

# **Animal models and imaging methods for translational research in the field of radiation oncology**

**Antje Dietrich**

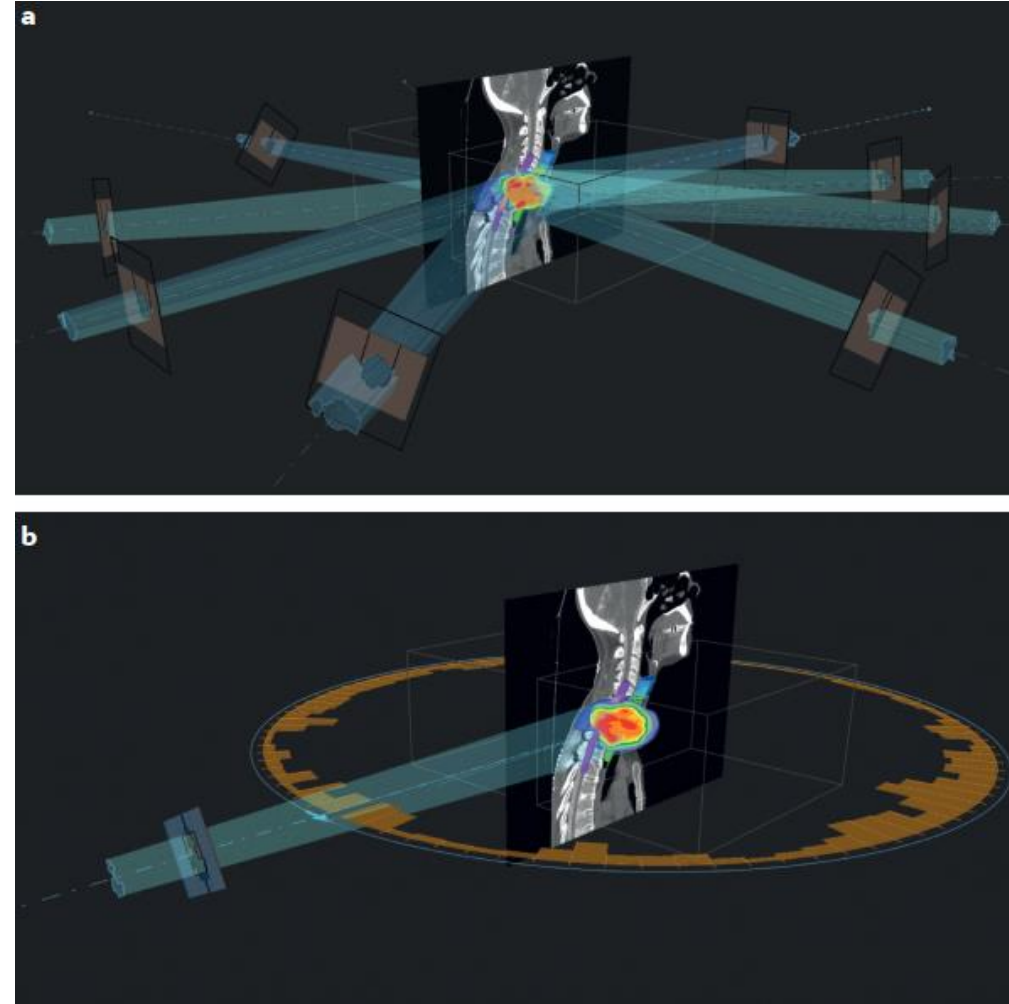
German Cancer Consortium – Partner Site Dresden

OncoRay - National Center for Radiation Research in Oncology

23.11.2023

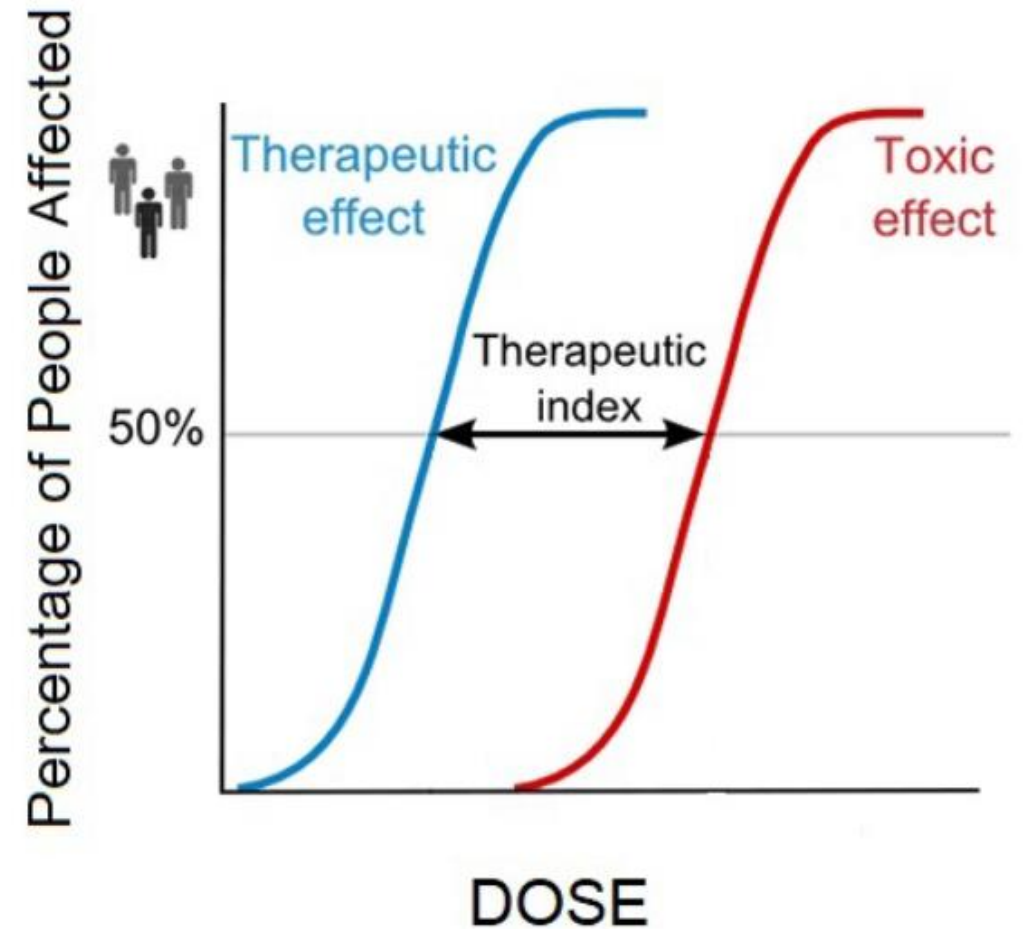
# Radiotherapy

- Today: with optimal diagnosis and treatment every second cancer patient can be cured
- Radiation is involved in ~50% of these successful cases (alone or in combination)
- Radiotherapy (RT) is a very precise and highly individual treatment option



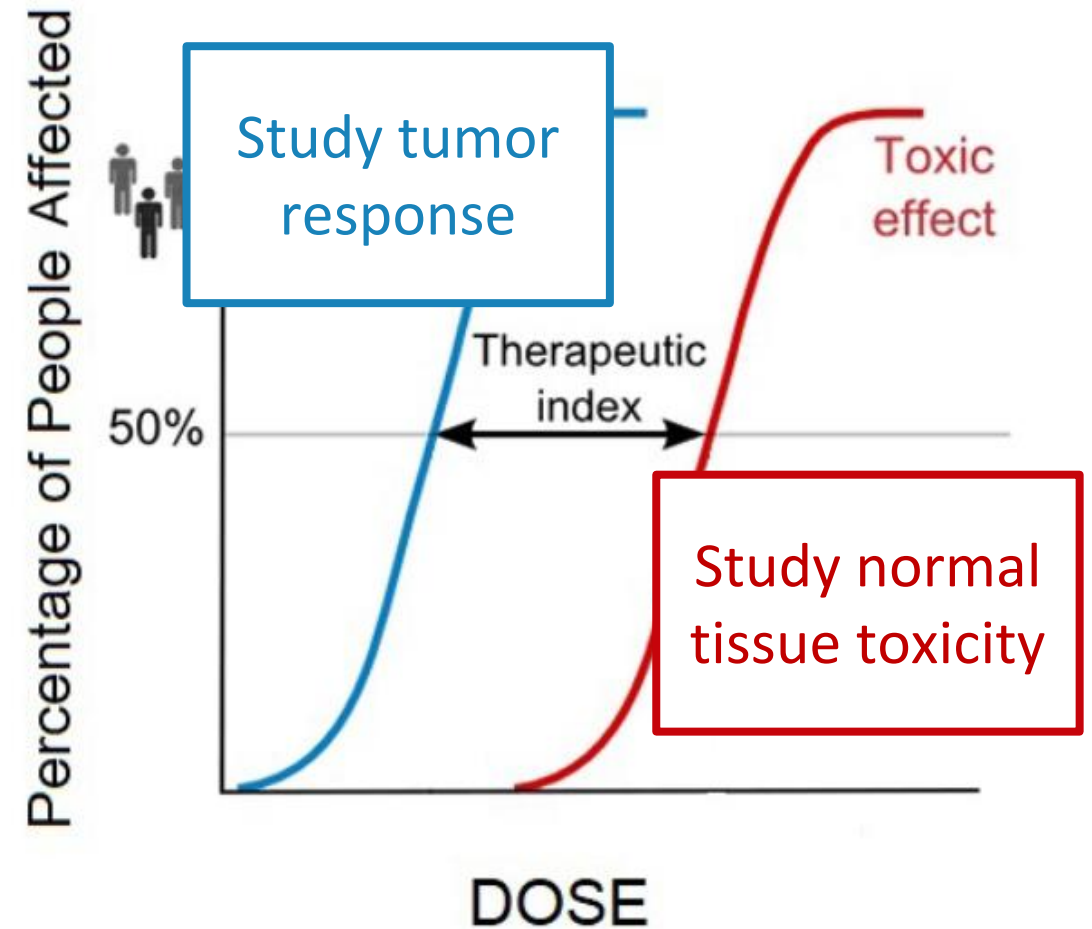
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→ goal: kill all cancer stem cells within normal tissue tolerance level
  - Overall aim of translational radiooncology: widen the therapeutic window



# Radiotherapy

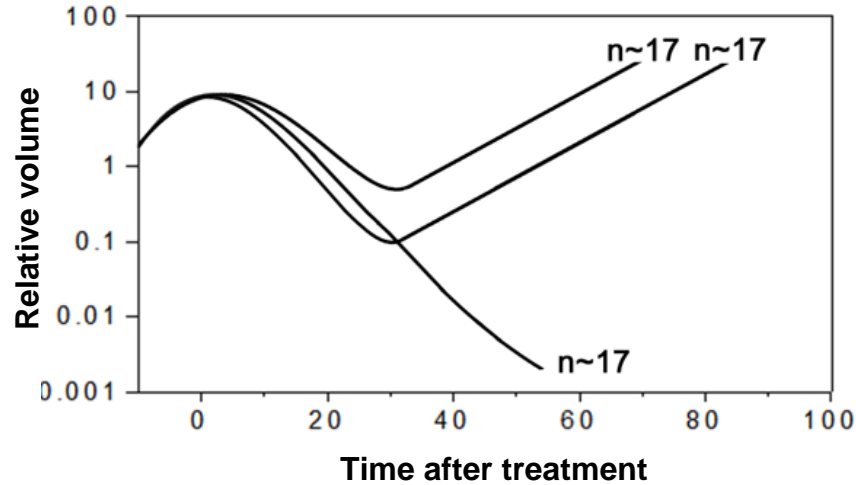
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# Preclinical models and endpoints

Study tumor response

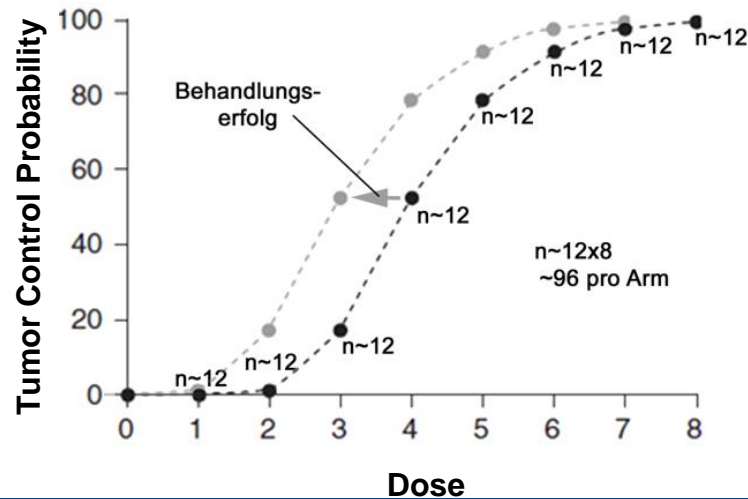
Growth delay



Research for *curative* treatment:

