Preclinical Assessment of Efficacy of Radiation Dose Redistribution Based on Intratumoral FDG-PET Uptake

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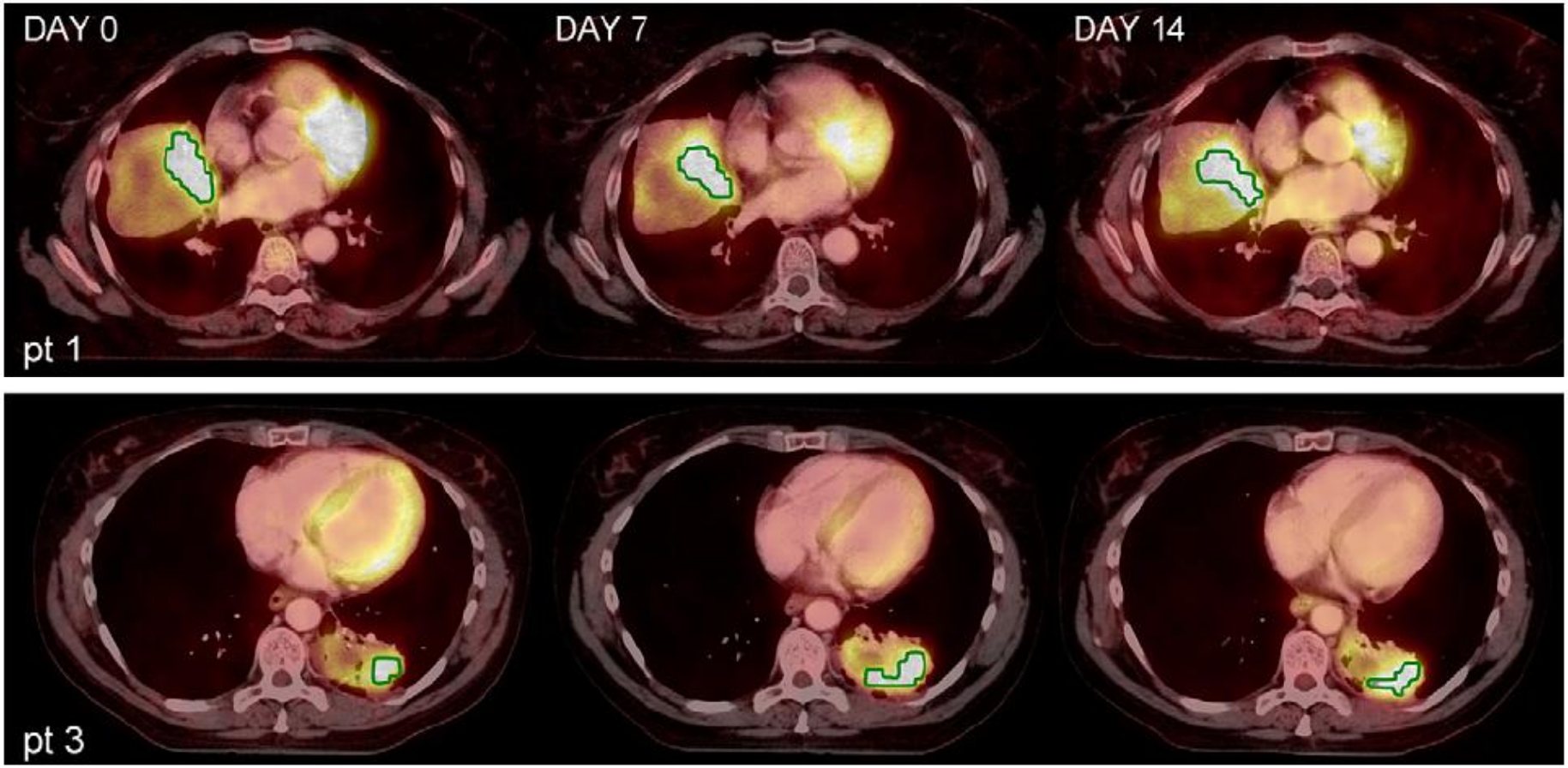
RT and intratumoral heterogeneity of FDG-PET uptake

