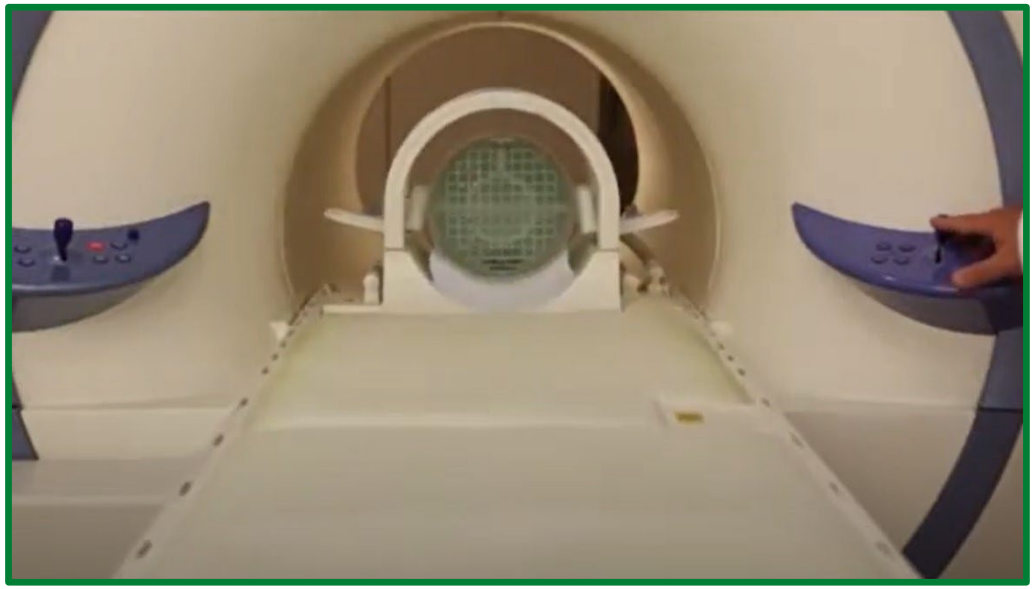


$$\omega_{Larmor} = \frac{d\phi}{dt}$$

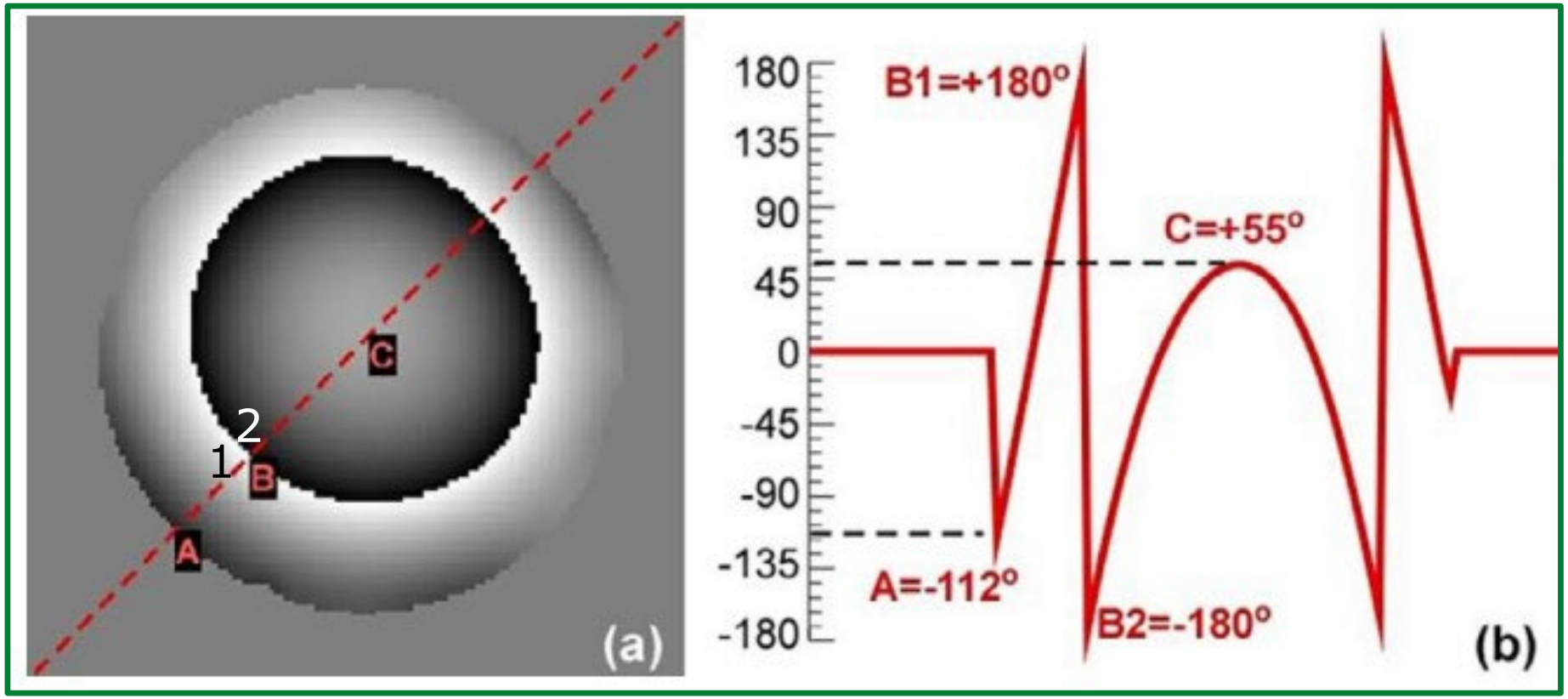
Proton Resonance Frequency_ Phase



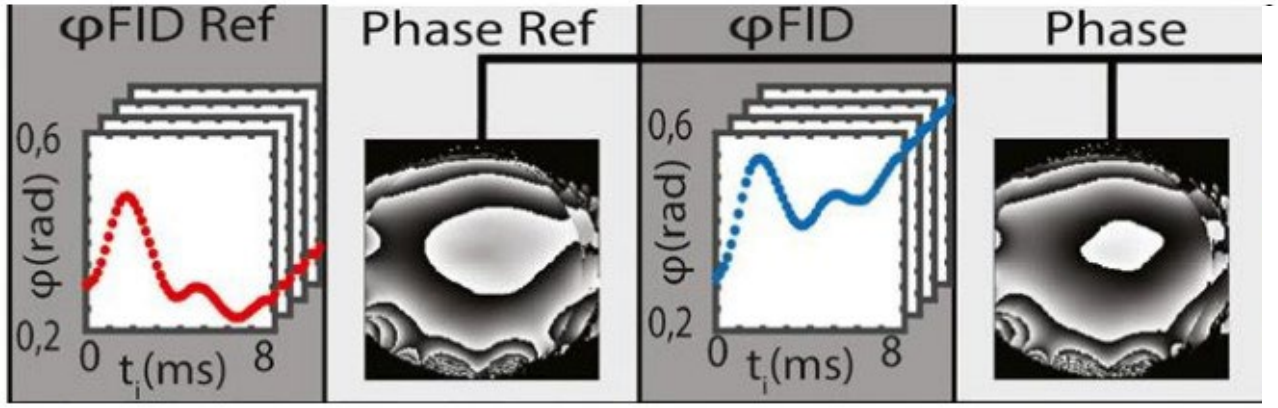


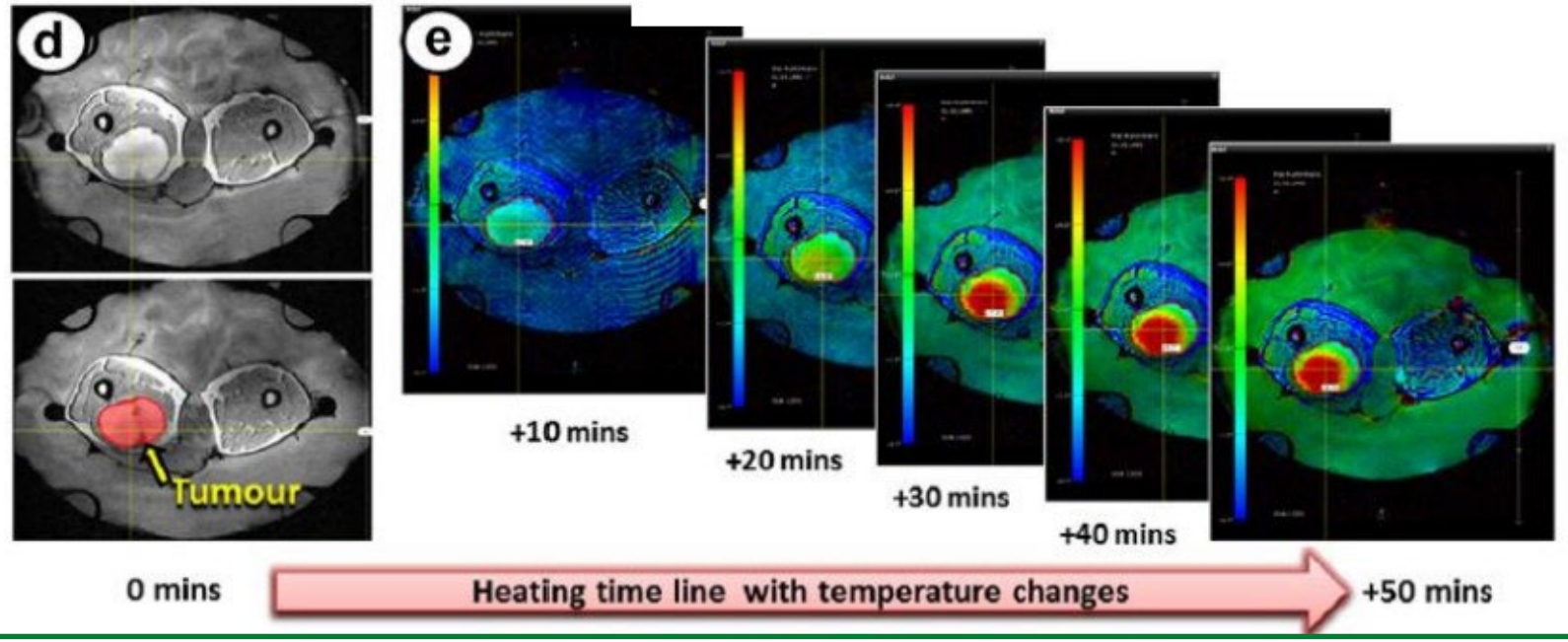


Proton Resonance Frequency_ Phase



MRT_Proton Resonance Frequency (PRF)