- Should use curative endpoints

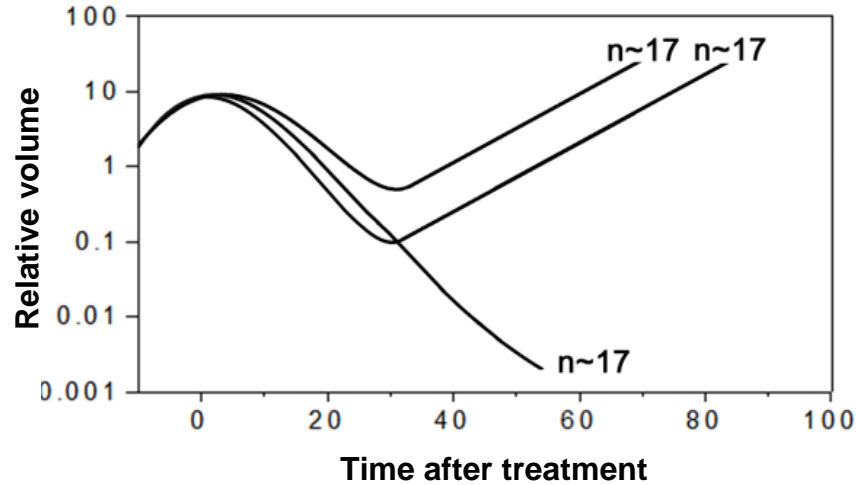
Tumor control



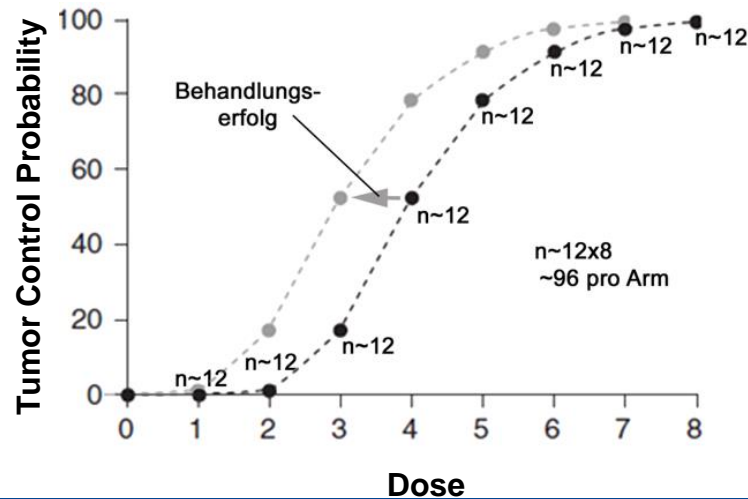
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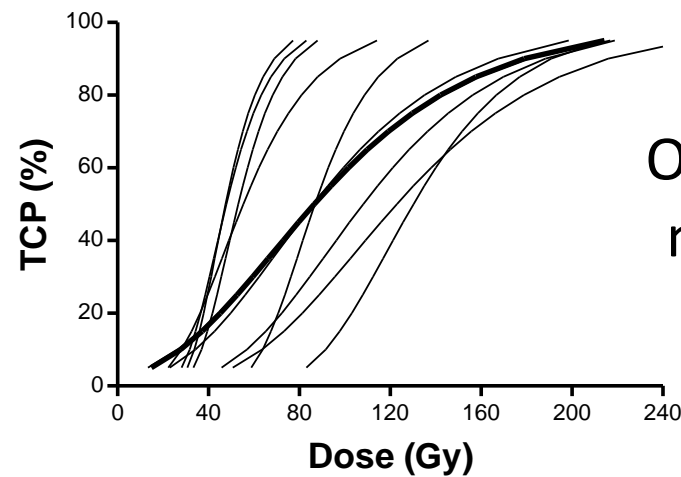


Tumor control



Research for *curative* treatment:

- Should use curative endpoints
- Should account for heterogeneous tumor response

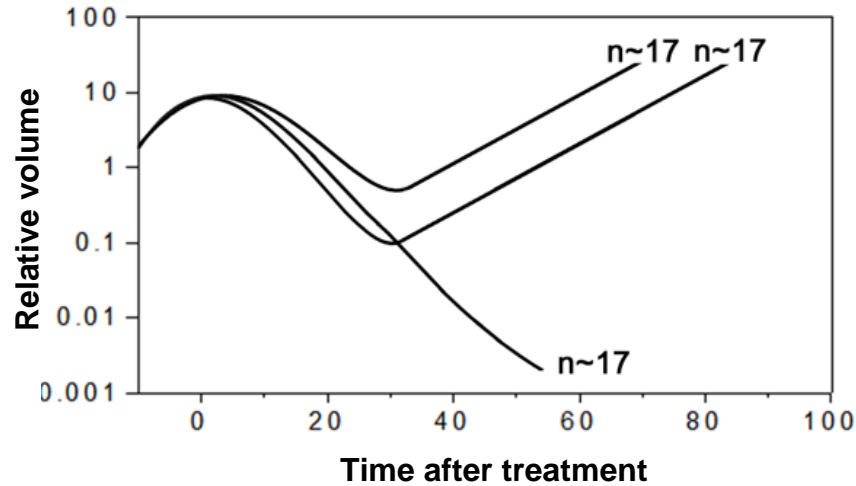


One model is not enough

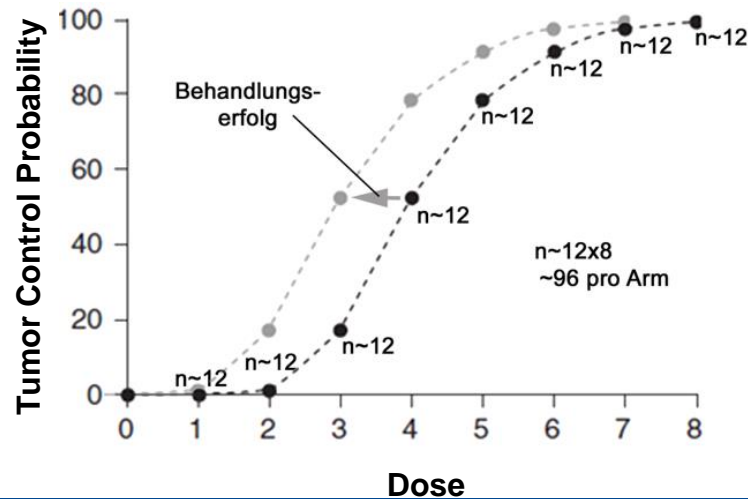
# Preclinical models and endpoints

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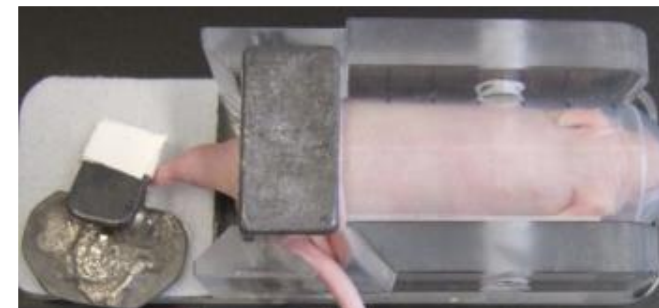
Tumor control



Subcutaneous xenografts



Easy to irradiate and to follow-up



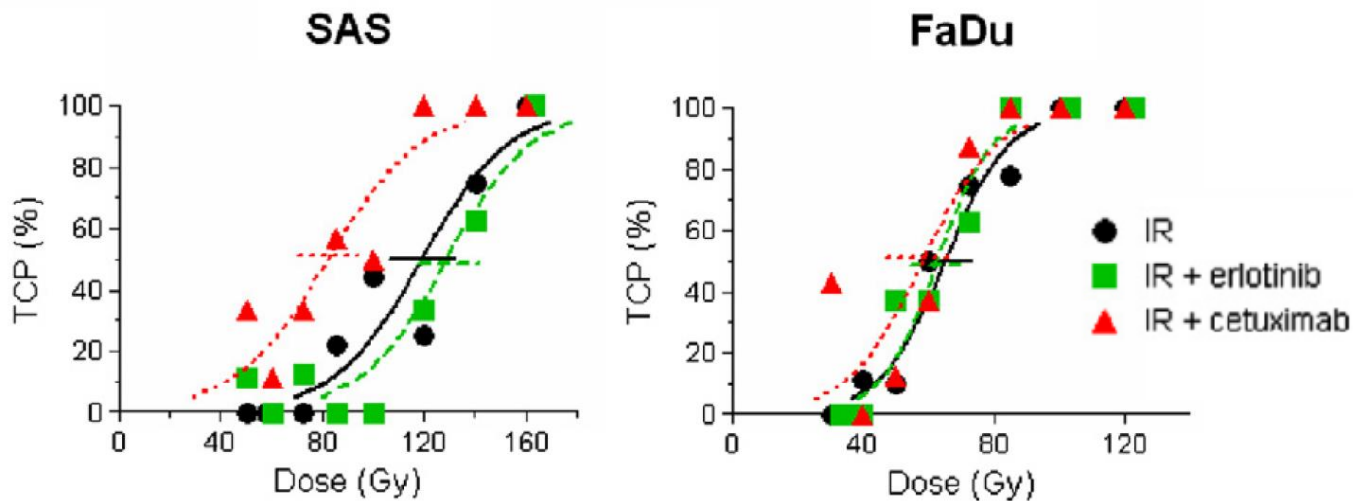


# Combination of RT and anti-EGFR in HNSCC

Study tumor response

Tumour	GT <sub>v5</sub> in days [95% CI] (p-value*)			
	control	erlotinib up to f.s.	cetuximab d0	cetuximab d0,2,5,7
SAS	13 [10-14]	37.5 [26-63] (<0.001)	47.5 [34;55] (<0.001)	66 [49-75] (<0.001)
FaDu	13.5 [10-14]	21 [10-29] (0.025)	18 [14-23] (0.005)	22 [11-23] (0.034)

Growth delay does not always translate into tumor control

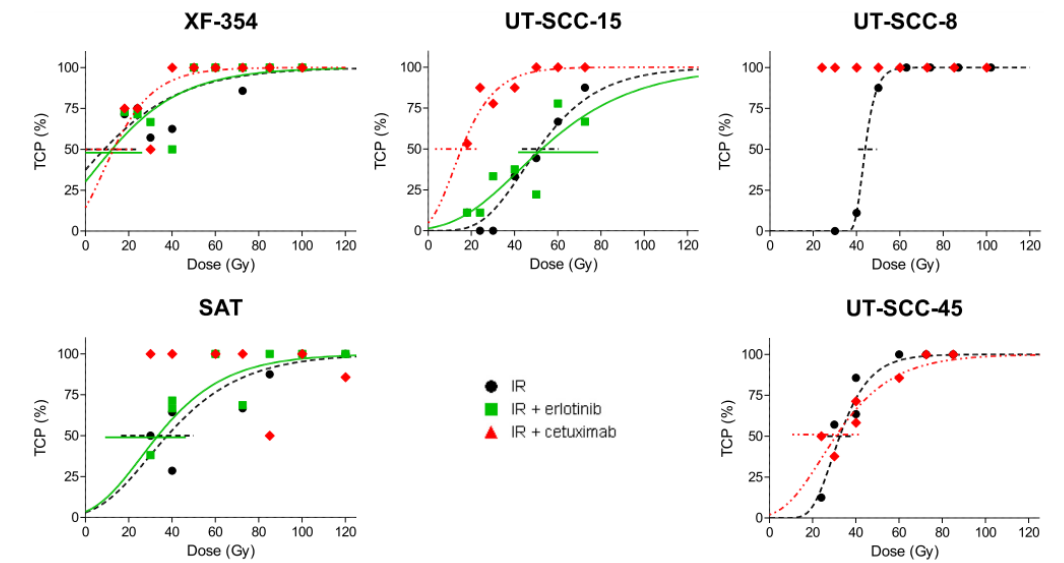
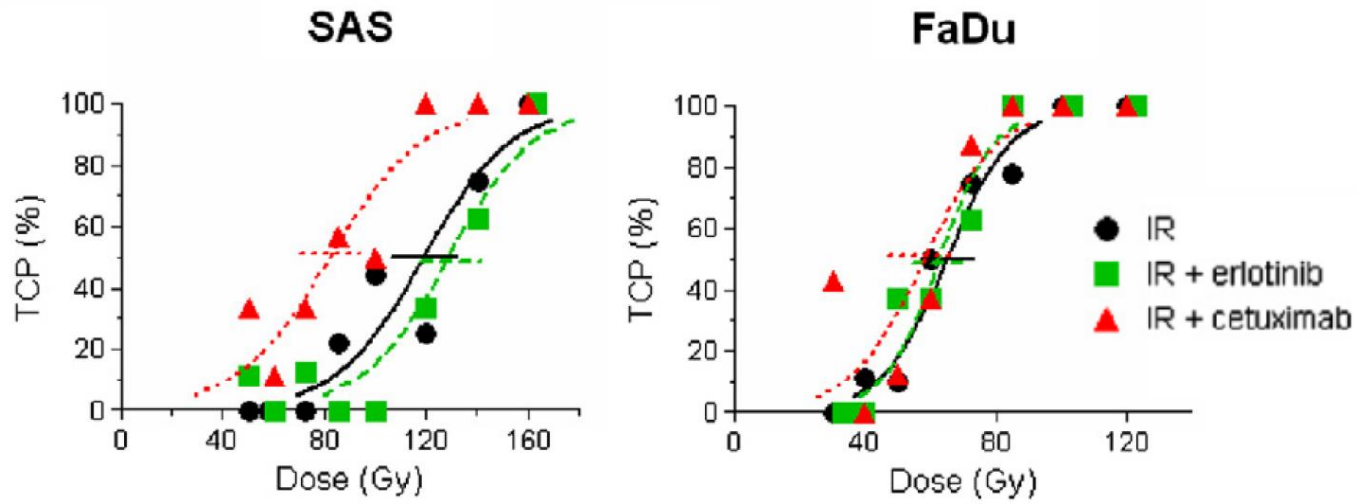
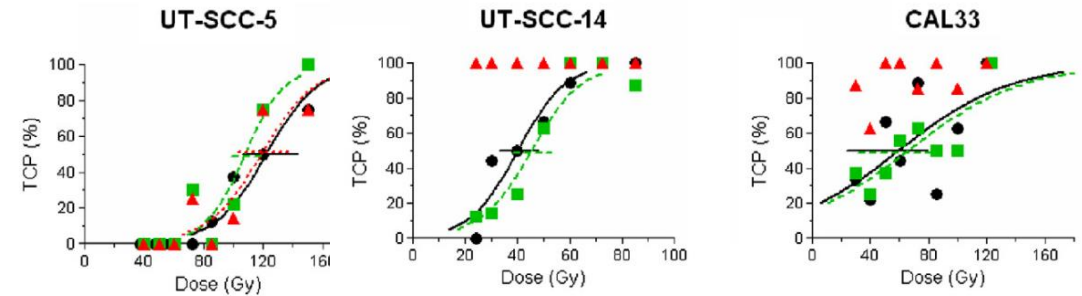




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# HNSCC xenograft models mirror patient tumor molecular profiles