- Standard of care in RT is *uniform irradiation*
- Biological heterogeneity can be imaged by PET
- Intratumoral heterogeneity responsible for treatment failure
  - High uptake areas remain stable during therapy
  - Location residual disease corresponds to high FDG uptake prior to treatment
  - High FDG uptake after therapy is prognostic for worse survival

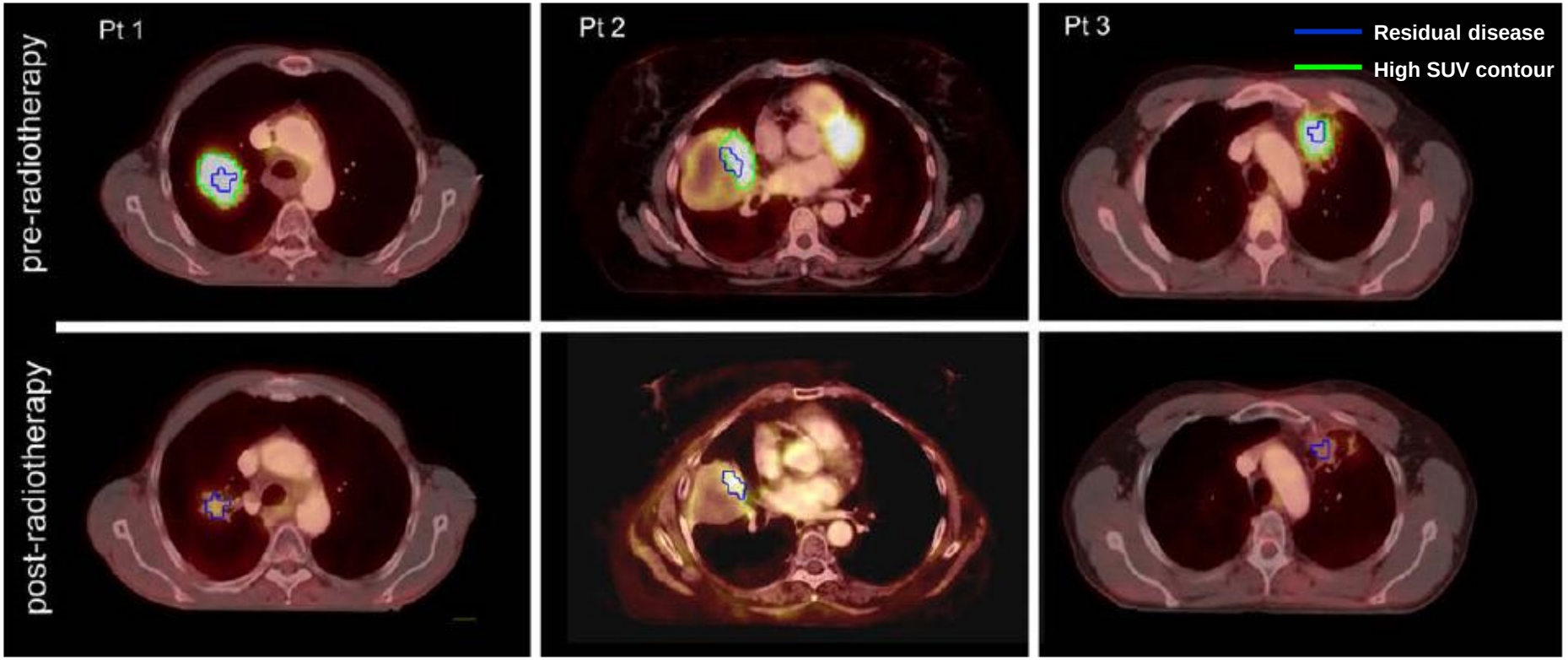
SUV uptake patterns during radiotherapy remain stable