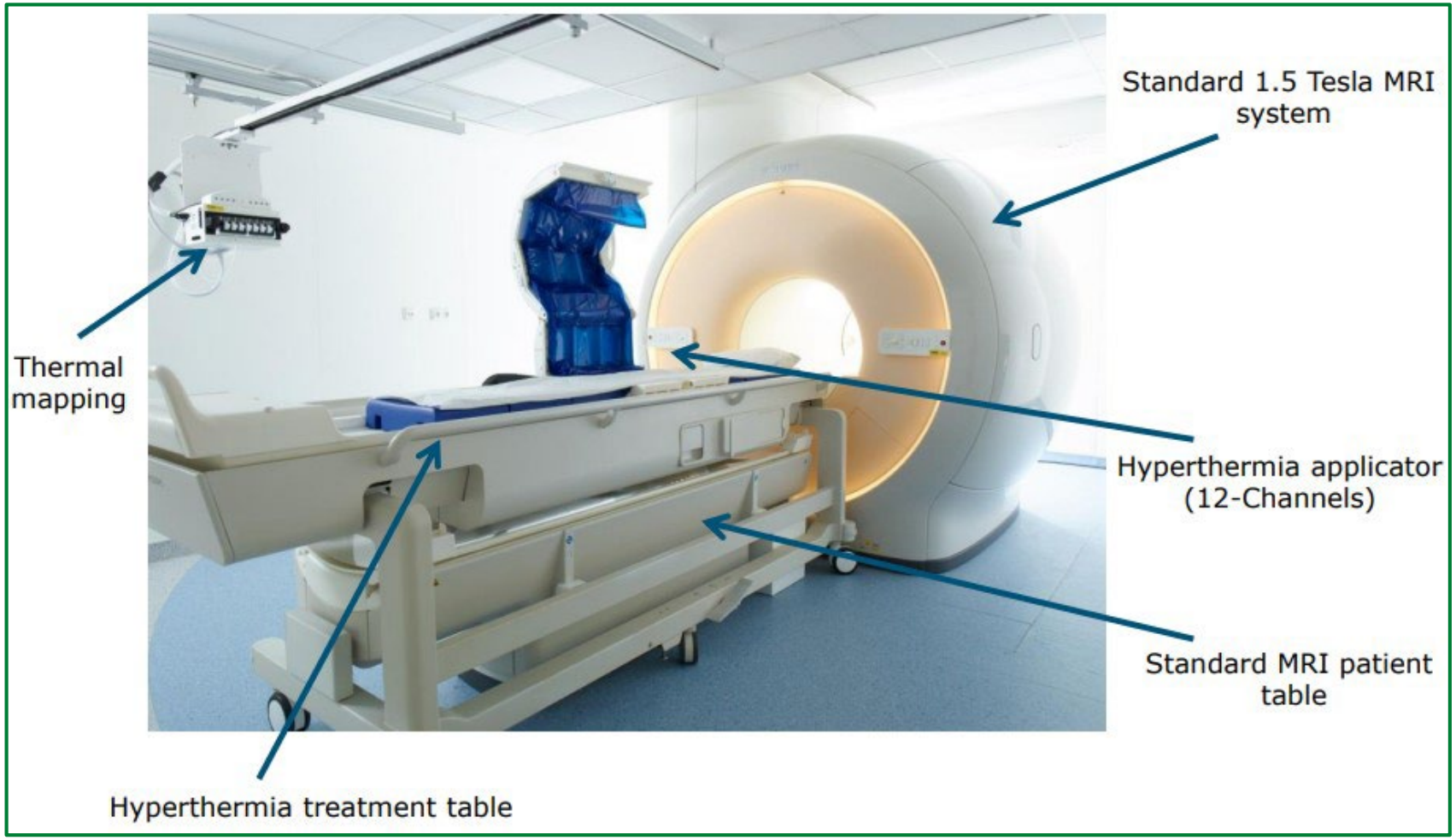


$$\Delta T = \frac{\phi(T) - \phi(T_0)}{\gamma \alpha B_0 TE}$$

α = -0.01ppm/°C

= 0.6 Hz/°C @ 1.5T

Hybrid MRT system at LMU Klinikum



SigmaVision Software

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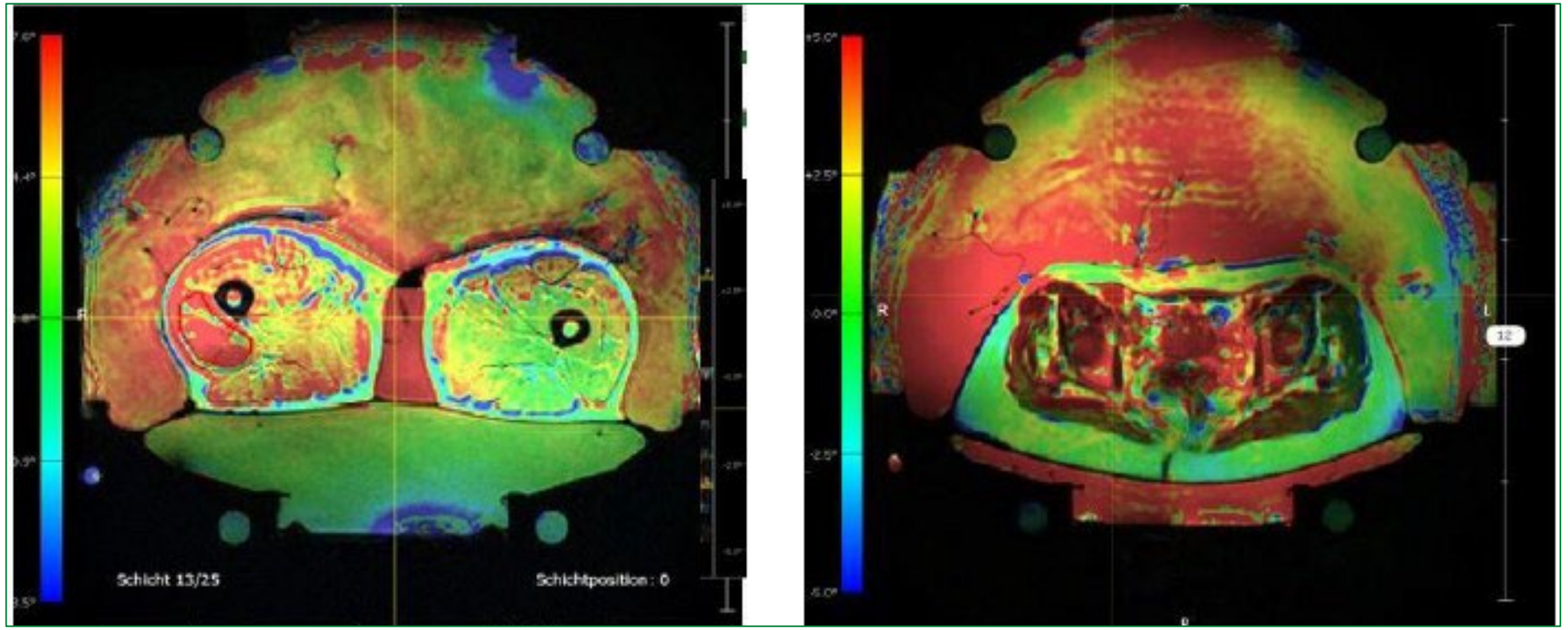

Challenges of MRT[4]

- PRF method: linearity, largely tissue type indepedent :

1) Spatio-temporal Static Magnetic field alterations or field drift

2) Intra / Inter –scan motion

3) Temperature induced magnetic susceptibility changes of fat /water like – tissues, perfusion..

↓

MRT not capable of substistuting Invasive/ Thermometry

(4): Odeen H. et al., Prog Nucl Magn Reson, 2019

Research topic and goals

- Research Topic :

Comprehensive analysis of the precision of Magnetic Resonance Thermometry during MR-guided deep-regional Hyperthermia Treatment (HT) of Soft-Tissue Sarcoma (STS)

- Research goals :

- Analysis of MRT temporal precision [4] during mild HT of STS (lower extremities, pelvic region)

- Impact of patient gross and gastrointestinal air motion induced errors on MRT precision

- Agreement of MRT precision in pre-treatment conditions (No heating) and during treatment

- Predictive power of similarity metrics (Jaccard [5], Average Haussdorf Distance) applied on internal air and patient anatomy changes throughout each treatment

- Increase in temperature degrades MRT precision by increasing intestinal air motion

(4): Feddersen. et al., Cancers, 2021,(5): Vilas-Boas Ribeiro et al, Cancers, 2021

Materials & Methods

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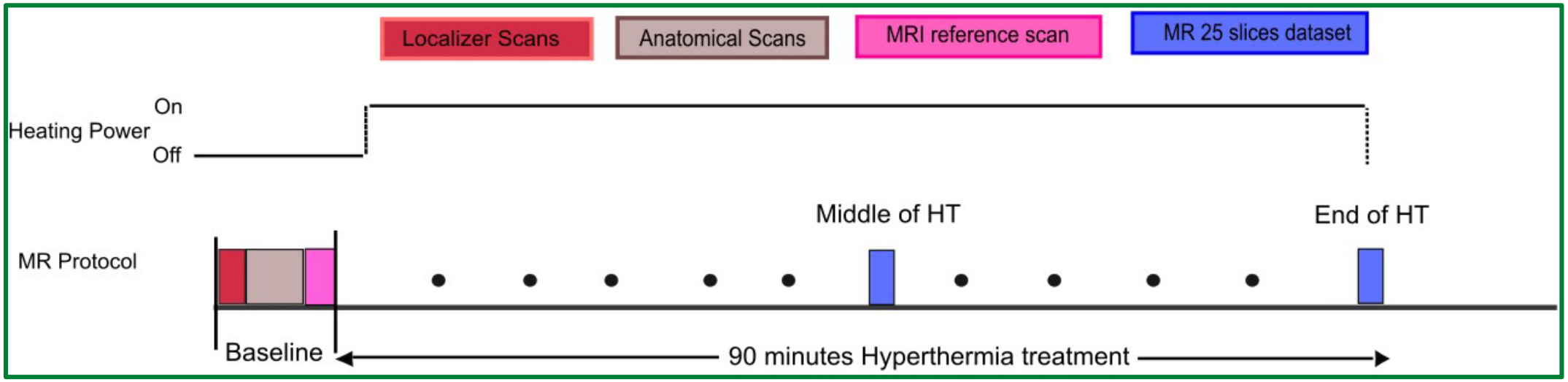
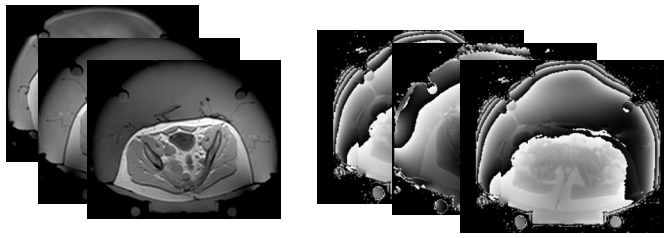
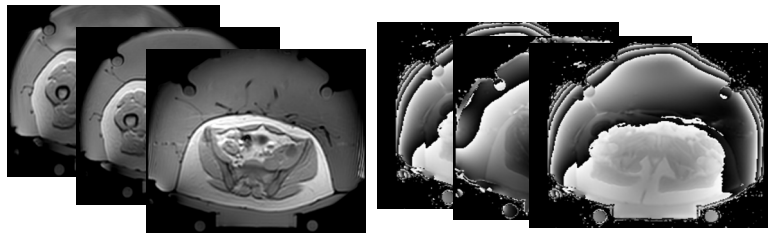
Hyperthermia treatment characteristics (From 2020 – 2022)		
Treatment region	Pelvis	Lower Extremities
Number of patients	16	16
Total number of sessions	81	120
Sessions per treatments	6 ± 4	7 ± 4
Duration (min) of each session	90 ± 2	90 ± 3
Double Scans per session	9 ± 1	9 ± 1
Maximum heating power (W)	770 ± 170	510 ± 190
Number of sessions with probes	26	12