Study tumor response

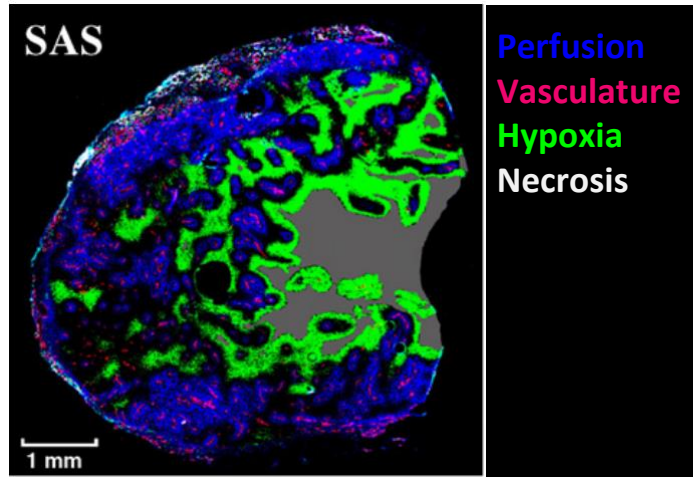
Patil, Linge, Löck, Krause et al.,  
in submission and available soon

- Classification of xenografts into known molecular subtypes possible
- Mesenchymal subtype has high resistance, similar to patients
  
- 3-gene signature developed on patient cohorts is also significantly stratifying xenografts based on their radiosensitivity

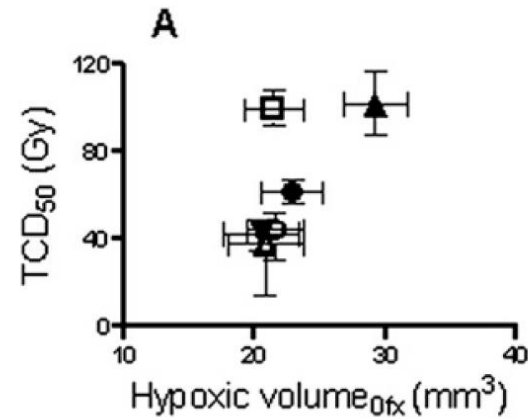
# HNSCC xenograft models mirror patient tumor micromilieu

Study tumor response

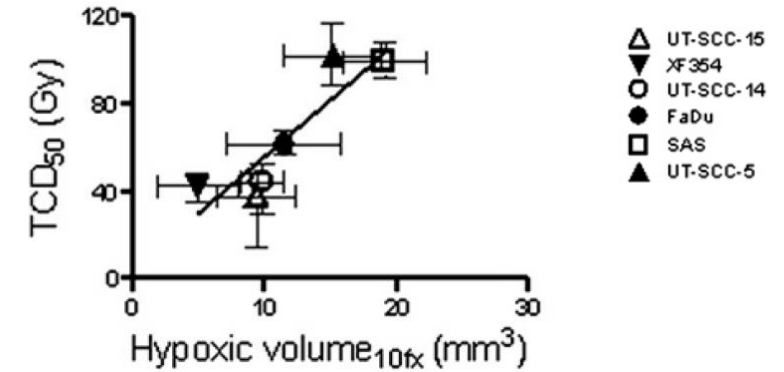
Xenografts



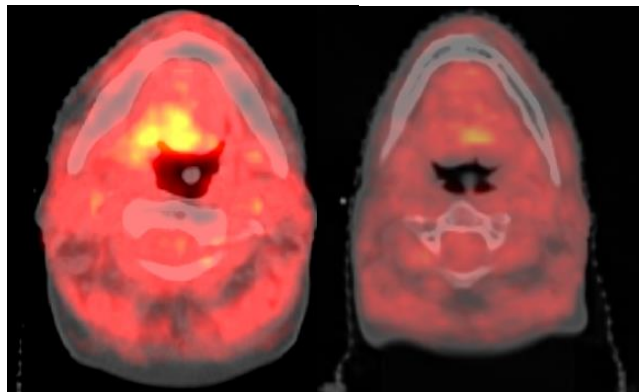
Before treatment



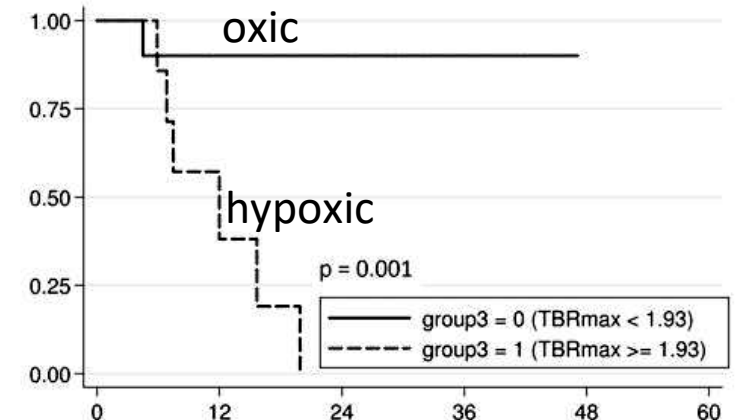
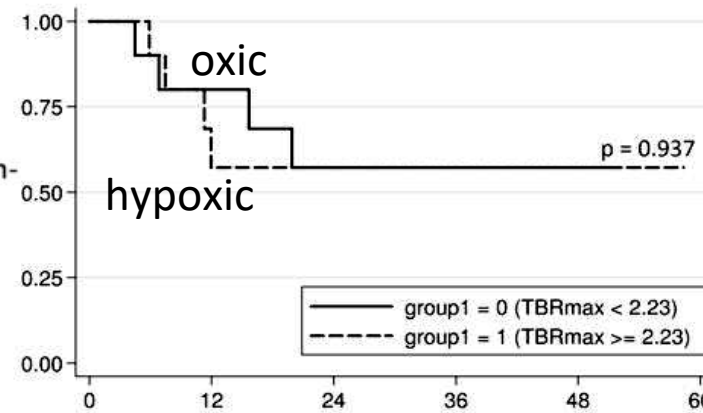
After 10 fx RCT (photons)



Patients (FMISO-PET)



Local-progression-free survival



**DKTK** German Cancer Consortium

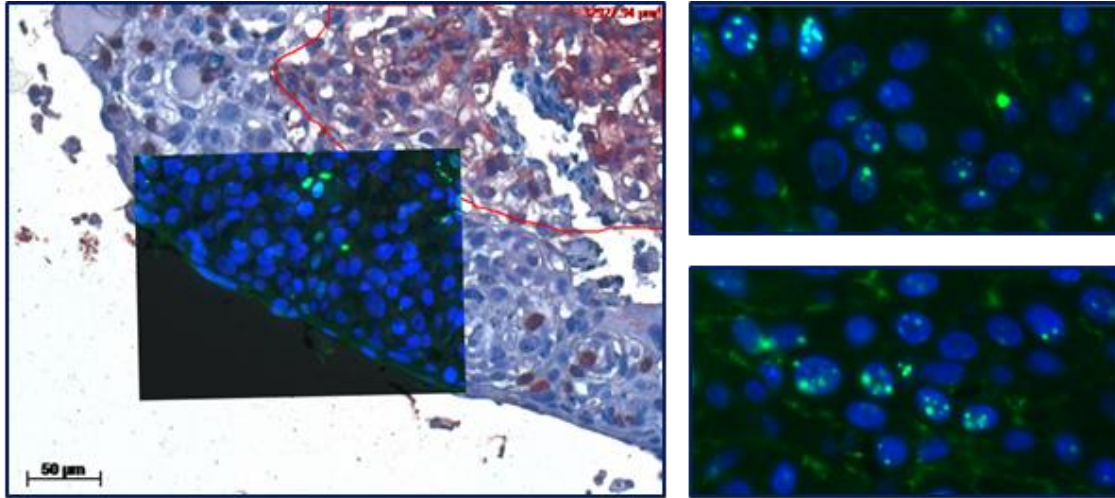
Yaromina et al., Int J Radiat Oncol Biol Phys 2011  
Zips et al., Radiother. Oncol. 2012, validated in Löck et al. 2017



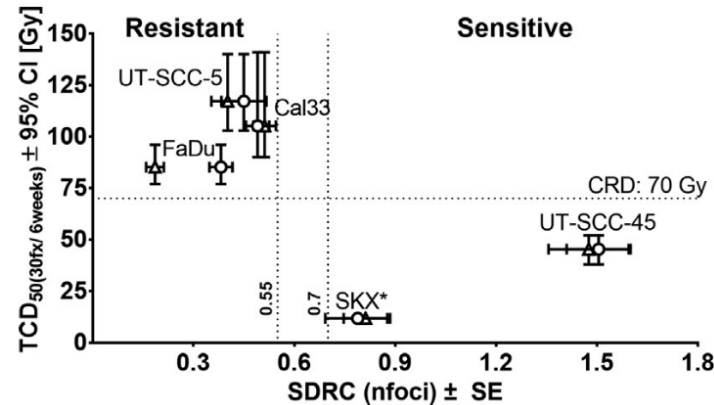
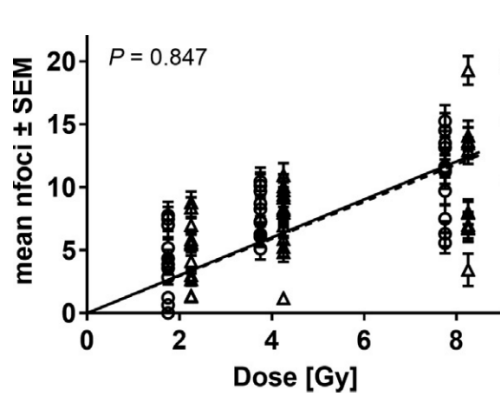
**dkfz.**  
German Cancer Consortium  
Partner site Dresden

# HNSCC xenograft models mirror patient tumor DNA repair

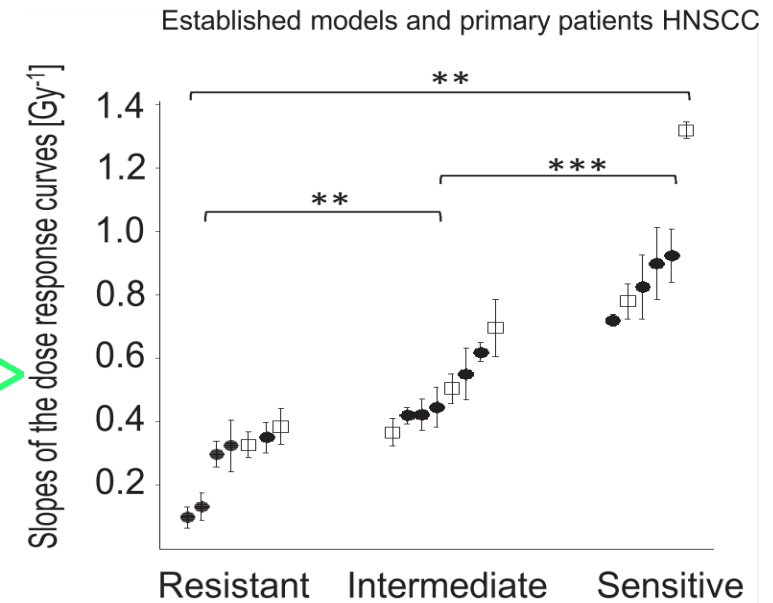
Study tumor response



- Residual **gammaH2AX** foci (24 h after RT) represent un-repaired DNA double strand breaks
- Slopes of dose-response in oxic areas correlate with radio-sensitivity



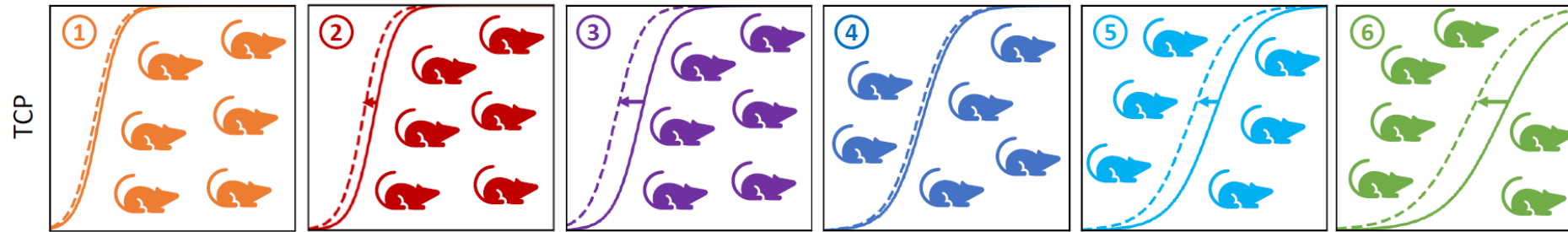
Patient biopsies align with preclinical results



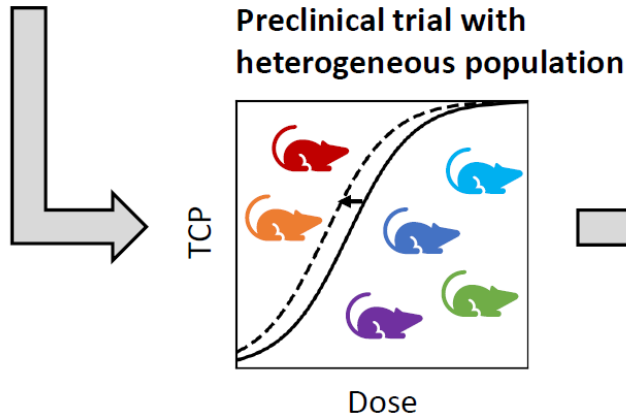
# Re-use of existing data and samples

Study tumor response

Graphical Abstract  
**Precinical trial with 6 individual tumour models** (control vs experimental arm)



Dose



Since 2014	Project	# Histology specimen
Koi et al	Hypoxia_nimorazole EGFR	247 368
Müller et al	Radiomics	101
Rassamegevanon et al	ex vivo biopsy (1) in vivo (1) ex vivo biopsy (2) ex vivo tumour	708 443 413 783