Aerts et al, IJROBP 2008



Identification of “therapy-resistant” areas prior to treatment

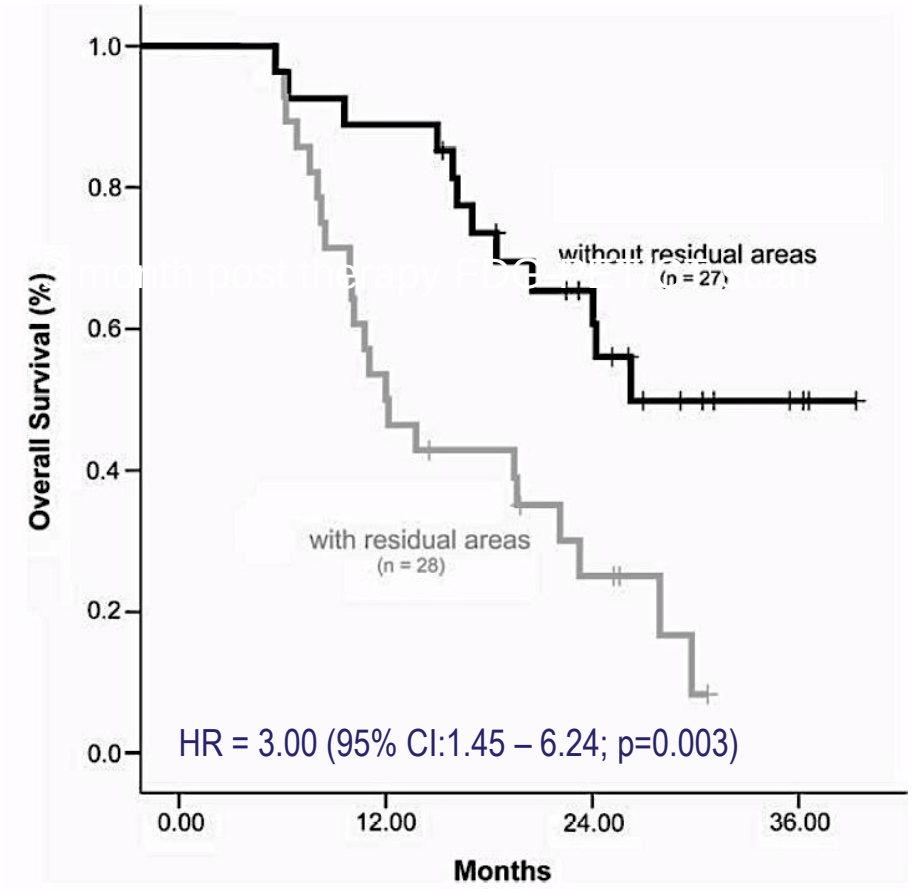
Aerts et al, Radiother Oncol 2009 and Lung Cancer 2011



- Residue largely corresponds with the 50% SUV high uptake area pre-RT (OF > 70%).
- Residual areas are almost completely located within the GTV (OF > 91%)
- Validated in external datasets of PHM (Toronto, Canada) and Nijmegen (the Netherlands)

Follow up analysis: Post radiotherapy PET/CT scan vs. survival

Aerts et al, Radiother Oncol 2009



Patients with residual disease (= high FDG uptake) already at 3 months after end of radiotherapy show a worse overall survival

Radiation boosting of potentially radioresistant subvolumes

- Higher dose to the most radioresistant regions

  => higher tumor control probability (TCP)

- How to increase dose: up to normal tissue constraints
  - Uniform boosting
    - escalate dose to entire tumor (van Baardwijk et al, JCO 2010)
  - Selective boosting
    - target dose to a specific feature (e.g.: high FDG-uptake)

How to improve patient outcome with all these results: Moving from imaging only to treatment decisions

Ongoing Clinical trial: Randomized phase 2 trial

PET boost trial in NSCLC (NKI / MAASTRO)

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PET in lung cancer RT

The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer

Wouter van Elmpt [a,*], Dirk De Ruysscher [a], Anke van der Salm [a], Annemarie Lakeman [b], Judith van der Stoep [a], Daisy Emans [a], Eugène Damen [b], Michel Öllers [a], Jan-Jakob Sonke [b], José Belderbos [b]

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Preclinical FDG-uptake based Dose Painting by Contours (DPC): Hypothesis and Objectives

Specific hypothesis :

Heterogeneous irradiation delivery based on ^{18}FDG-PET enhances tumor growth delay.