MR Thermometry maps Construction





Reference dataset

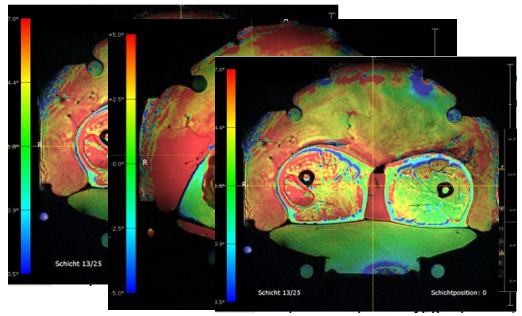


Middle of HT dataset

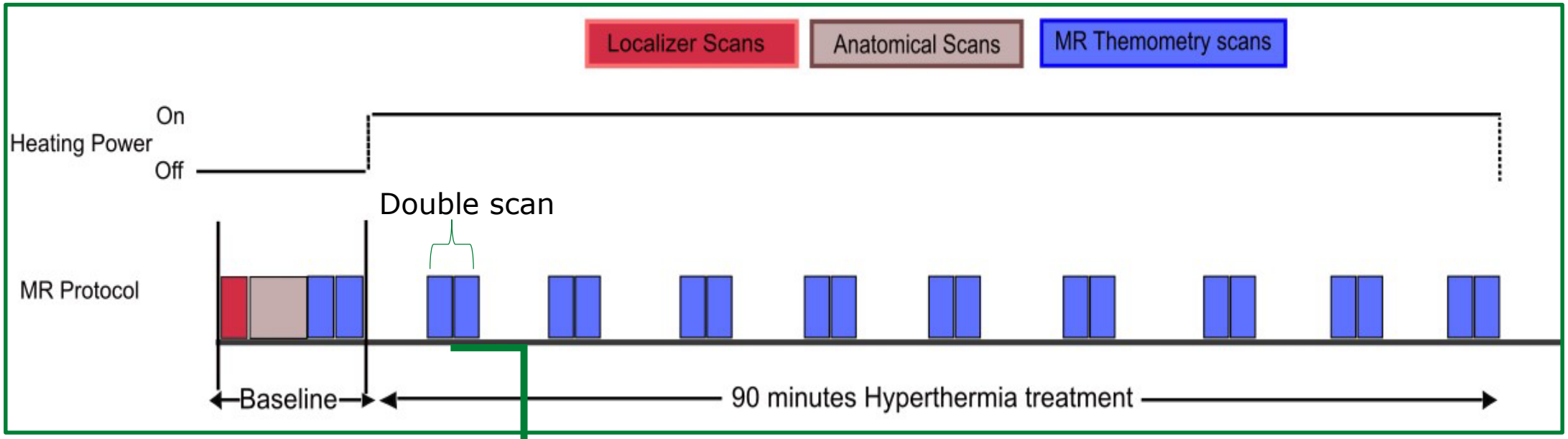
$$\Delta\phi = \phi(T) - \phi(T_{ref}) = \gamma\alpha B_0 TE\Delta T$$

$$\Delta\phi = \phi_j - \phi_{j+1} = angle\left(I_j * I_{j+1}^*\right) = \tan^{-1}\left(\frac{Re(I_{j+1})Im(I_j) - Re(I_j)Im(I_{j+1})}{Re(I_j)Re(I_{j+1}) + Im(I_j)Im(I_{j+1})}\right)$$

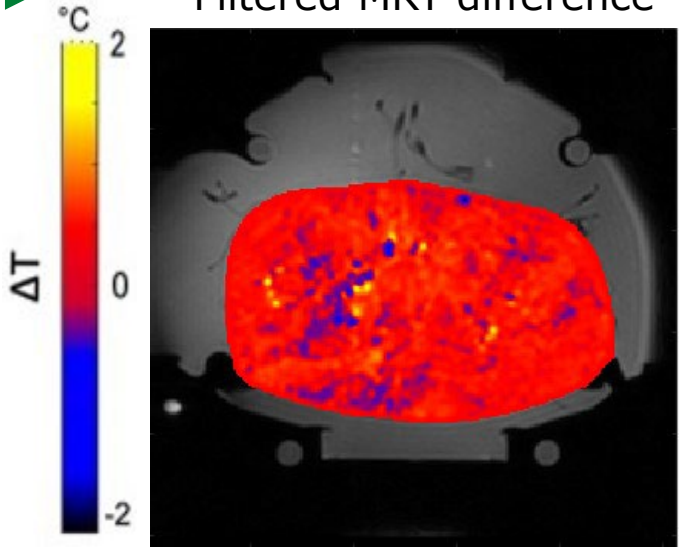
MRT volume dataset

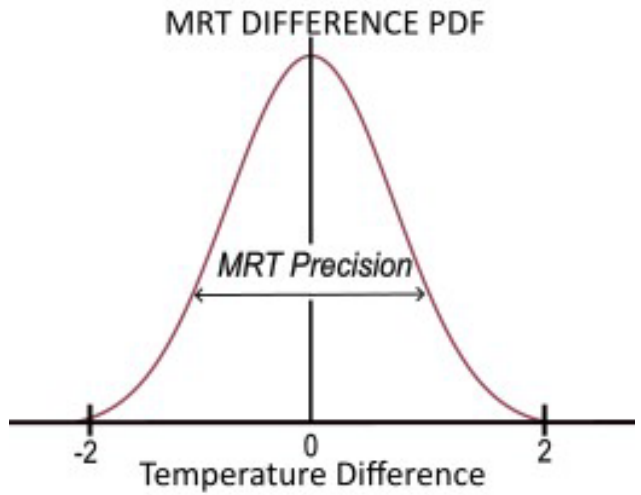


Clinical protocol (6)



Filtered MRT difference

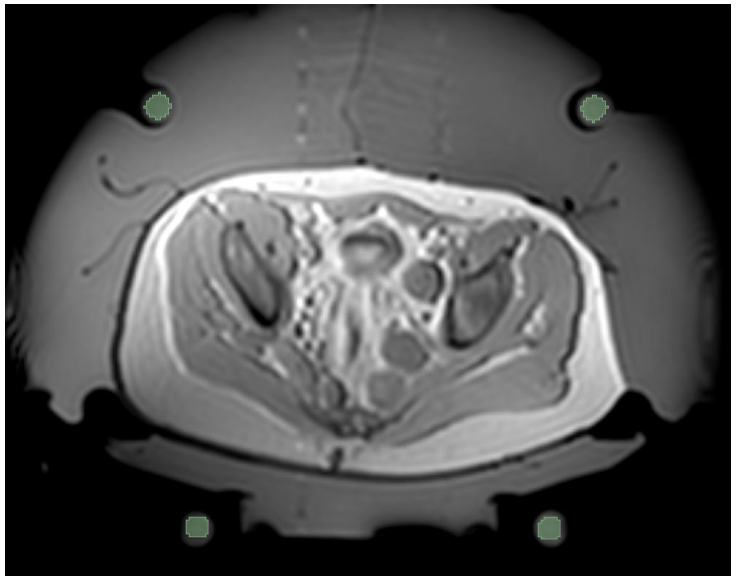


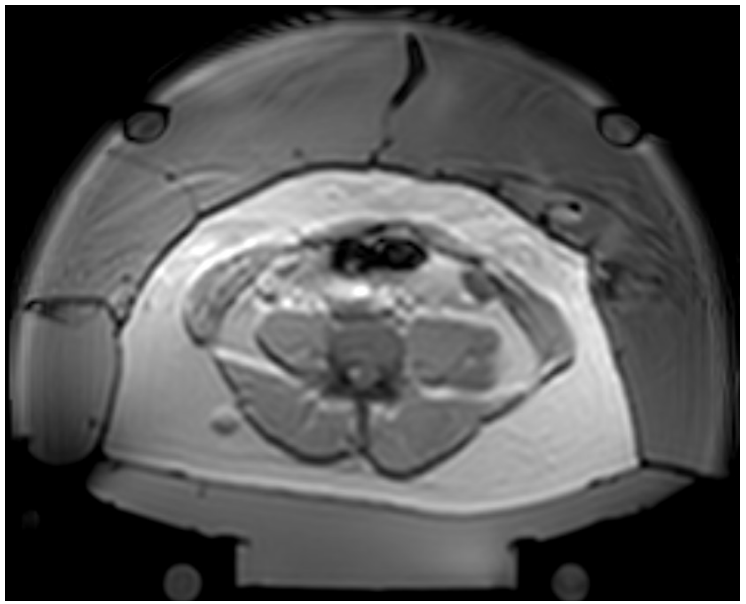


(6): Vilas-Boas Ribeiro et al, AAPM, 2020

MRT maps post processing

- Drift correction (Silicone Tubes)
- Low SNR masking
- Exlusion of inaccurate data points [5]
- Or Inter-Quartile Range (IQR) detection of outliers