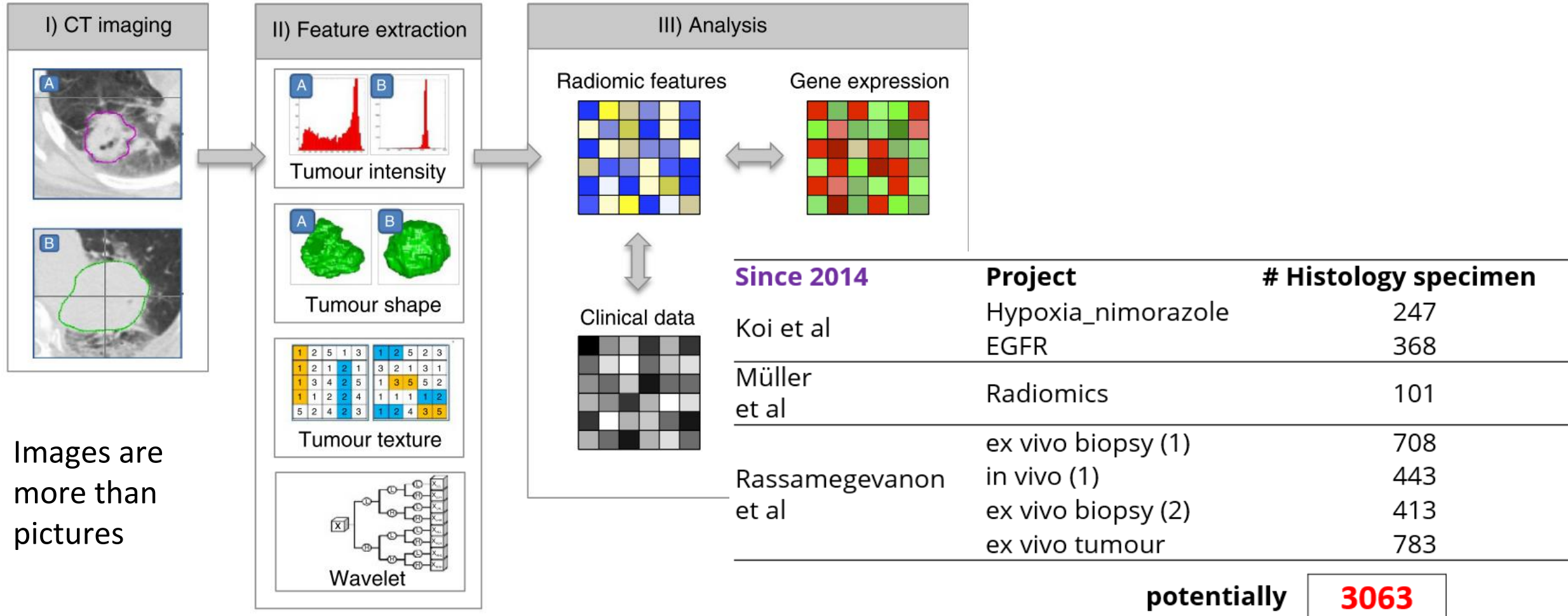
potentially

**3063**



# Re-use of existing data and samples

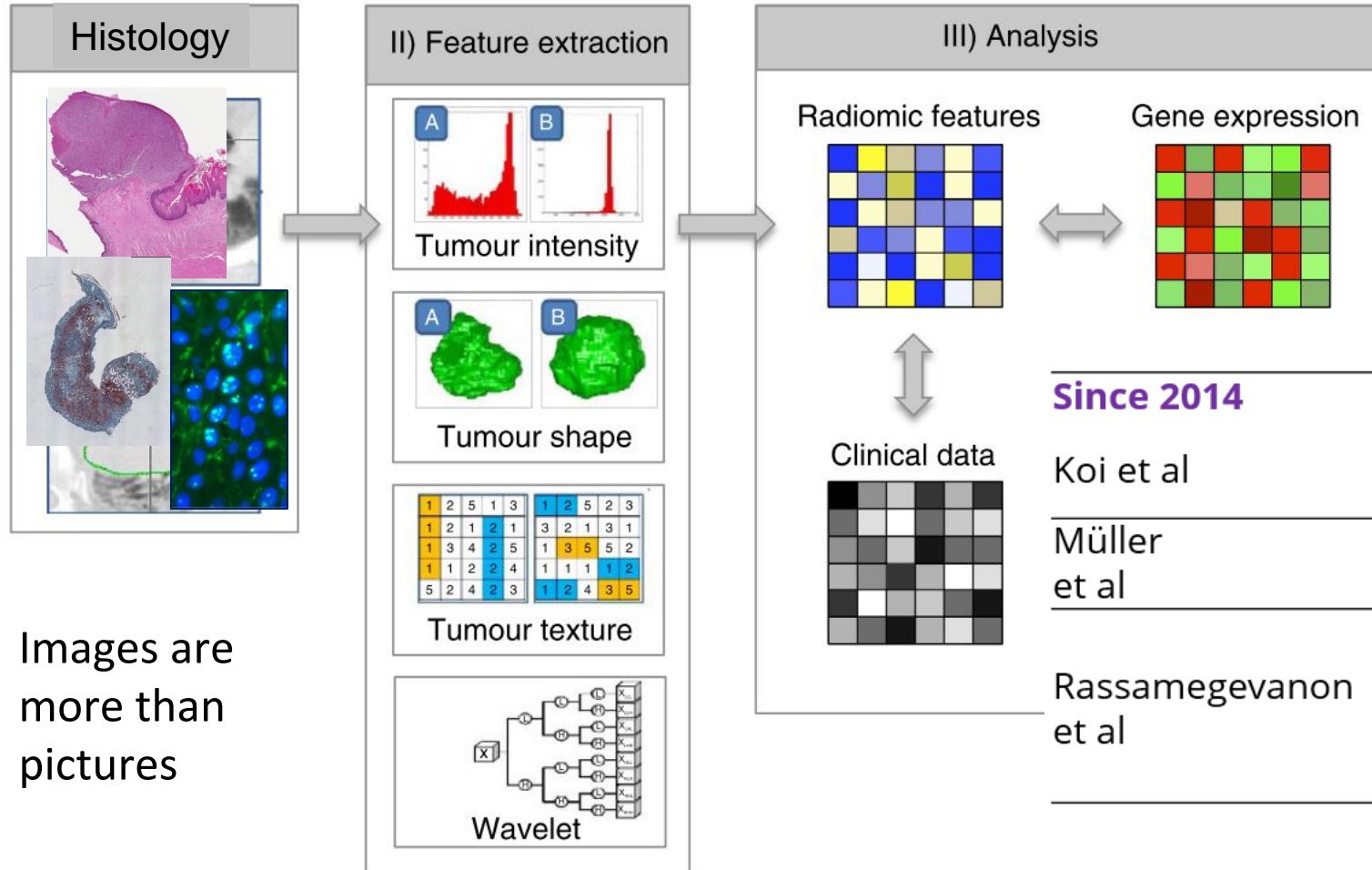
Study tumor response



Images are more than pictures

# Re-use of existing data and samples

Study tumor response



Images are more than pictures

➤ Preclinical data can help to enhance interpretability for digital pathology approaches

Since 2014	Project	# Histology specimen
Koi et al	Hypoxia_nimorazole	247
	EGFR	368
Müller et al	Radiomics	101
Rassamegevanon et al	ex vivo biopsy (1)	708
	in vivo (1)	443
	ex vivo biopsy (2)	413
	ex vivo tumour	783

potentially

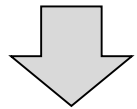
**3063**



# Re-use of existing data and samples

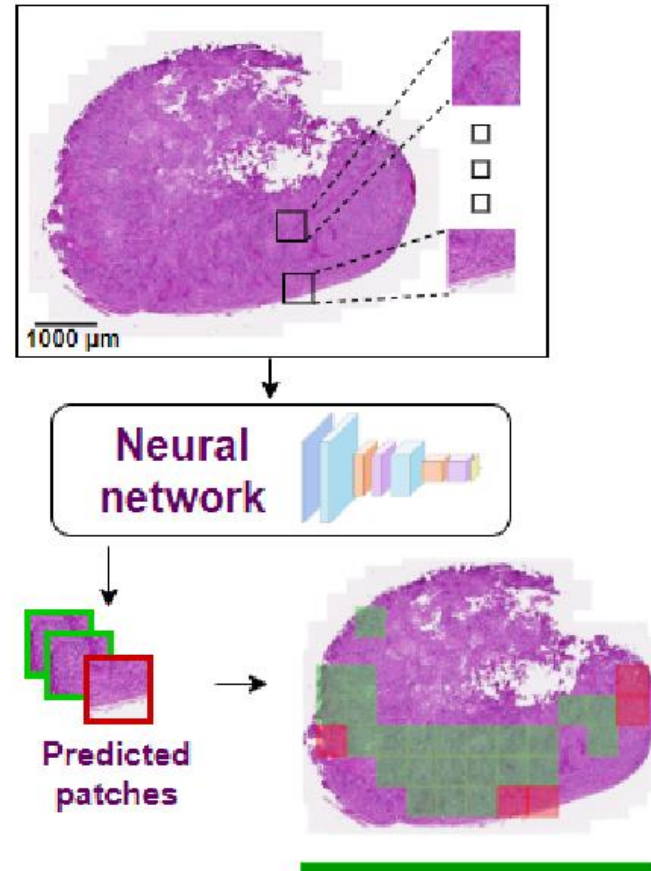
Study tumor response

n=72 HE-stained tumor sections of 10 HNSCC xenograft models (untreated)



## Outlook:

- Validation in other data sets (precl. & patient)
- Integration of treatments
- Transfer to other markers
- Usage of methods for interpretable AI



# Subcutaneous xenograft models: GBM

Study tumor  
response



<u>Cell line</u>
HGL21
LN-229
A7
U-87 MG
U-251 MG

- Subcutaneous GBM xenografts do not mirror patient tumor radioresistance

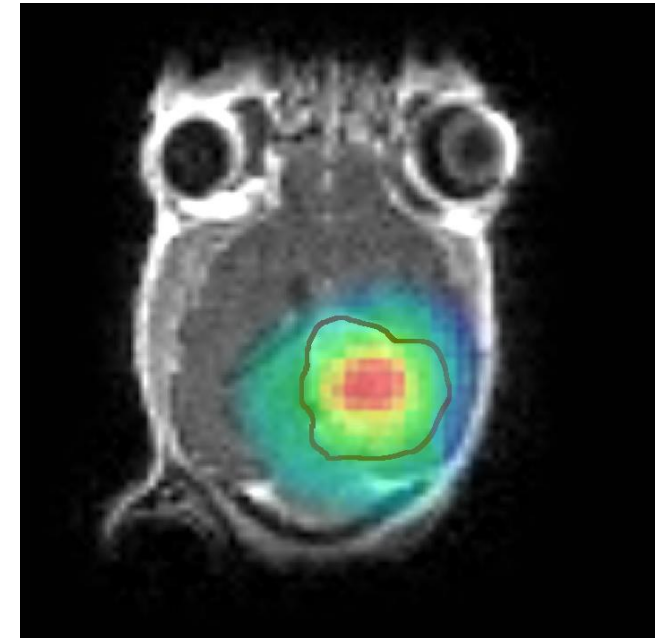
# Subcutaneous xenograft models: GBM

Study tumor response



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Are orthotopic models better?



?

- Subcutaneous GBM xenografts do not mirror patient tumor radioresistance

Dietrich, Büttof, von Neubeck et al., in  
submission and available soon

## G7-mCherry

Provided by Prof. Anthony Chalmers, University of Glasgow  
Kössinger et al. Sci Rep. 2020;  
doi: [10.1038/s41598-020-72322-x](https://doi.org/10.1038/s41598-020-72322-x)

# Orthotopic xenograft models: precise irradiation

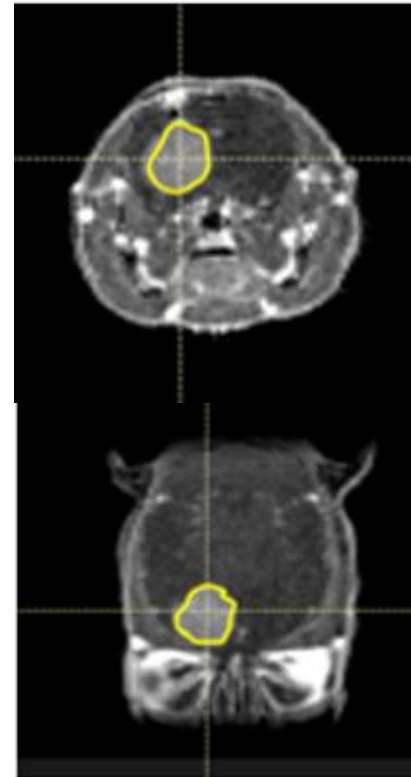
Study tumor response



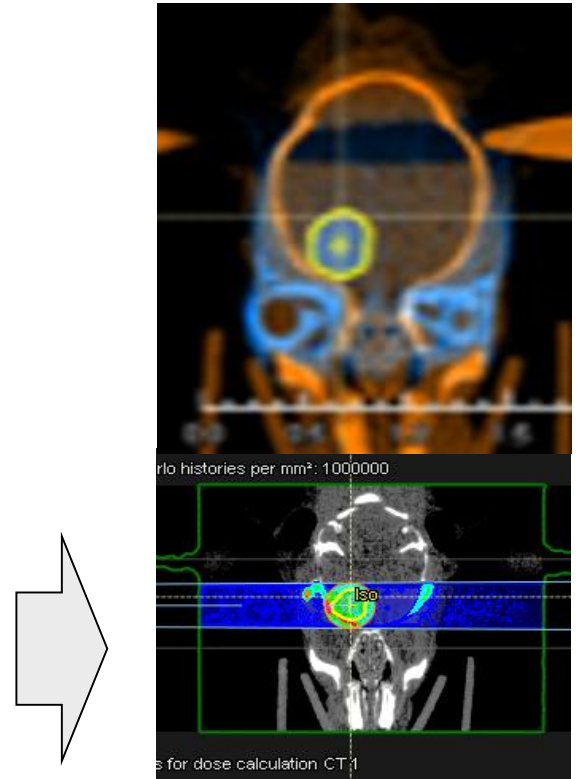
Precise Irradiation:  
SAIGRT: Small Animal Image-guided Radiotherapy