Objectives:

- To develop and validate the methodology for FDG-uptake based dose painting in a rat tumour model using clinical imaging and RT platforms

- To evaluate the efficacy of FDG- PET uptake based radiation dose painting

Preclinical FDG-uptake based DPC: Experimental Design

Tumor model: Rhabdomyosarcoma R1 tumour of the Wag/Rij rat (size = 5-8 cm^3 at RT)

To compare **growth delay** (**Time to reach 3 x V_{start}**) after:

1. Uniform irradiation;
2. "Hot Boost": 40% higher dose to the 30% of GTV with the highest FDG-PET uptake;
3. "Cold Boost": 40% higher dose to the 30% of GTV with the lowest FDG-PET uptake;
4. Sham Irradiated.

Mean Tumor Dose = 12 Gy

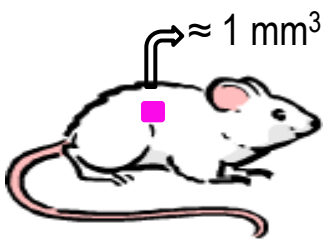
BTV Mean Dose = 15 Gy

$D_{gradient}$ = 0%,40%

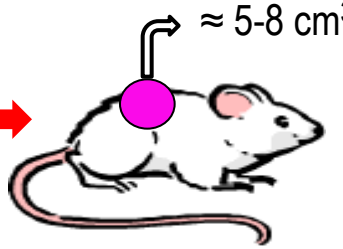
Preclinical FDG-uptake based DPC: Workflow

Tumor model: Syngeneic Rhabdomyosarcoma R1 of the Wag/Rij Rat

Tumour implantation

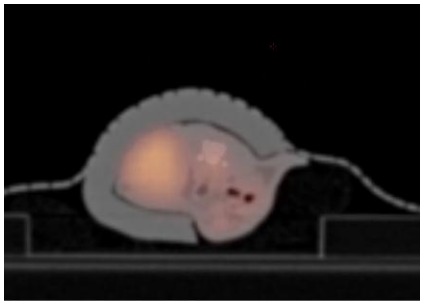


4-6 weeks

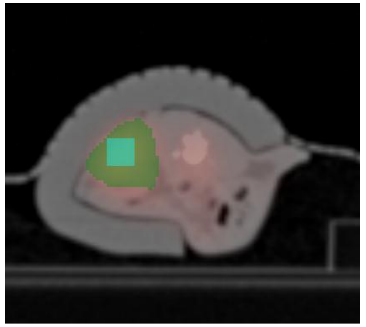


1-2 days

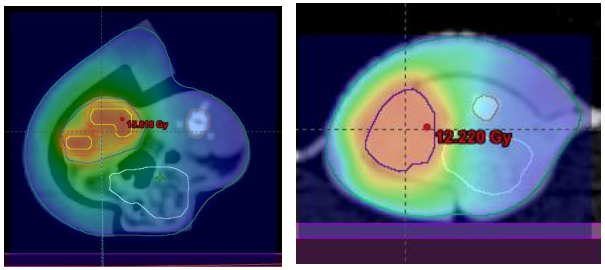
^{18}FDG PET-CT
(2 hrs post-injection)



PET-CT Contouring



Treatment Planning
(Homogeneous or FDG-high Boost)