(5): Vilas-Boas Ribeiro et al, Cancers, 2021

MRThermometry maps

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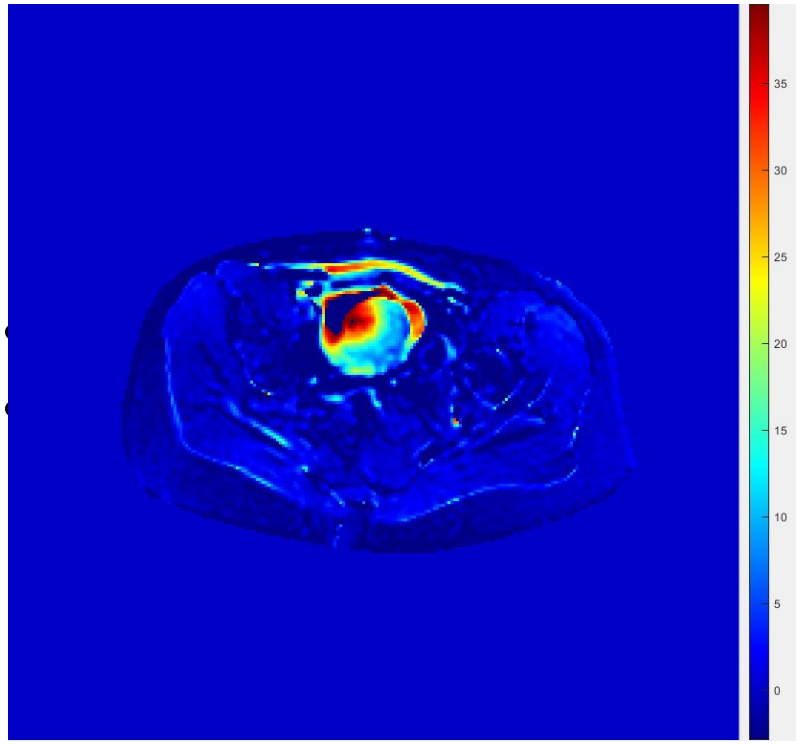
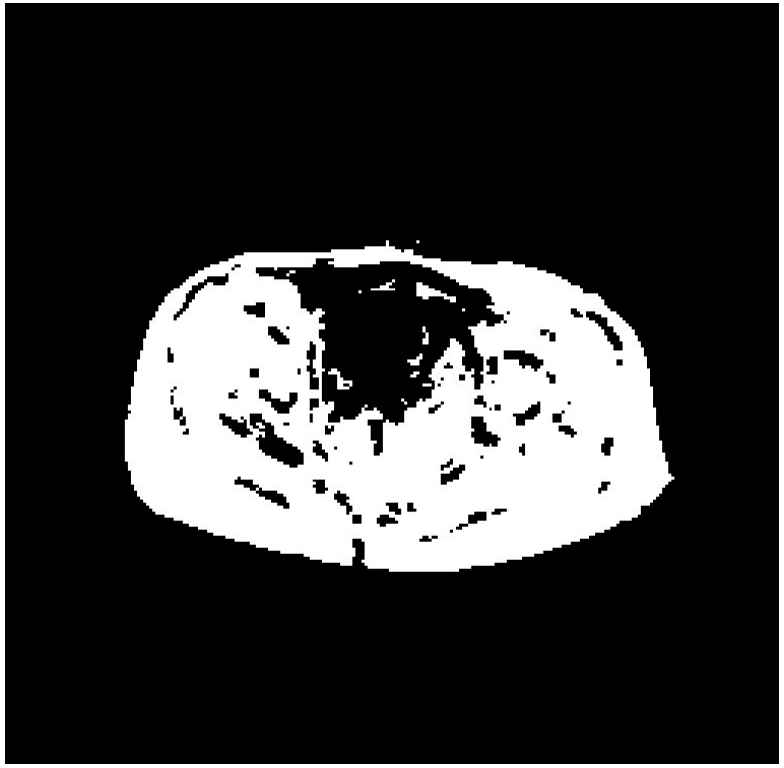


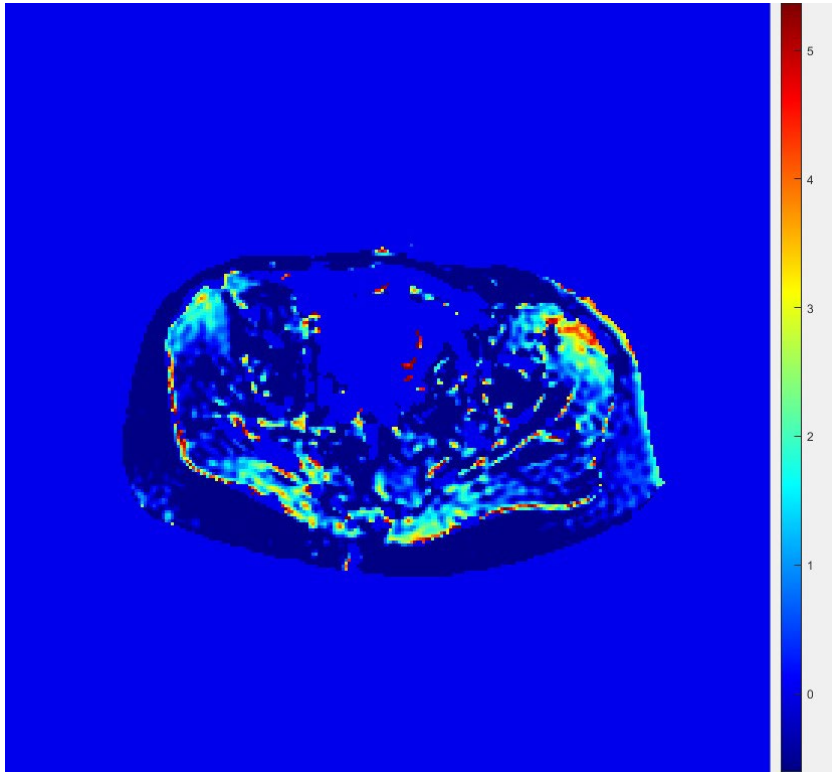
MRT

+



Mask

=



Masked MRT

Materials & Methods_Segmentation

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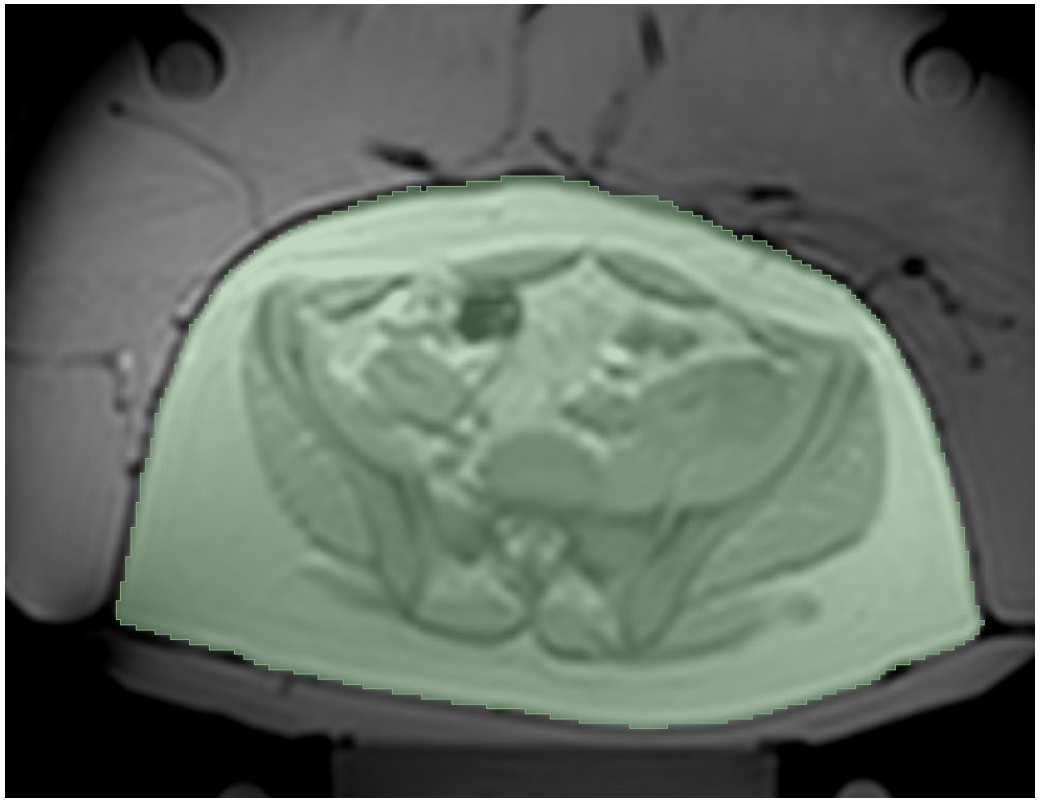
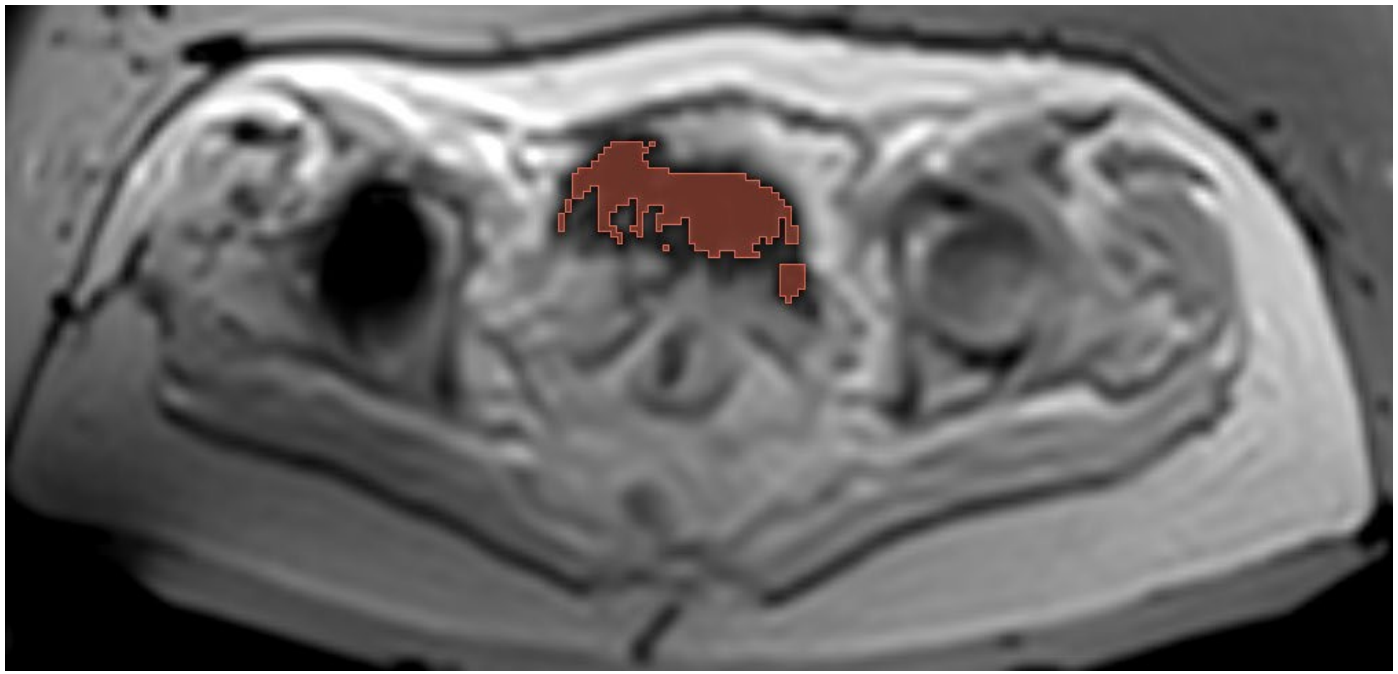
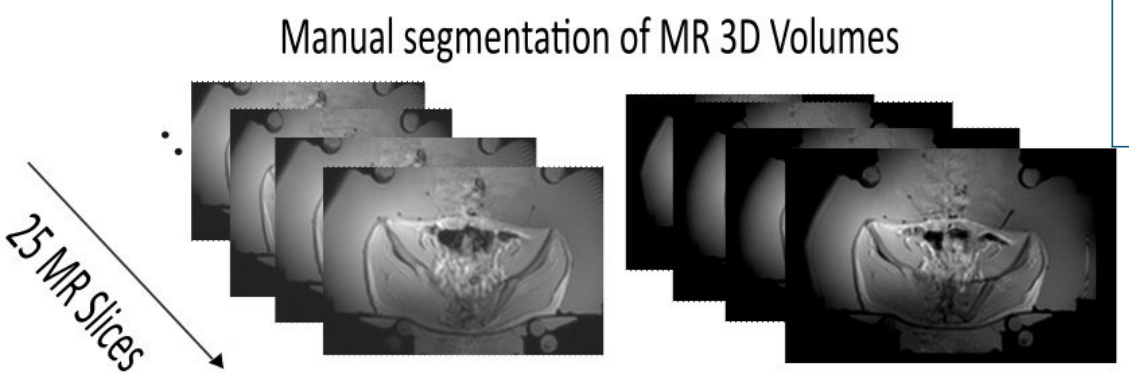
- Large amount of patient dataset → ≈18 MRI acquisitions or 25*18=450 slices / treatment
- Low spatial resolution of patient and air contours → Voxel size : (2 X 2 X 10)mm
- Manual contouring via 3D Slicer software → Total time / treatment : 6 h!