Mirror clinical workflow

Contouring on CE-MRI



Registration with CT and planning of field



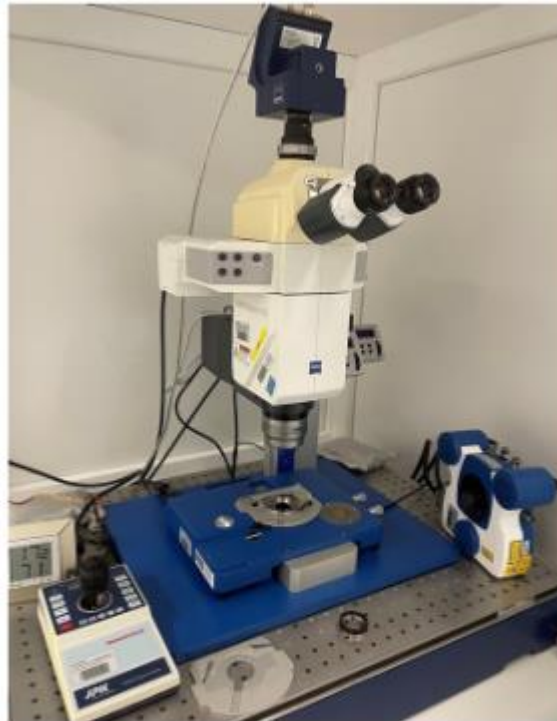
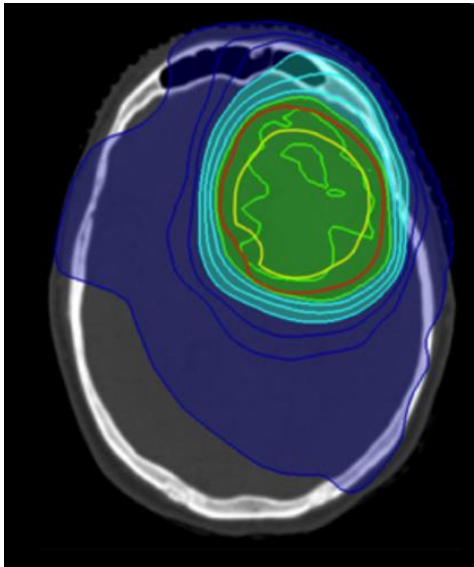
Tillner et al. PMB 2016, Büttof et al., in progress



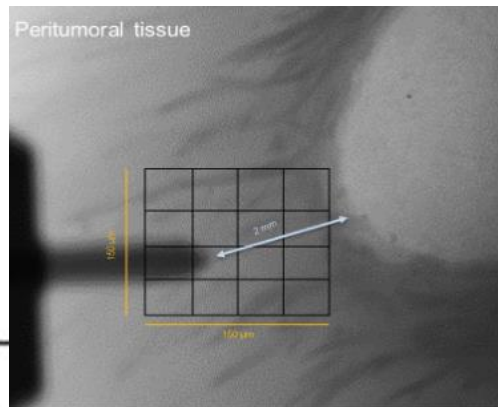
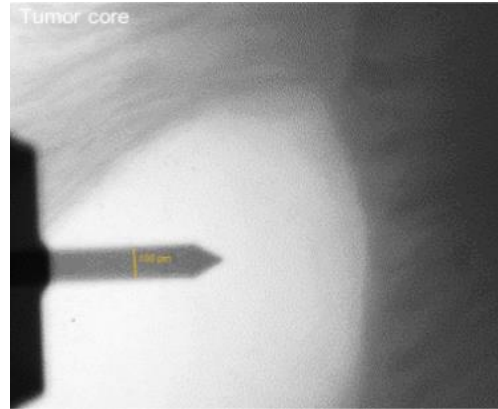
# Physical stiffness of the tumor and it's surrounding

Study tumor response

Definition of the clinical target volume (CTV)



Combined Atomic force -  
Light microscopy setup



Sankari et al., in prep  
*in cooperation with AG Taubenberger*



**DKTK** German Cancer Consortium



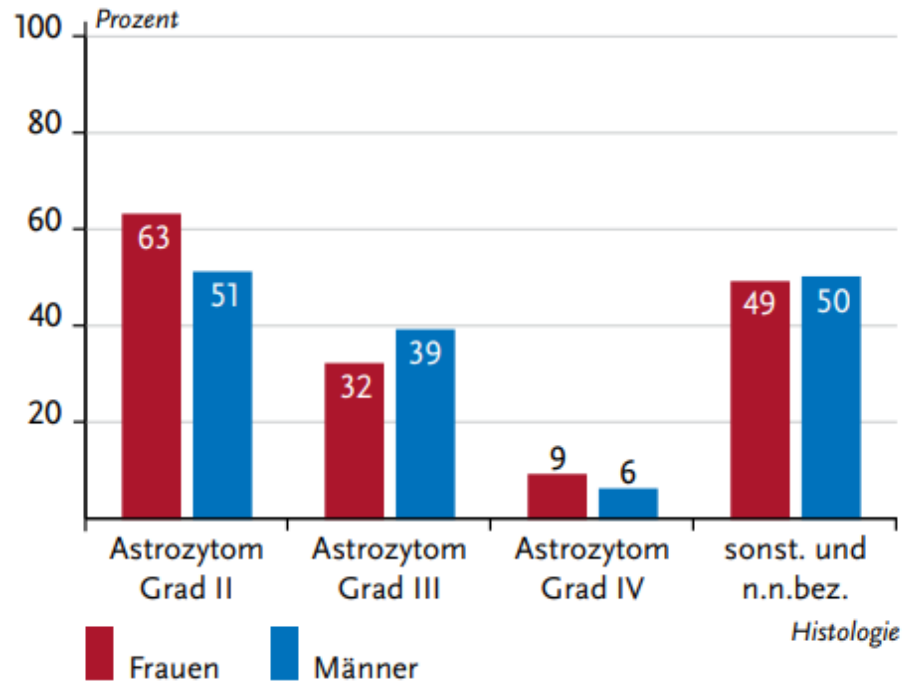
**dkfz.**  
German Cancer Consortium  
Partner site Dresden

# Translational proton therapy research

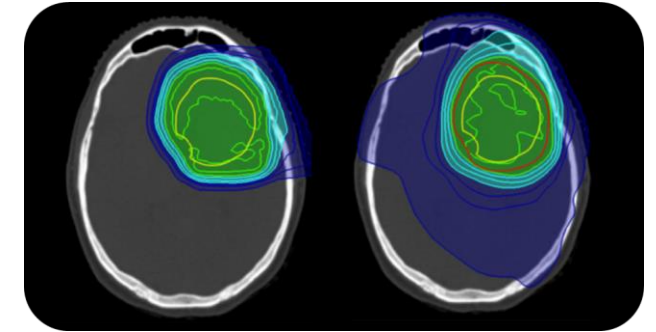
Study normal tissue toxicity

## CNS tumors

Abbildung 3.26.5  
Relatives 5-Jahres-Überleben nach Histologie  
und Geschlecht, ICD-10 C71, Deutschland 2015–2016



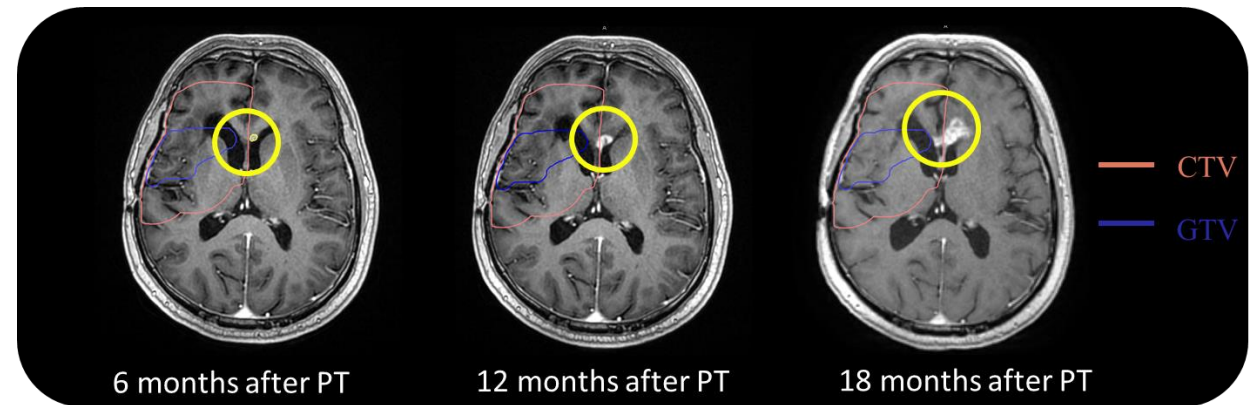
Therapy:  
Surgery, Radiation,  
Chemo, clinical trials



Protons

Photons

Normal Tissue toxicities:



6 months after PT

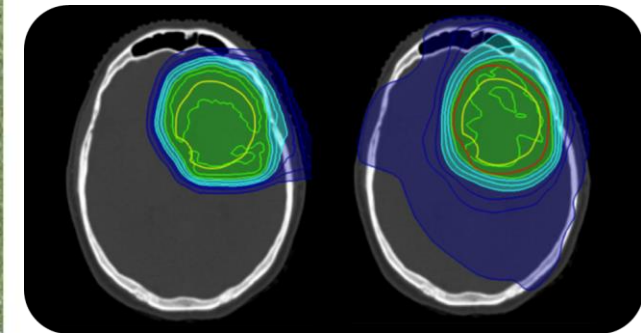
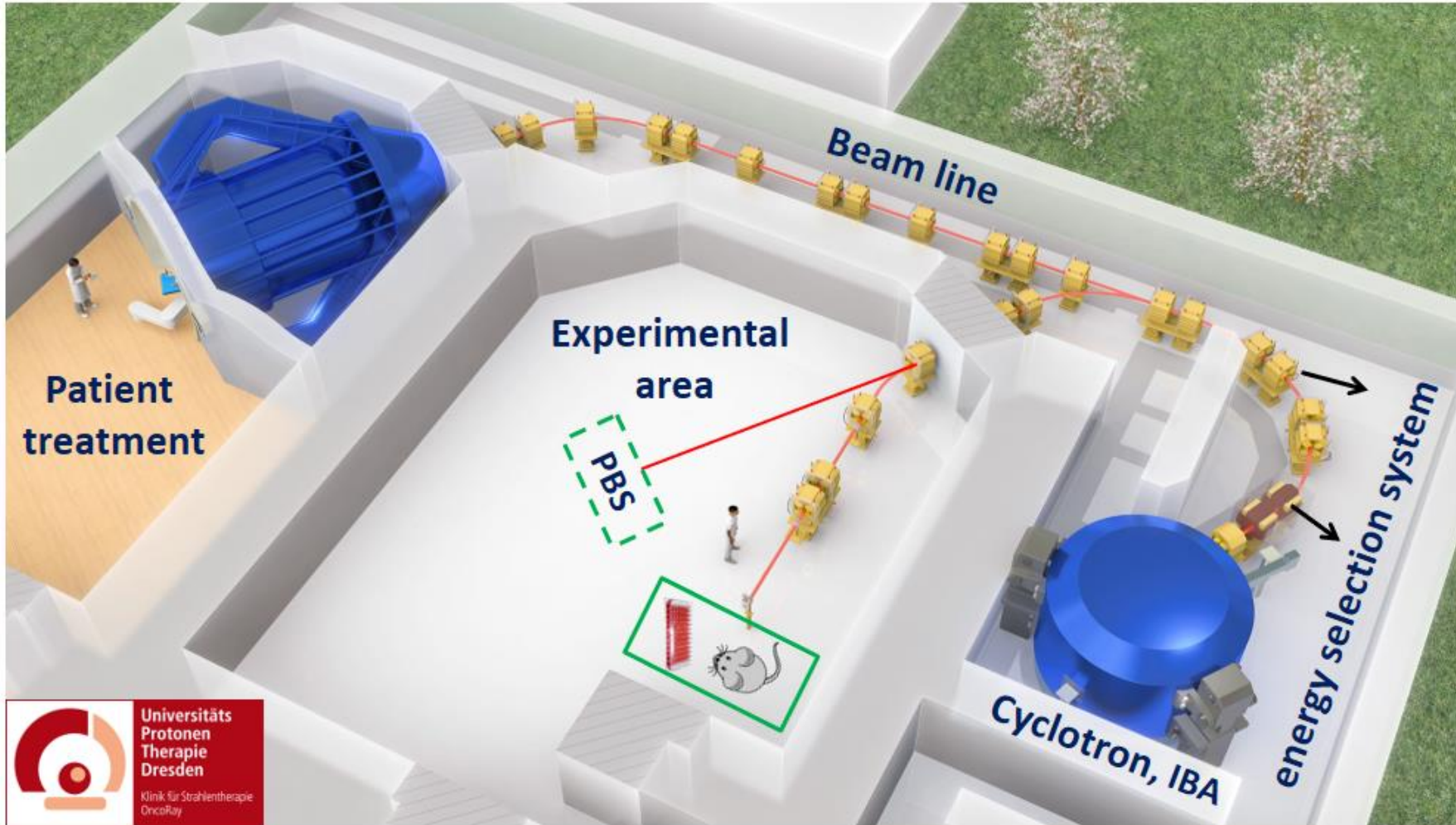
12 months after PT