Mean Tumour Dose → 12 Gy
For all RT groups

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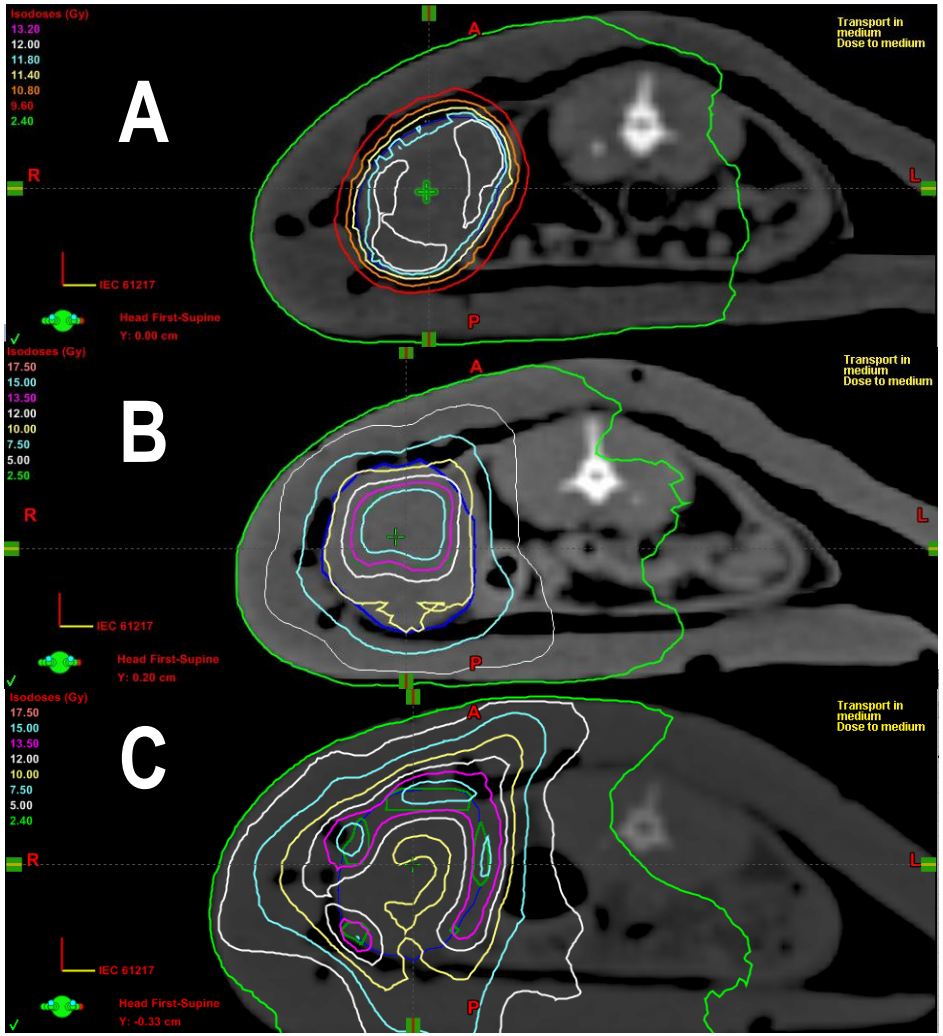
Example uniform dose distribution (A), hot boosting (B) & cold boosting (C)