Materials & Methods_Segmentation

- Adopted automatic segmentation techniques for prostate cancer patients treated at MR-Linacs
- Developed 3D U-Net-based automatic segmentation of patient volumes, fat segmentation
- MONAI Label : Free & open source platform which facilitates AI-based annotation



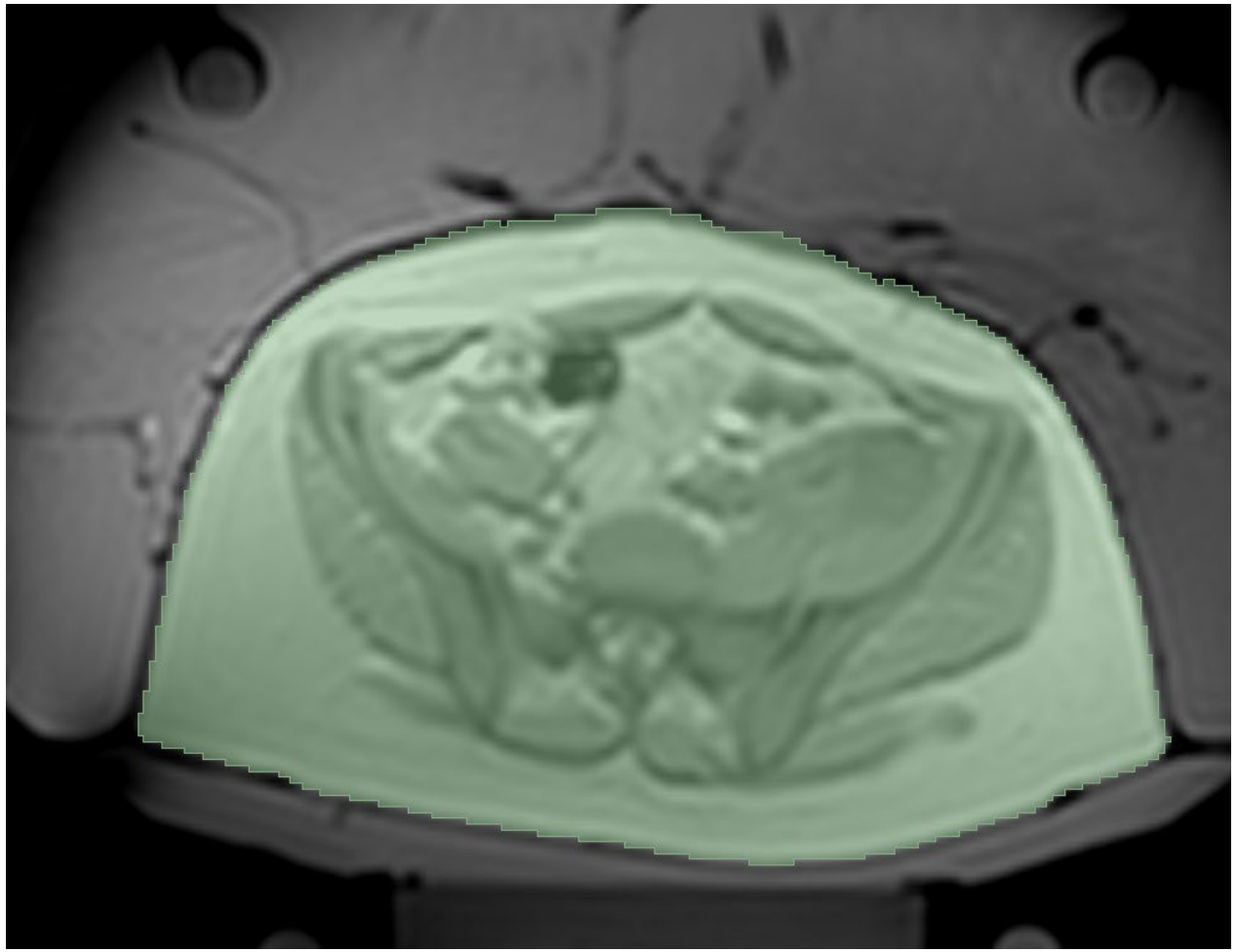
Volume binary masks (3D Slicer)