18 months after PT

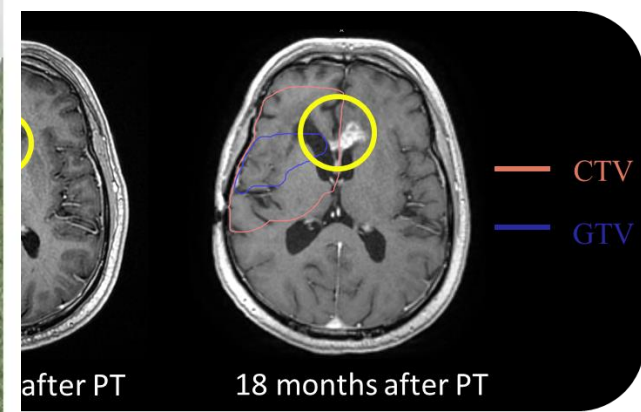


# Translational proton therapy research

Study normal tissue toxicity



Protons      Photons



# Investigation of radiation effects in subvolumes of the brain

Study normal tissue toxicity

**In vivo experiments:** Mainly whole-brain or half of the brain

**Clinical routine:** Smallest possible brain volume



**Aims:** Irradiation of brain subvolumina

Sparring of one hemisphere

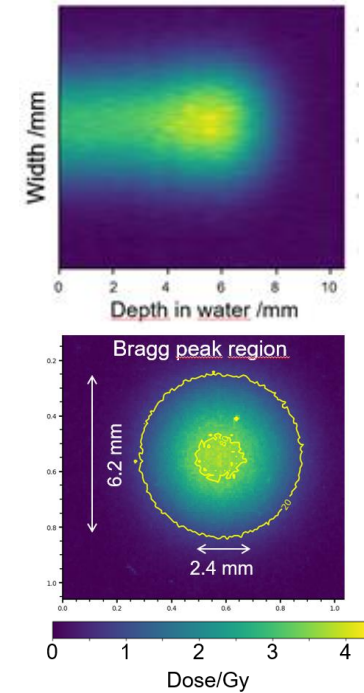
**Region of interest:** Hippocampus

→ Involved in neurogenesis, learning and memory formation



14 mm

10 mm

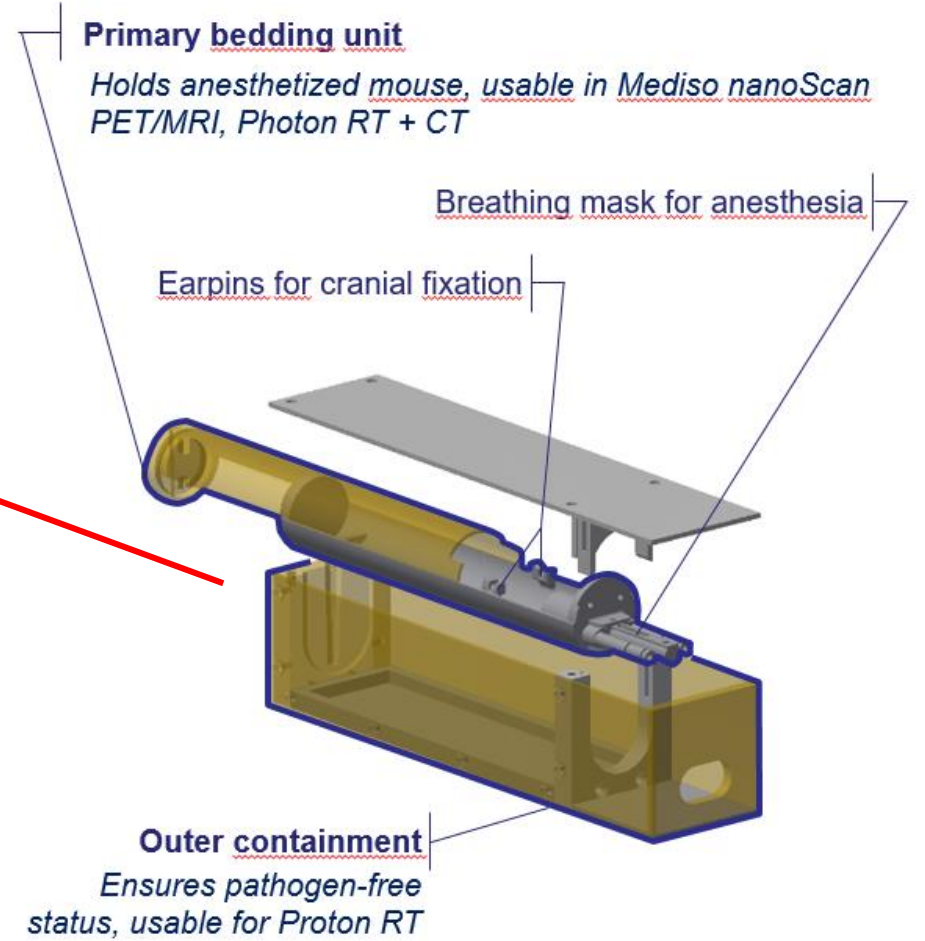
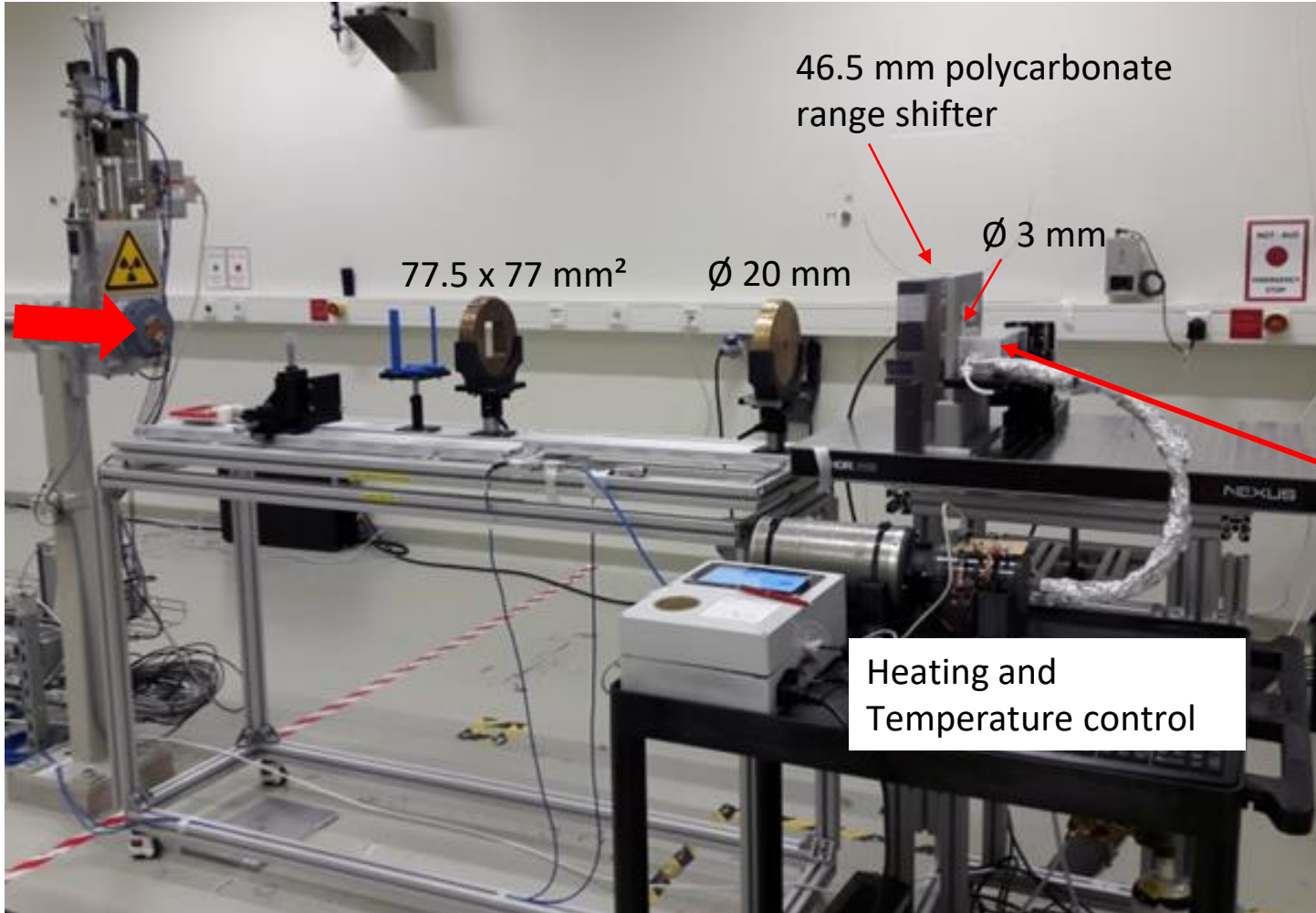


Reference radiation:  
200 kV X-rays  
(SAIGRT)



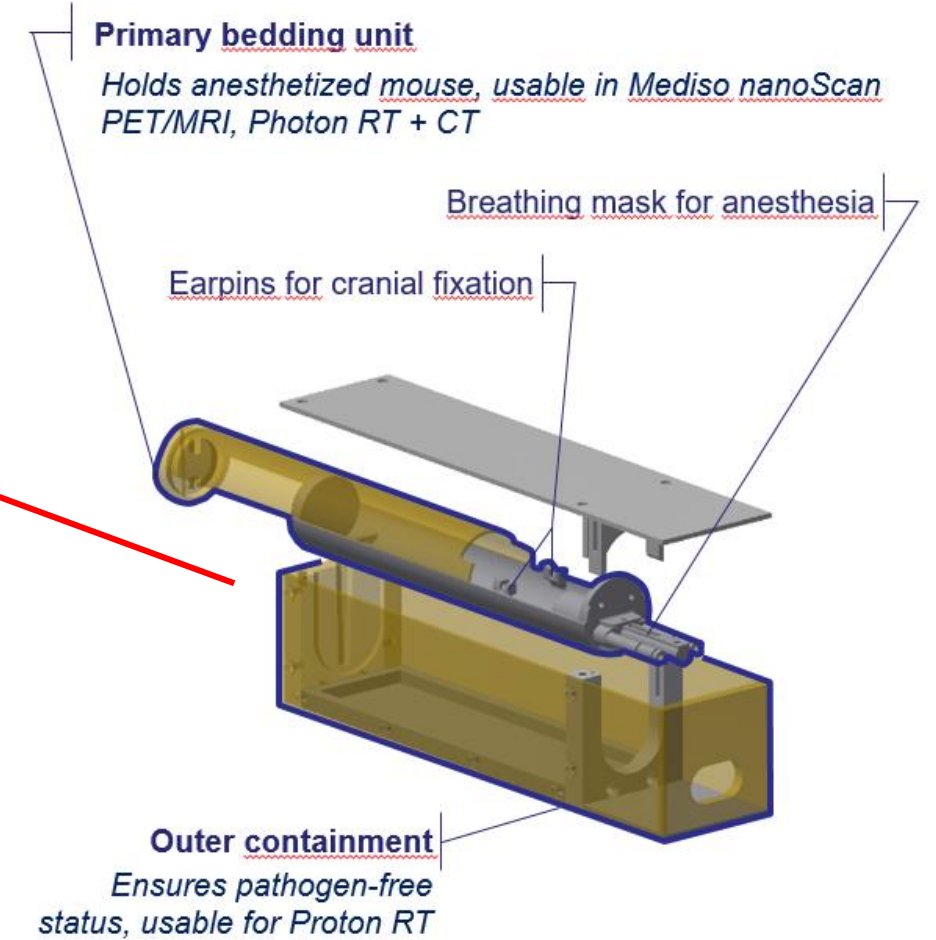
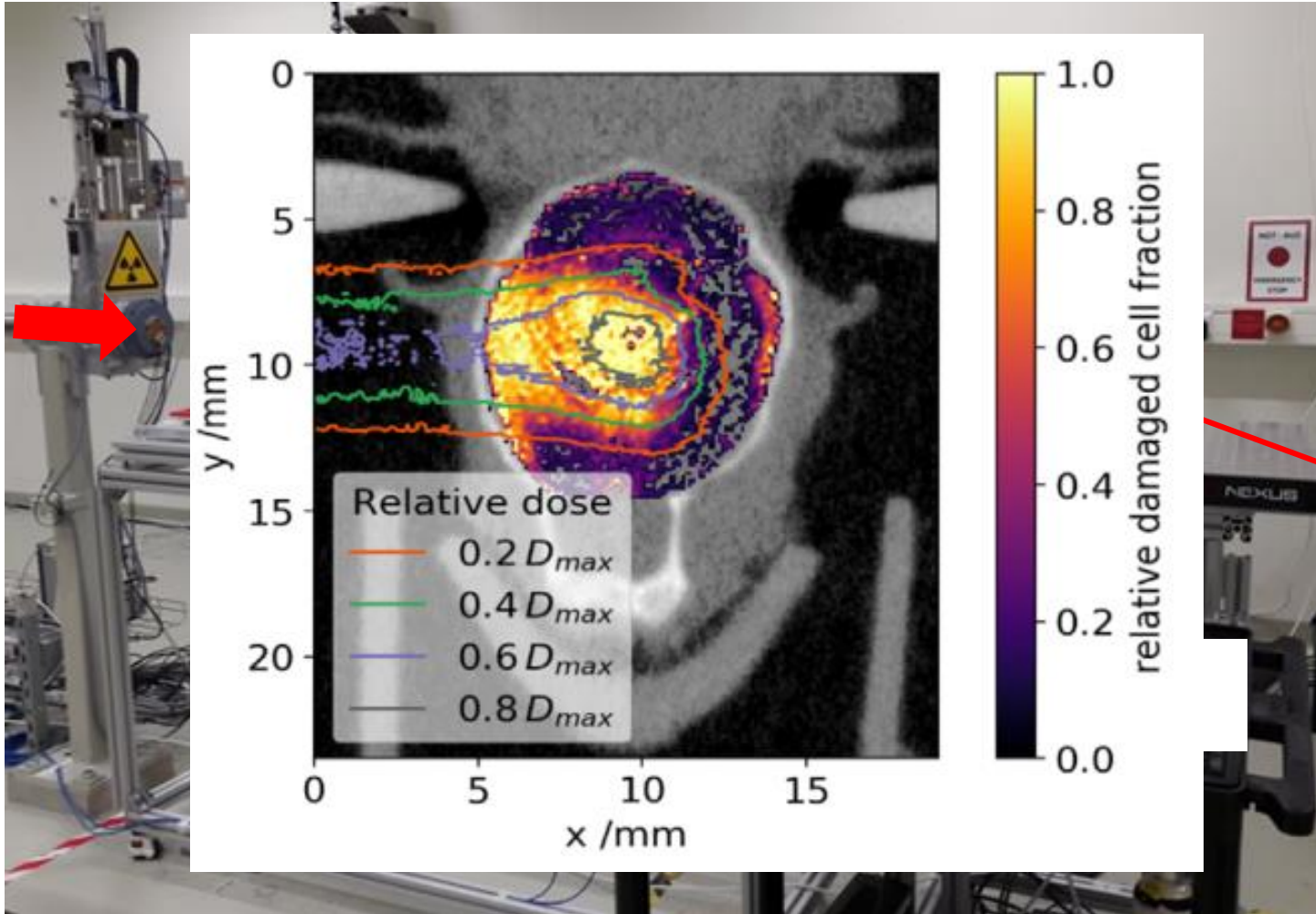
# Investigation of radiation effects in subvolumes of the brain