Trani et al, in preparation

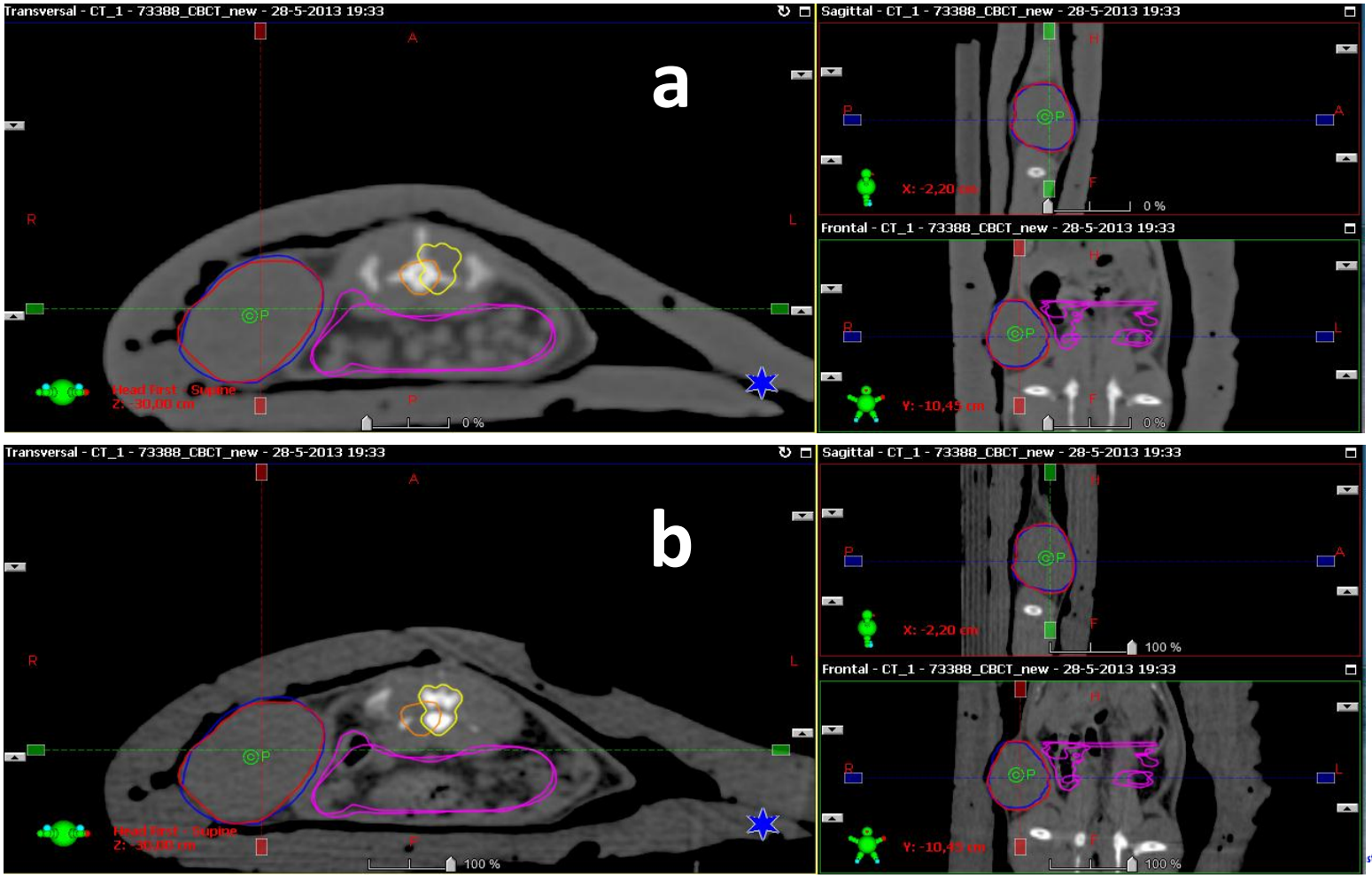


For "dose redistribution":

Mean tumor dose is forced to be the same between arm A, B and C!