CNN training

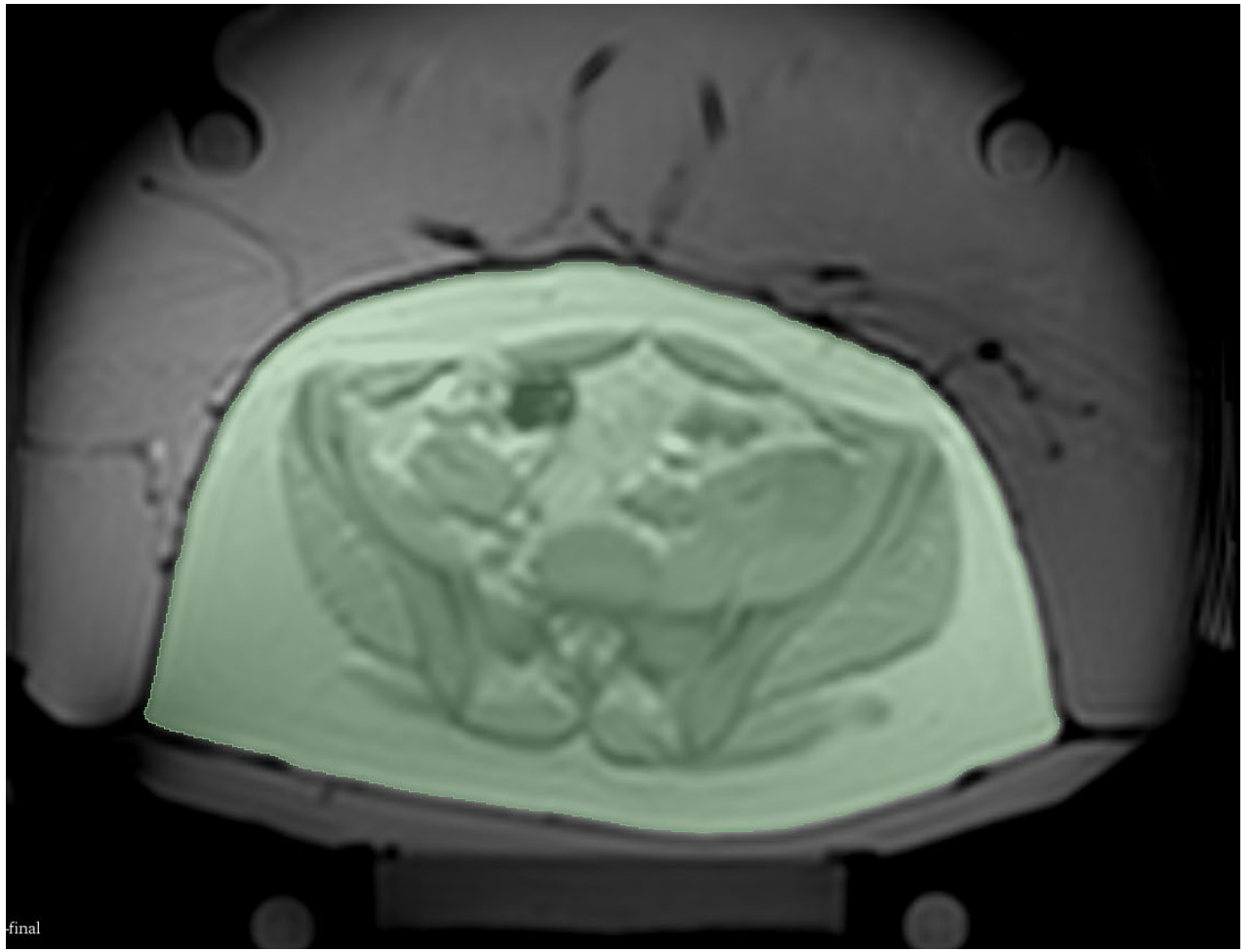
Refinement

Docker Container

Materials & Methods_Segmentation

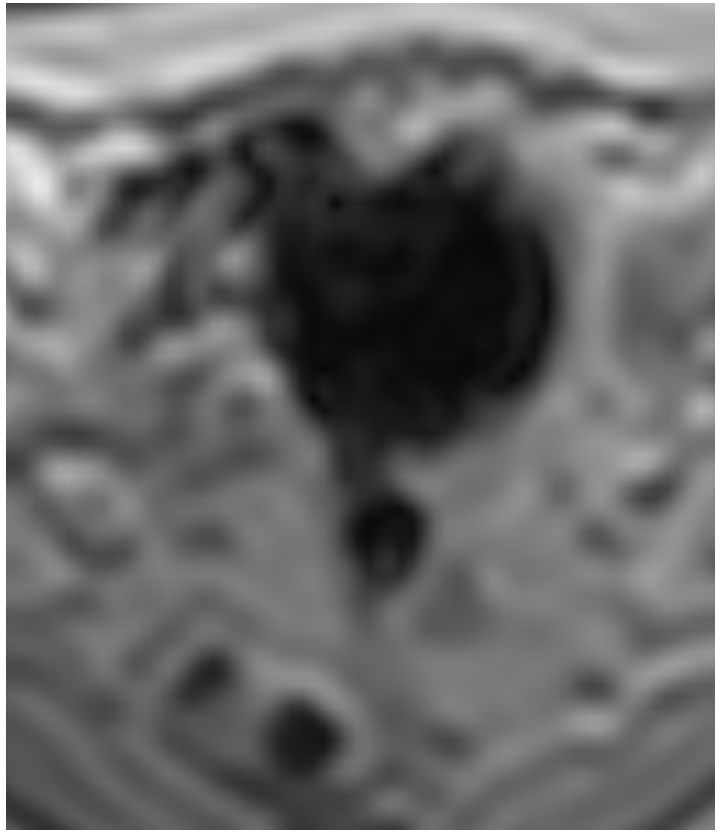


Low spatial resolution Patient Contour

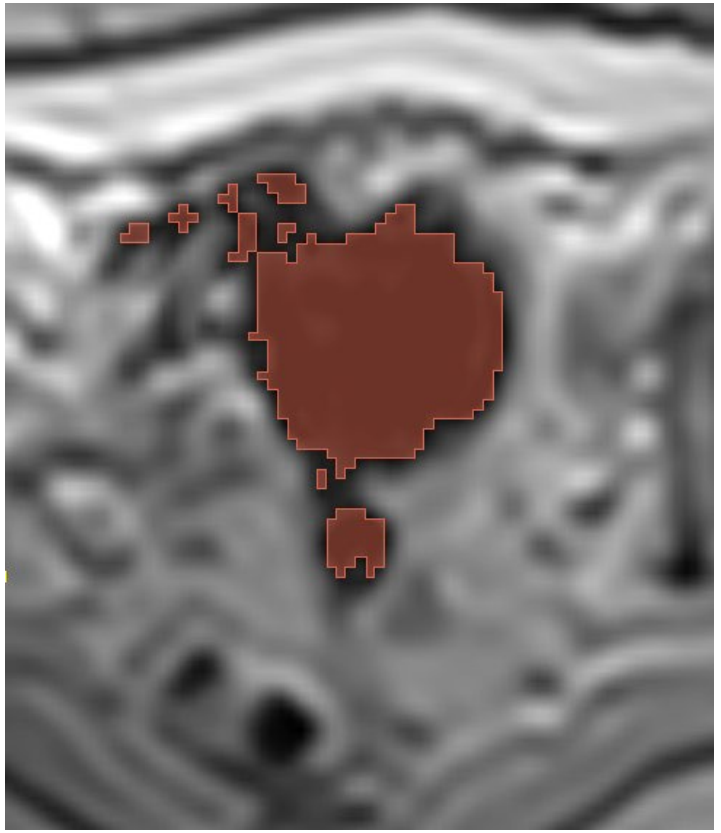


High spatial resolution Patient Contour

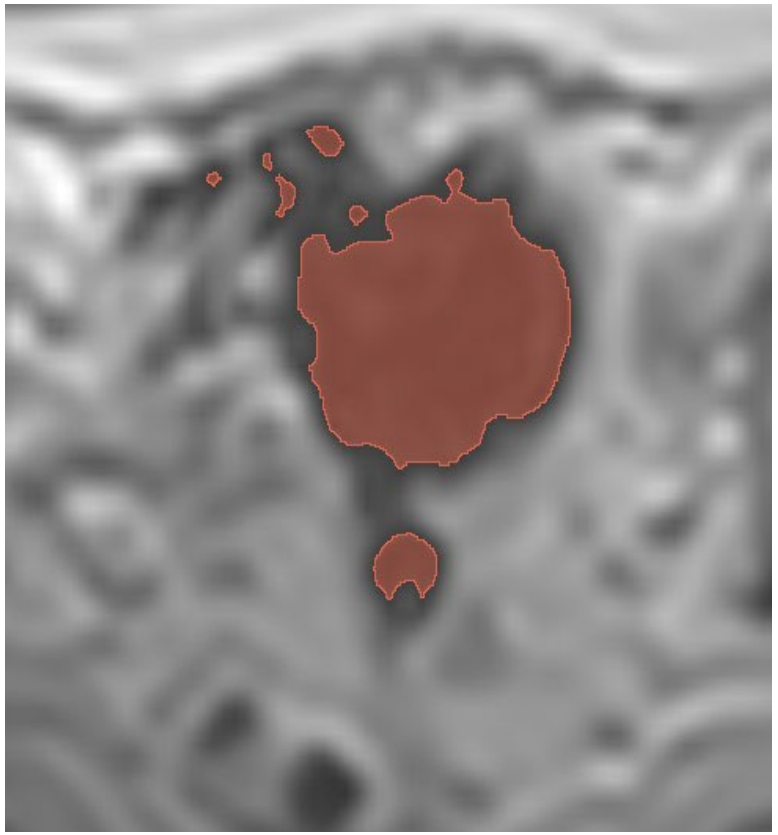
Materials & Methods_Segmentation



Unmasked Air



Low spatial resolution

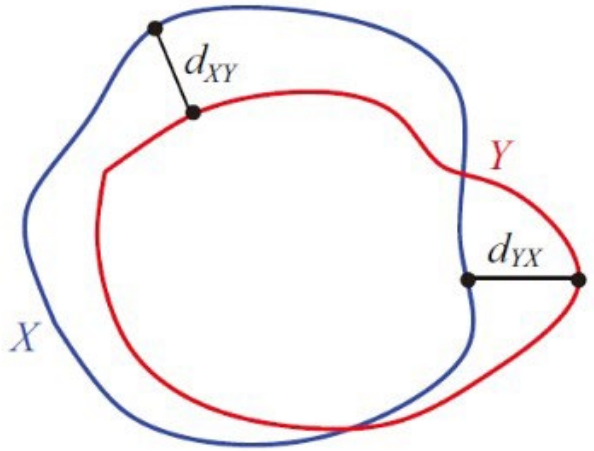


High spatial resolution

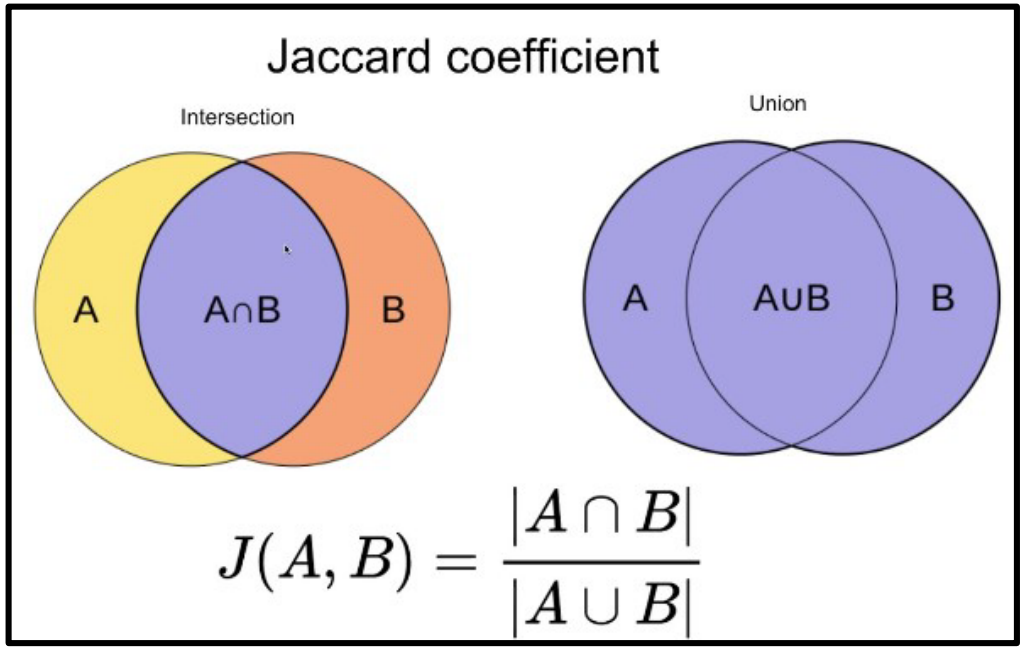
Materials & Methods_Similarity metrics

- Average Haussdorf Distance (Boundaries of Patient Contours)

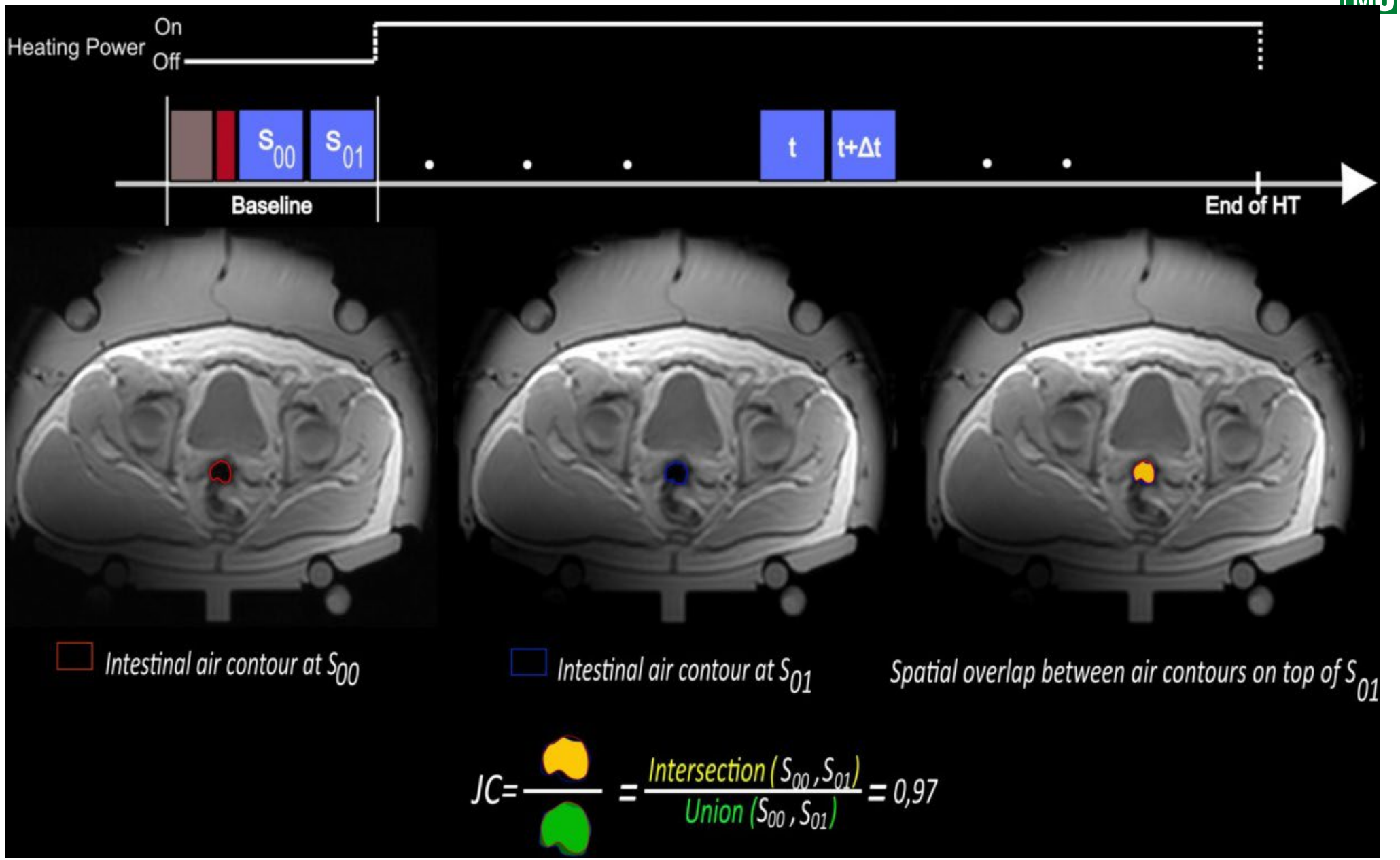
$$d_{AHD}(X,Y) = \left(\frac{1}{X} \sum_{x \in X} \min_{y \in Y} d(x,y) + \frac{1}{Y} \sum_{y \in Y} \min_{x \in X} d(x,y) \right) /2$$