Study normal tissue toxicity



# Investigation of radiation effects in subvolumes of the brain

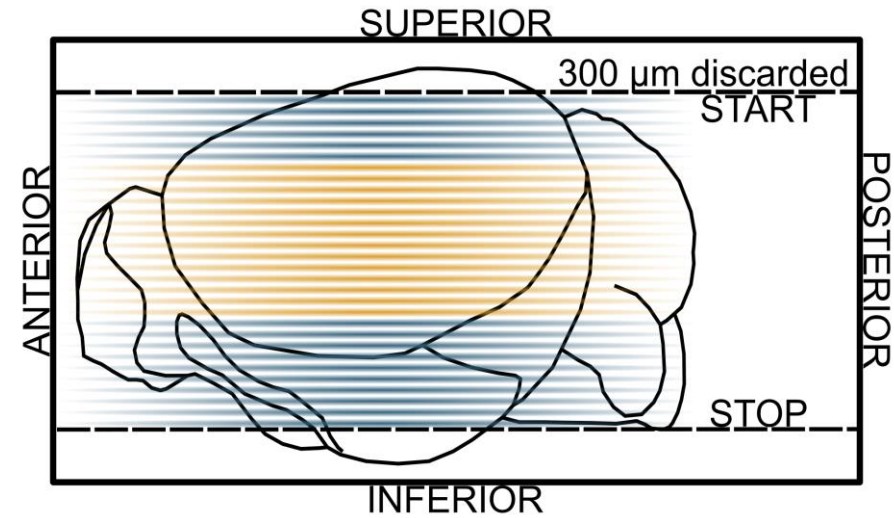
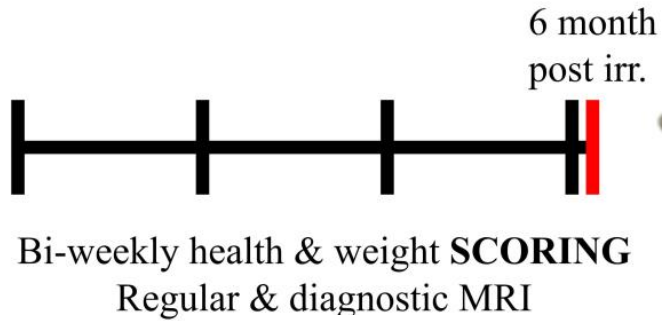
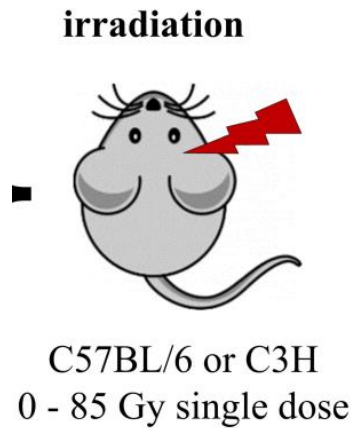
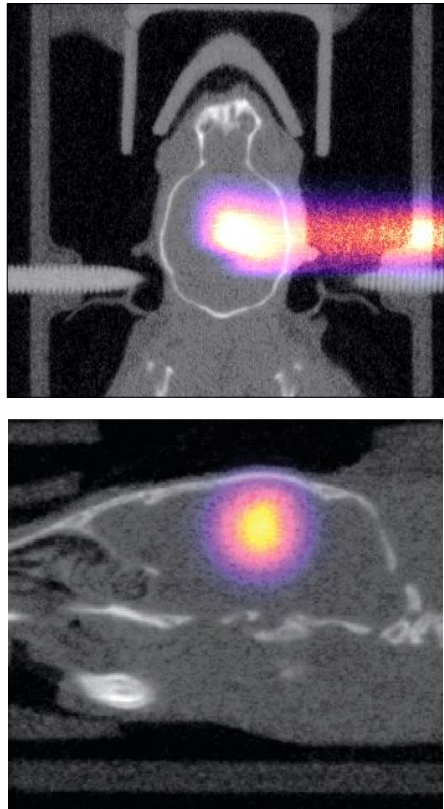
Study normal tissue toxicity





# Dose finding for radiation-induced brain toxicities

Study normal tissue toxicity



**Comprehensive whole-brain histology at final time point**

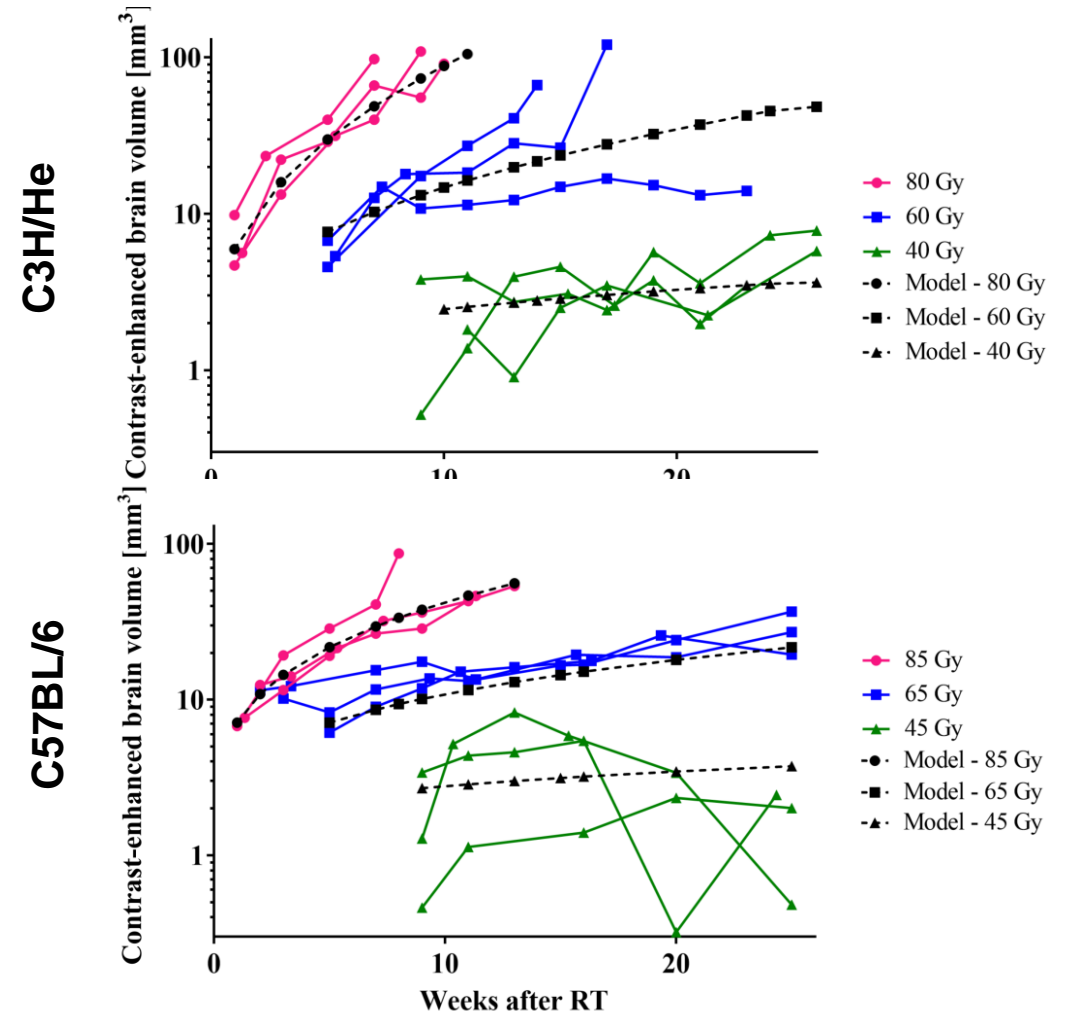
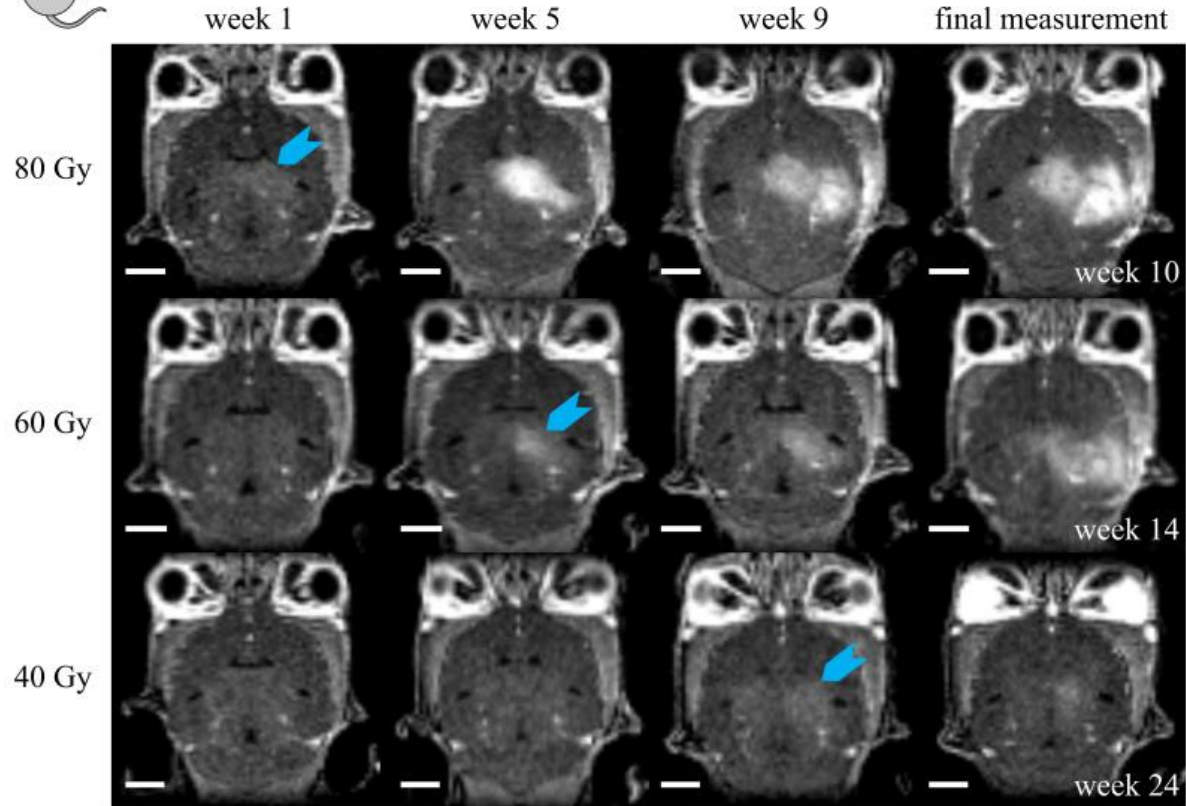
# Dose finding for radiation-induced brain toxicities

Study normal tissue toxicity

## MRI C3H/He



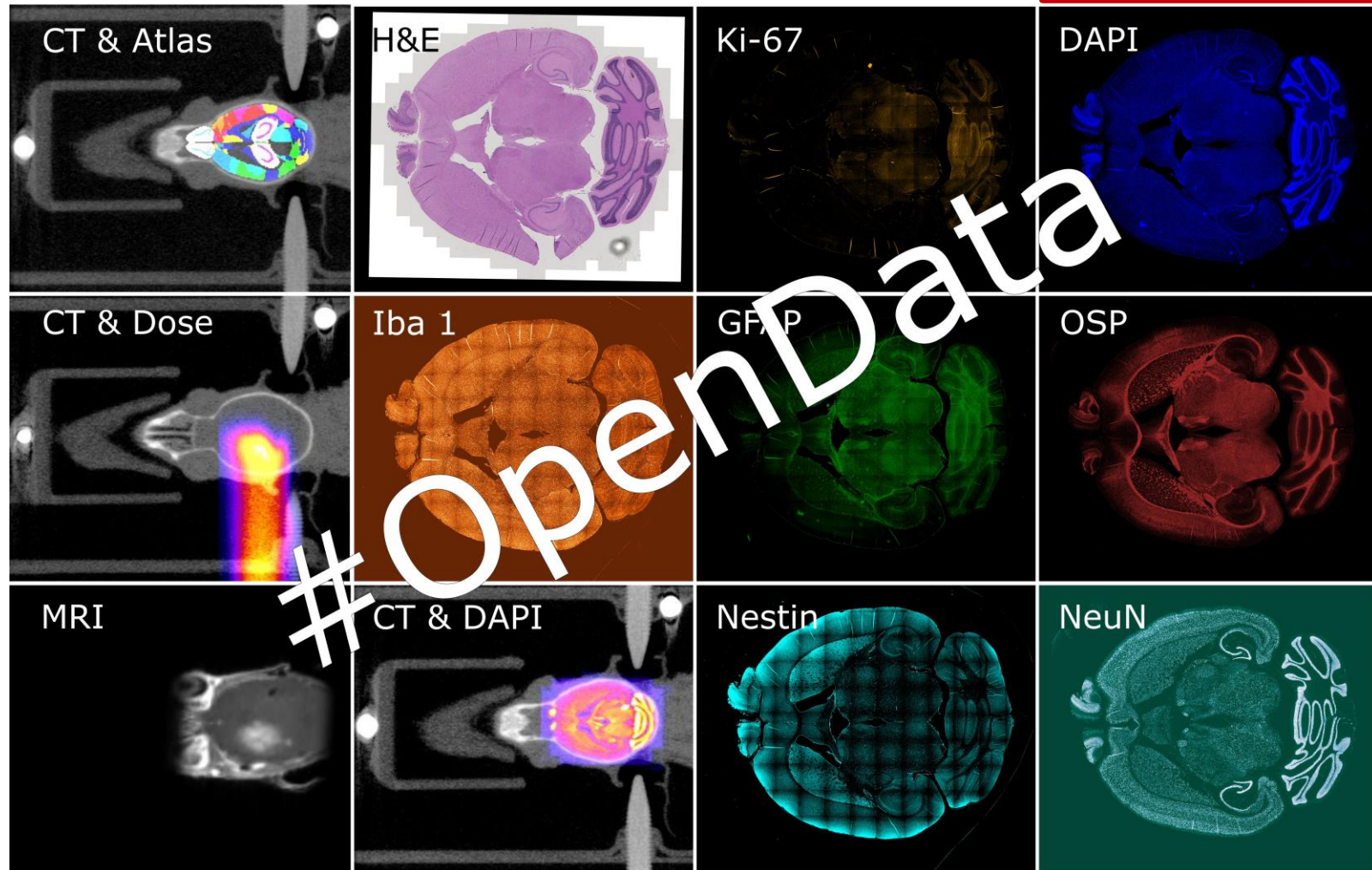
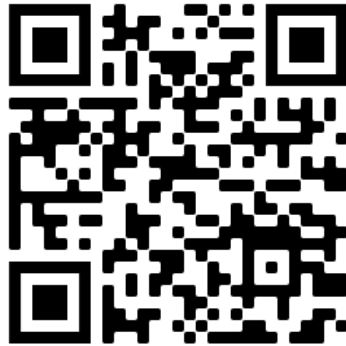
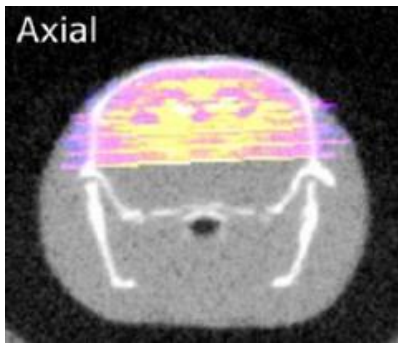
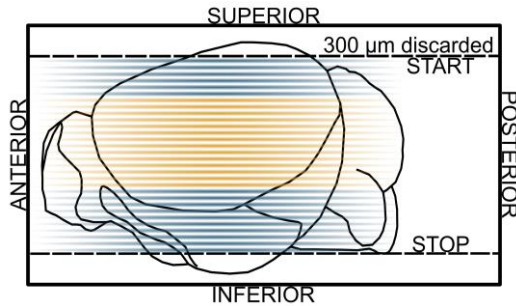
### T1 weighted, contrast-enhanced