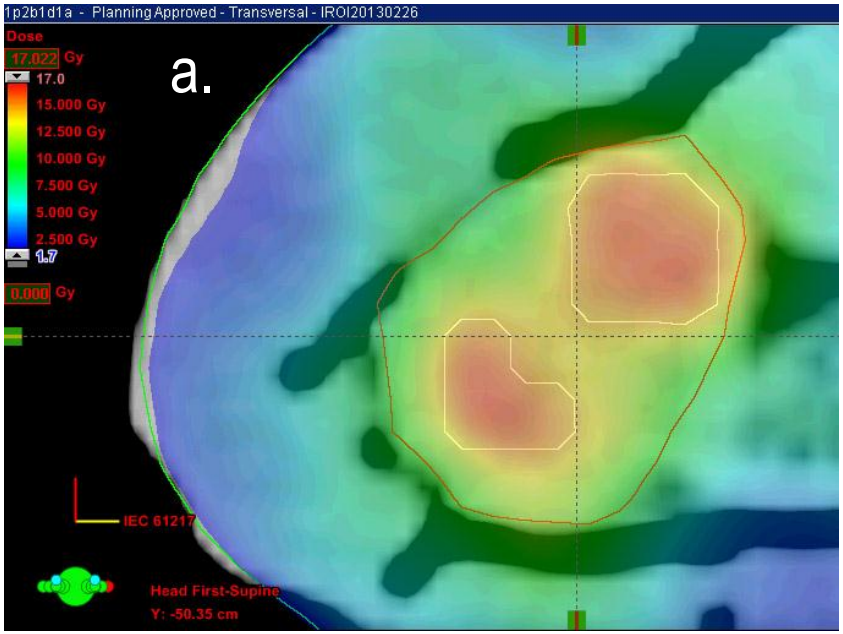
Planning CT vs. CBCT

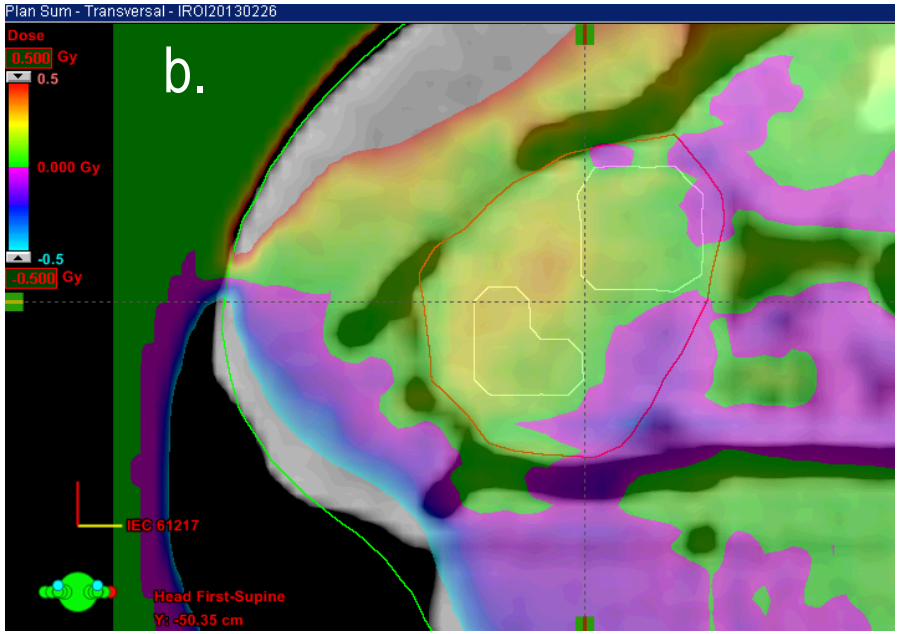
Trani et al, in preparation



Example of Planning CT vs. CBCT Dose Comparison

Trani et al, in preparation

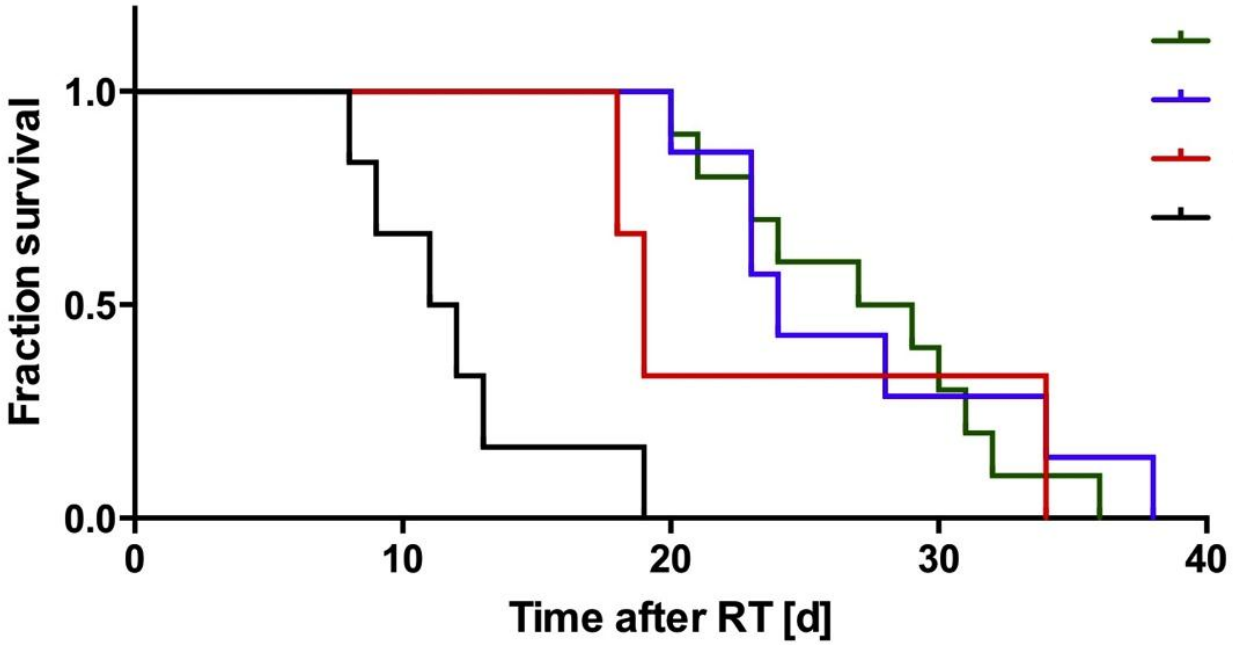


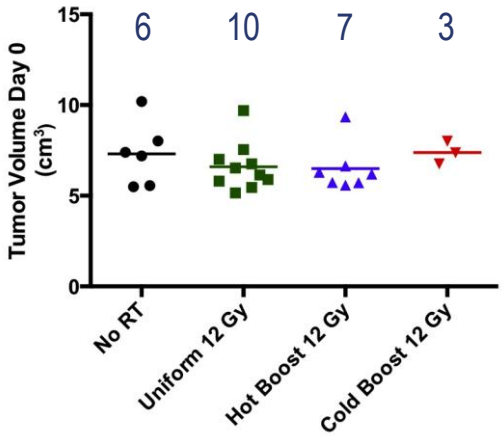


Mean Tumour Dose = 12 Gy; Mean BTV Dose = 15 Gy (**a**).

Maximum observed difference between CT and CBCT 3D-plan doses was below 3% of the maximum dose and ~4% of the prescribed mean tumour dose (-0.5 Gy < DD <0.5 Gy in panel **b**).

Preliminary results:
Tumour Growth Delay (Endpoint: Time to Reach 3xV_{start})





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Preliminary Conclusions

- **Technical feasibility of FDG-uptake based DPBC studies on clinical platforms**