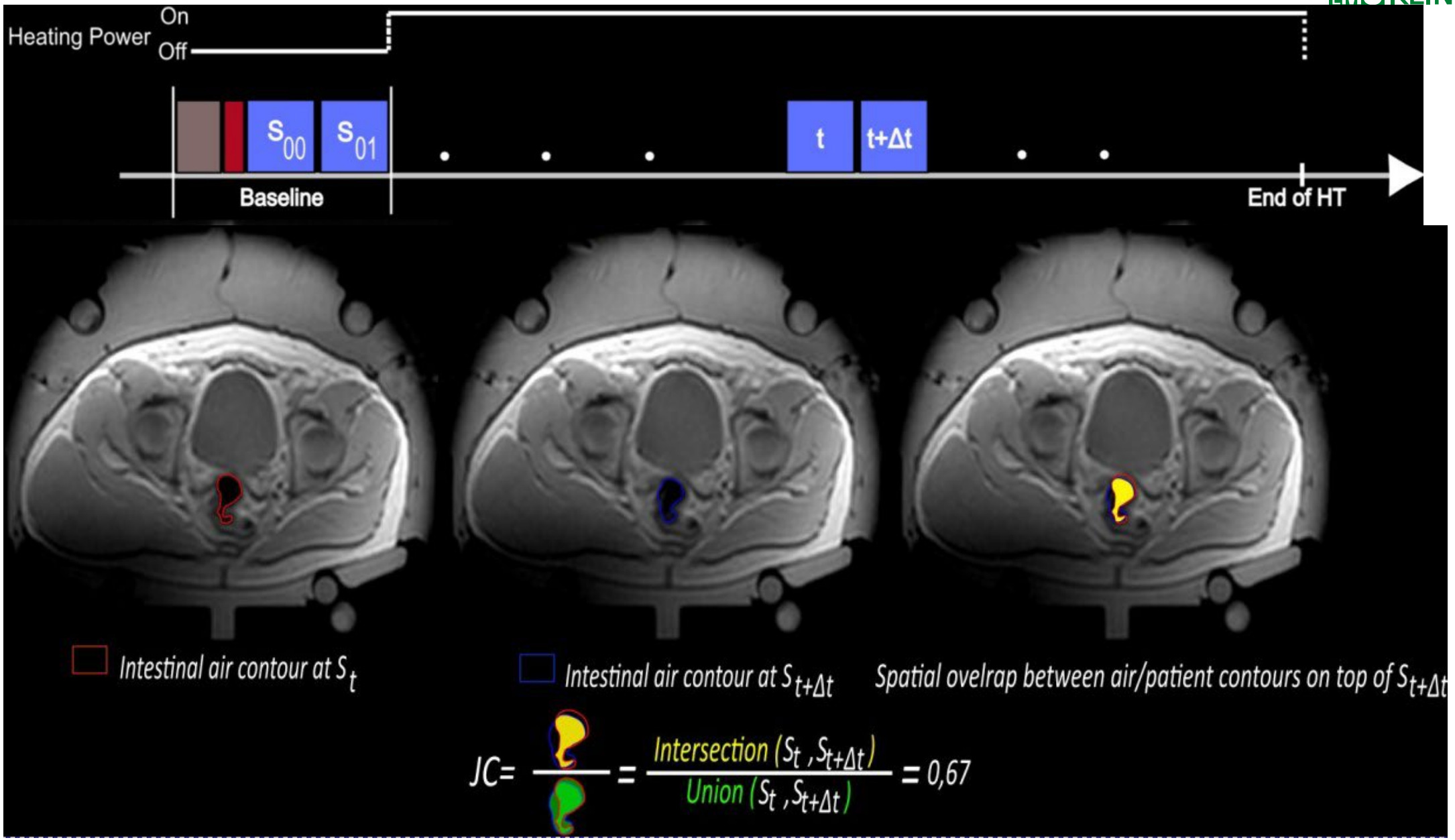
- Jaccard (JC) index (Air Contours)or(Boundaries of Patient Contours)