# Slice2Volume: open data set

Study normal tissue toxicity

Co-registration of all data into one coordinate system

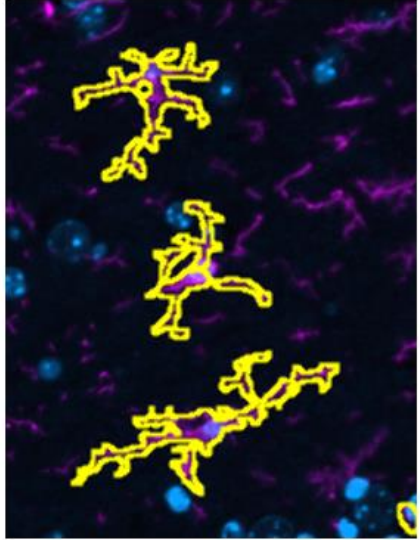




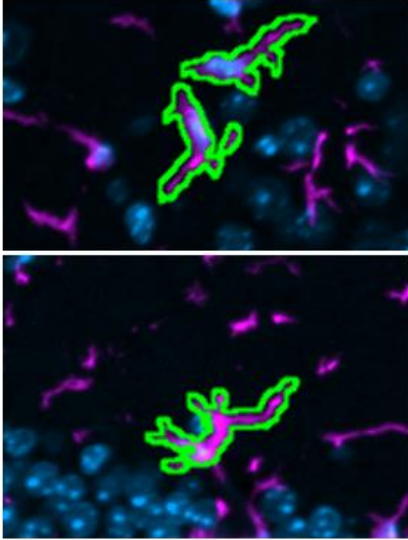
# Microglia activation in radiation-induced brain toxicities

Study normal tissue toxicity

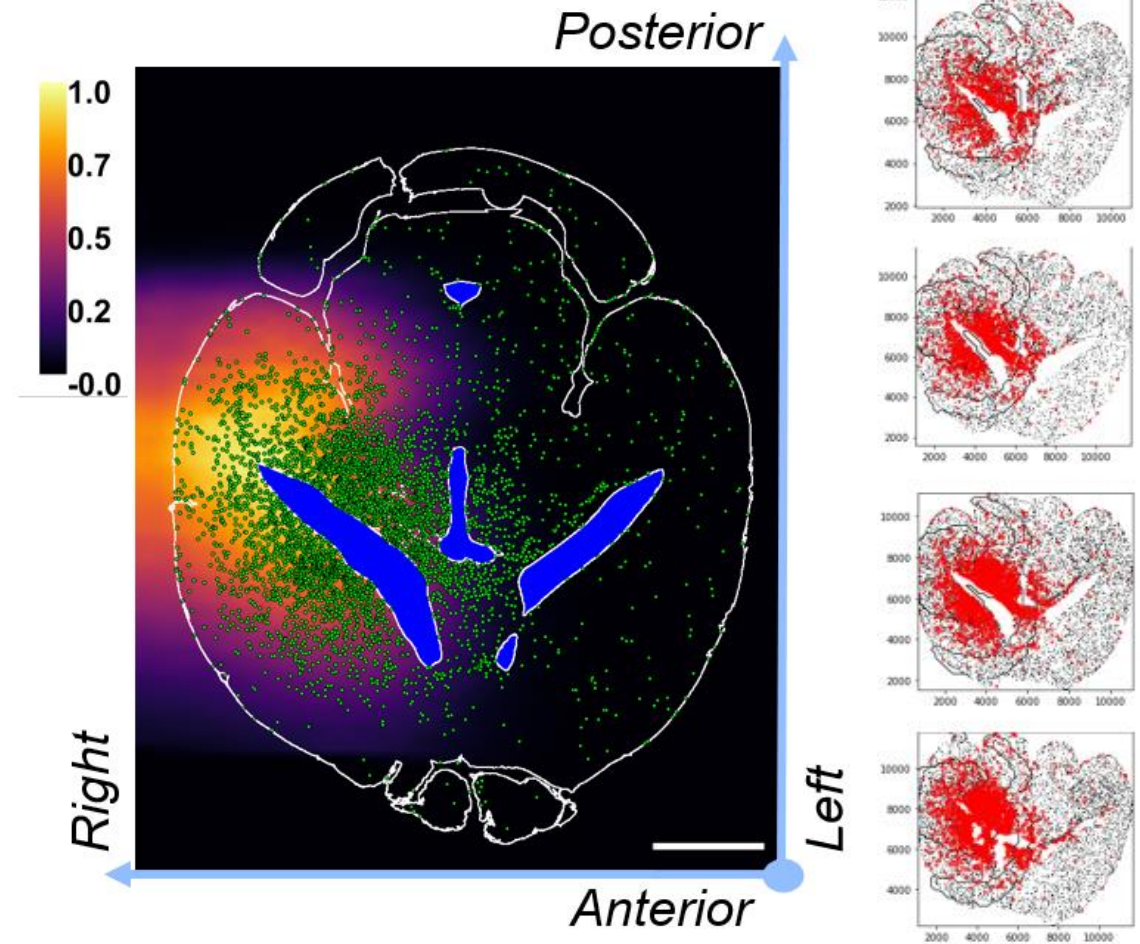
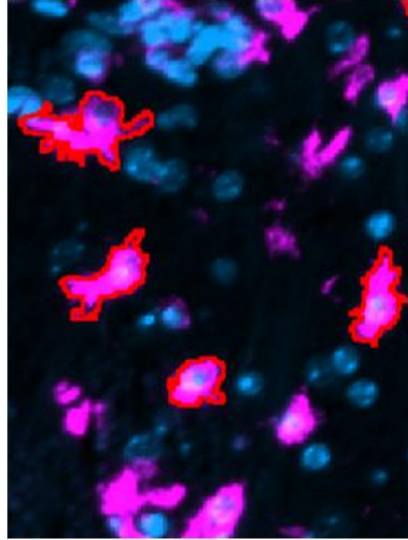
Non-activated



Activated



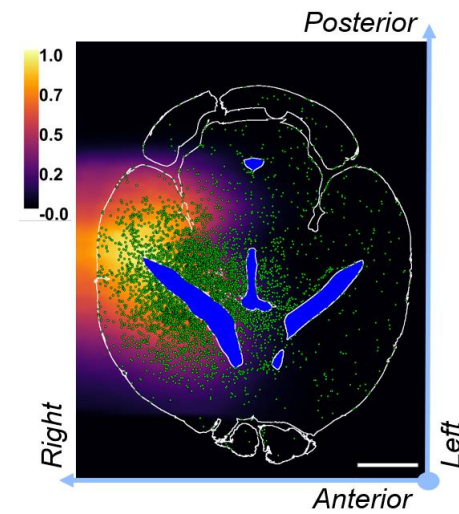
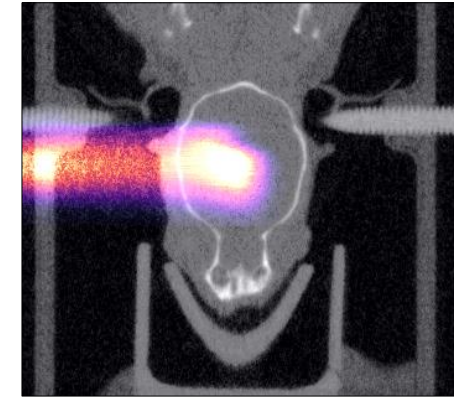
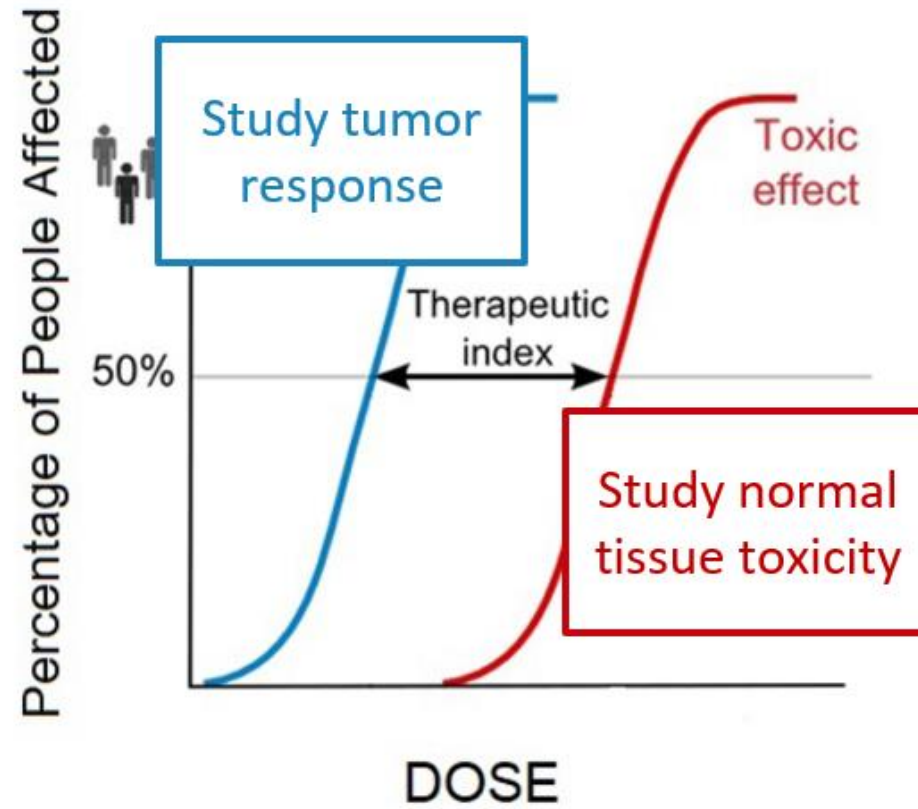
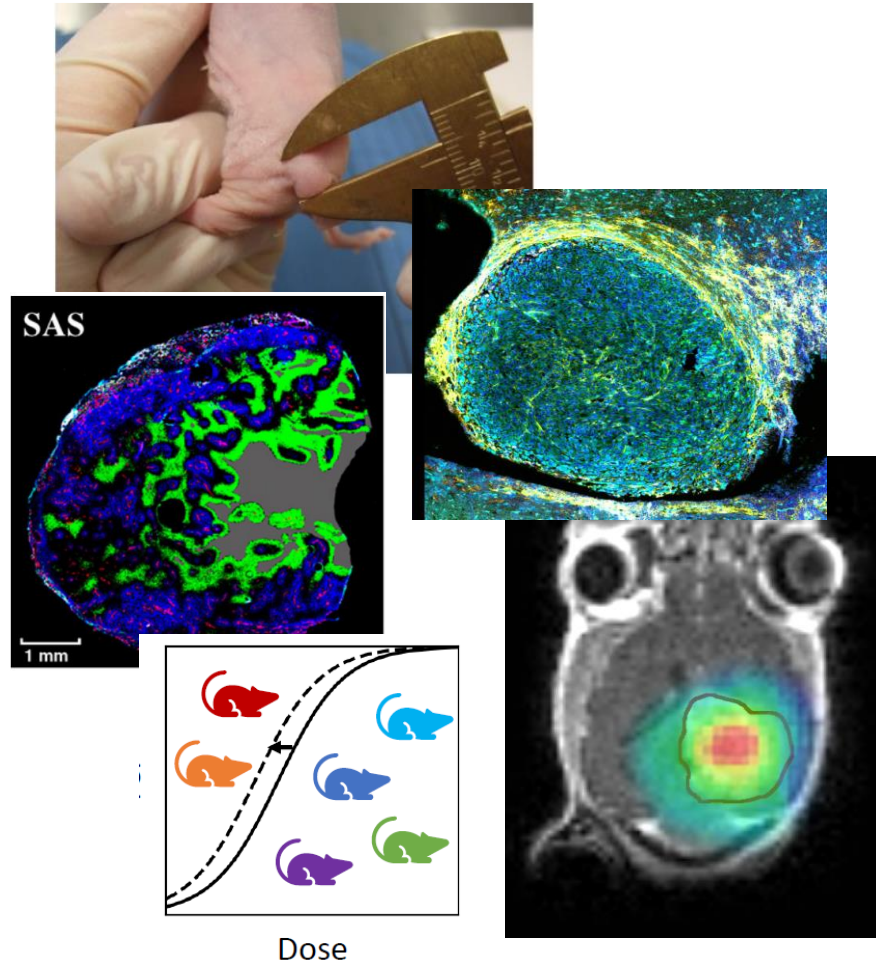
Highly activated



$C_i$  = circularity;  
 $A_i$  = Area;  $A_0$  = Area threshold

$$MScore = C_i \frac{(A_i - A_0)}{A_0}$$

# SUMMARY





**DKTK** German Cancer Consortium



Universitätsklinikum Carl Gustav Carus  
THE DRESDENERS.



**HZDR**

**HELMHOLTZ**  
ZENTRUM DRESDEN  
ROSSENDORF

**NCT**

Thank you!



**dkfz.**  
German Cancer Consortium  
Partner site Dresden