  - Development of a robust positioning and matching methodology
  - High accuracy can be achieved in delivery of complex dose distributions to a rat tumor
- So far, **no significant difference was observed in tumor growth delay after uniform RT and FDG-uptake based dose painting by contours** (dose redistribution, 12 Gy mean tumor dose)
- No higher toxicity observed in boost groups vs. uniform RT

Is it clinically meaningful to do dose redistribution based on FDG-PET?→ Full characterization of the tumor required

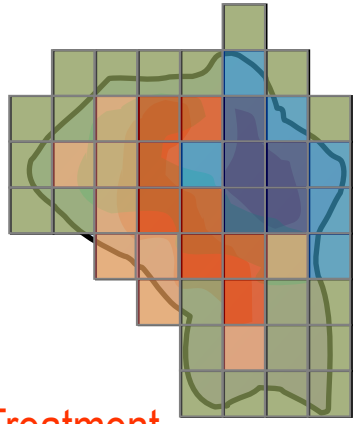
CT image
anatomic imaging

Hypoxia
'oxygen distribution'

Drug-uptake?

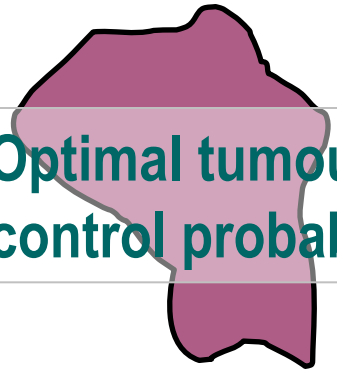
Imaging

Radiotherapy
dose re-distribution



Treatment

Optimal tumour control probability



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