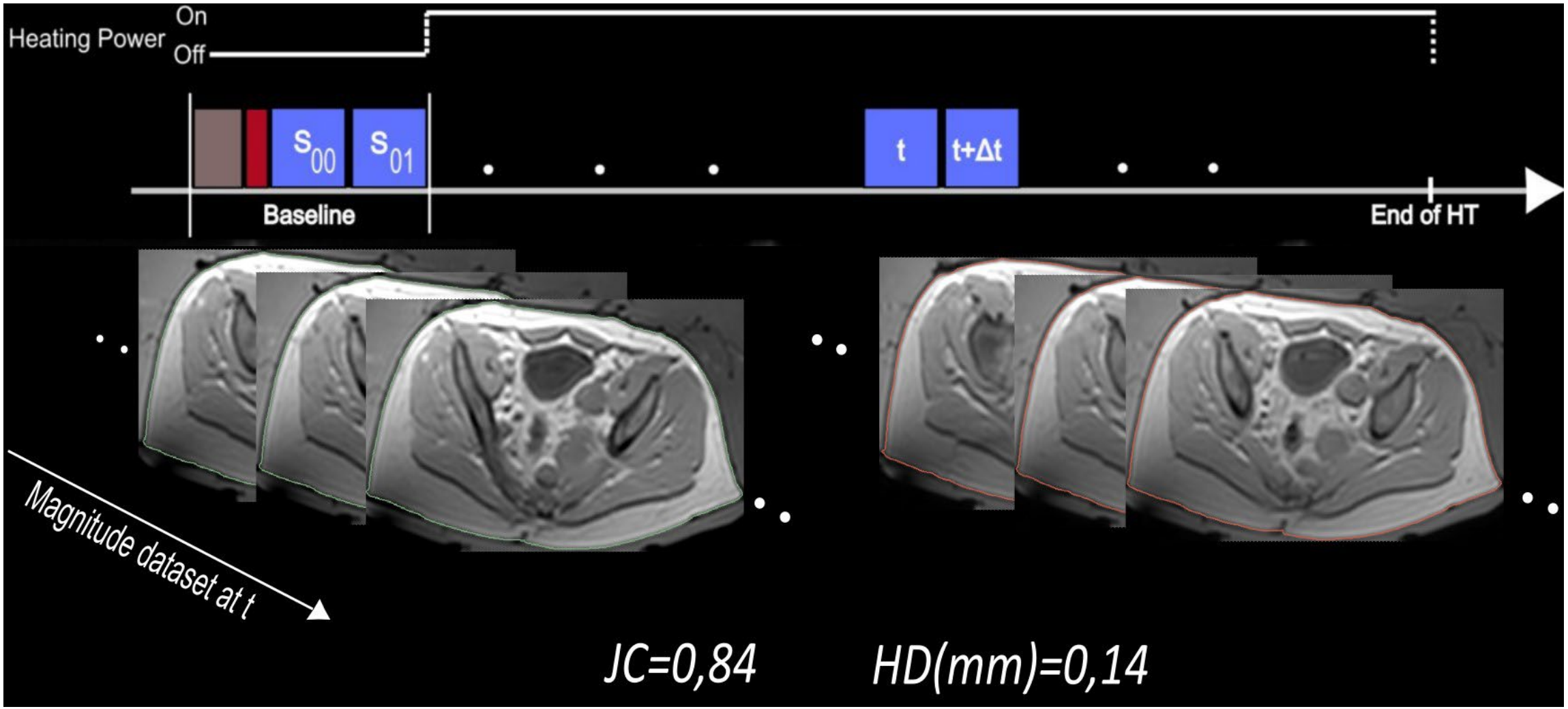
Materials & Methods_Similarity metrics



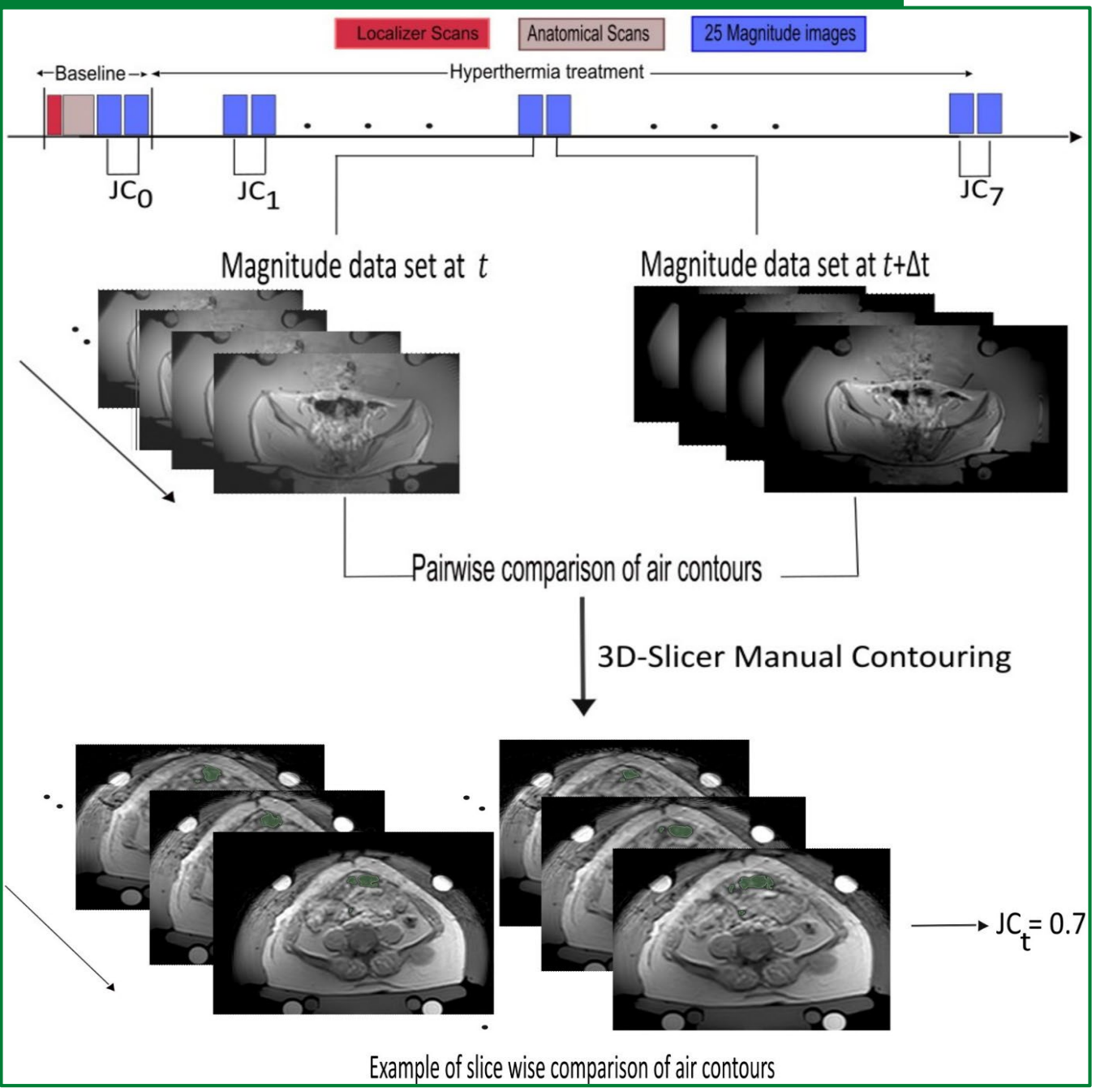
Materials & Methods_Similarity metrics



Patient motion during the treatment



Air motion during the treatment



$$JC_{baseline} = 0.5\ (0.1)$$

$$JC_{treatment} = 0.6\ (0.2)$$

Early results_ Calculation of MRT precision

	Offline processing		SigmaVision Software	
	Pelvis MAD/ σ	Lower Extremities MAD/σ	Pelvis MAD / σ	Lower Extremities MAD / σ
Baseline	0.3°C /0.8°C	0.1°C/0.4°C	0.3°C/ 0.9°C	0.2°C/0.6°C
Treatment	0.7°C /1.1°C	0.5°C/0.9°C	0.9°C /1.5°C	0.7°C/1.2°C

Mean TEM was always (0-0.1°C); Mean Absolute Deviation(MAD); standard deviation = σ;

(10): Vilas-Boas Ribeiro et al, AAPM, 2020

Future actions

- Segmentation masks of : Patients, air volumes, fat(?) using auto-segmentation algorithm and AI-assisted software MONAILabel

- Utility of patient masks for the correct calculation of MRT precision in baseline/treatment conditions

- MRT precision off-line post processing workflow VS SigmaVision Thermal maps

- ROC analysis for patient gross and gastrointestinal air-motion (for a larger patient dataset)

- Relation between air/patient motion similarity metrics VS MRT precision

AI_Clinical MRI

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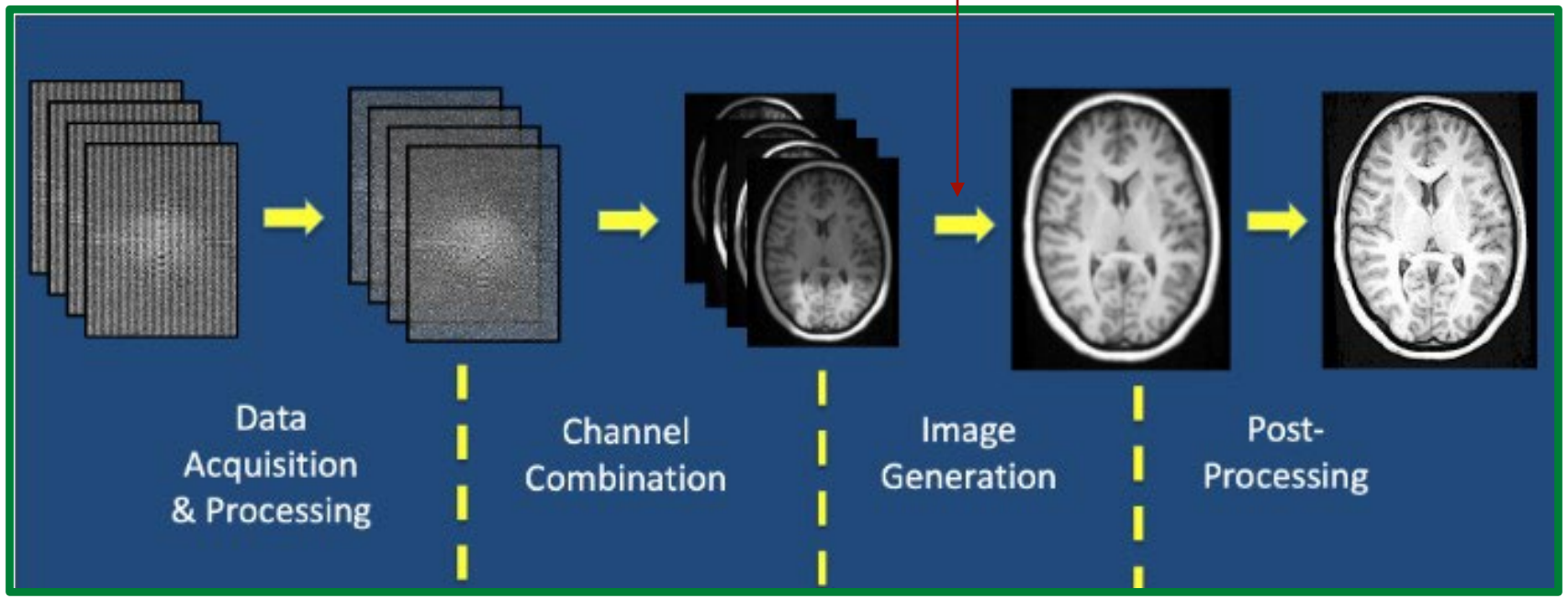
Deep Resolve Boost

Deep Resolve Sharp



AI_Clinical MRI

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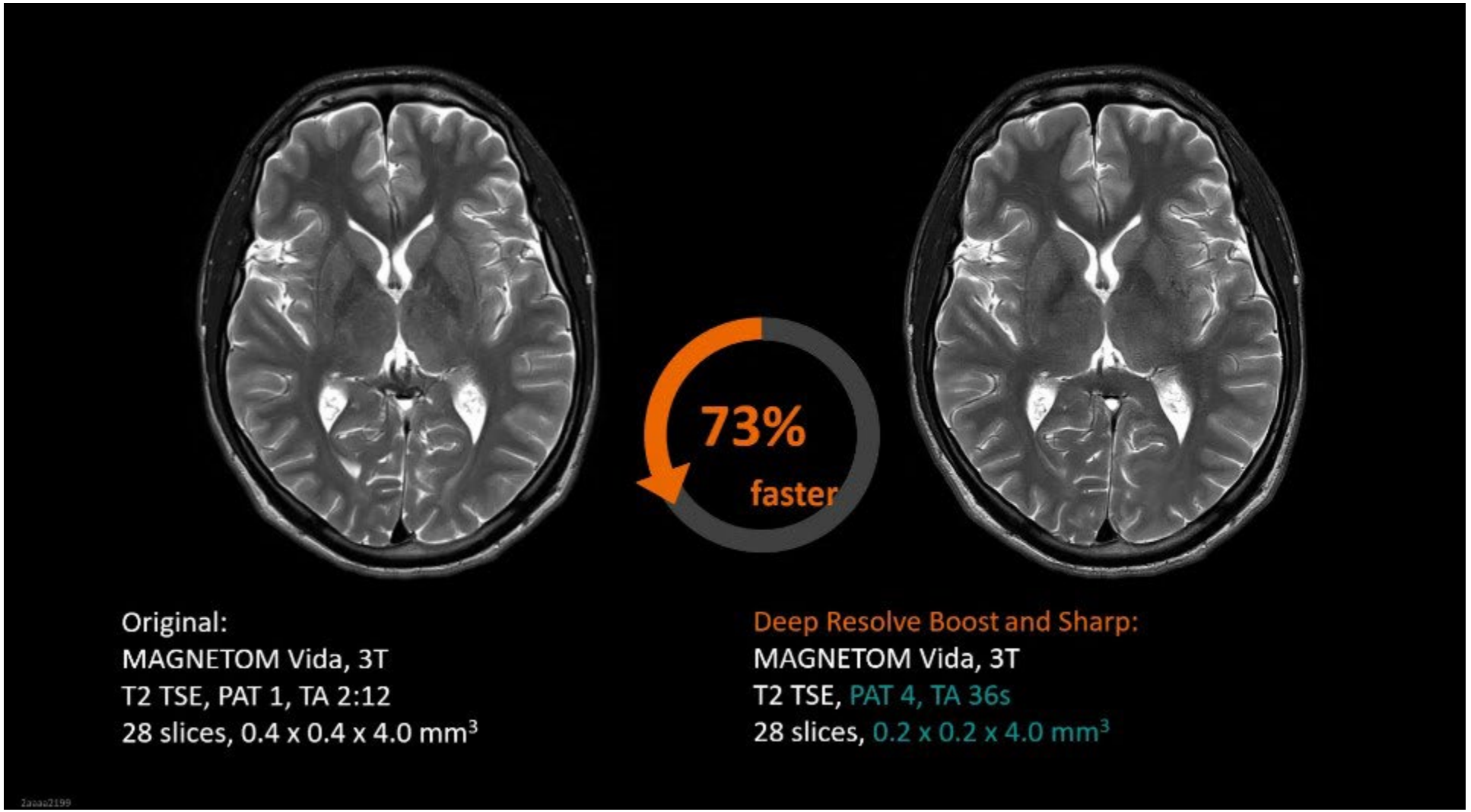

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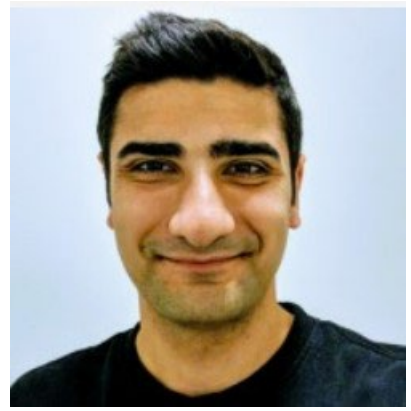

Thank you for your attention !!