Genetically-based analysis of dose surface maps for assessing toxicity post-RT

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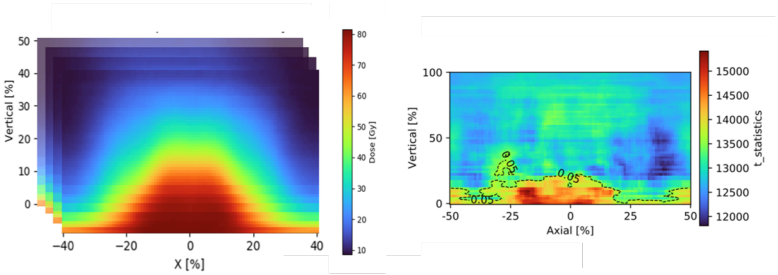
and the REQUITE/RADPRECISE consortium

Background

Single (whole) organ Physical Dose is not enough

Focus on INTRA-Patient heterogeneity

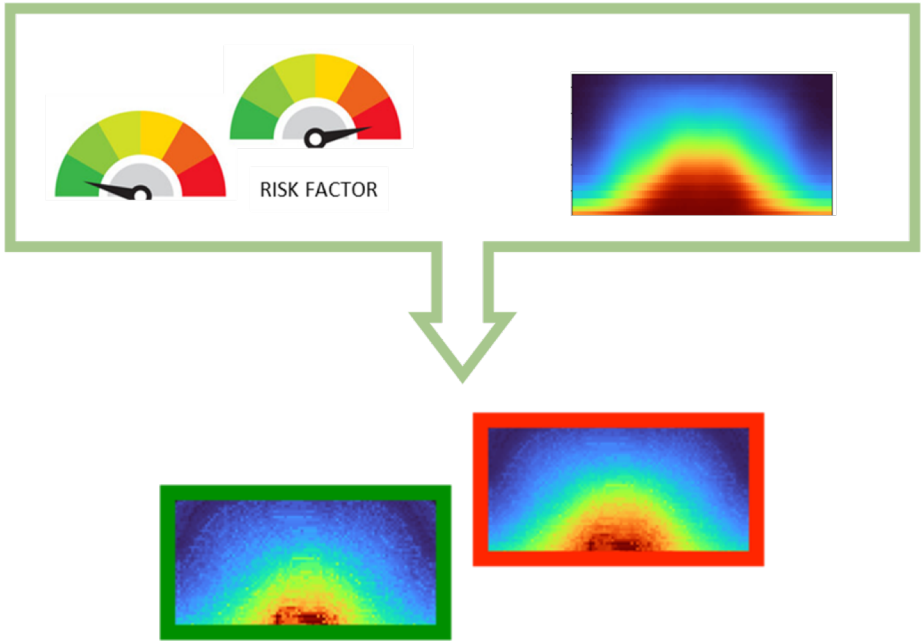


Voxel-based analysis offers biological intuitions on the possible functional sensitivity, (sub)organ cooperation and heterogeneity of the radiosensitivity across organs and tissues.

Focus on INTER-Patient heterogeneity

Patient-specific risk factors modulating the dose response relationships allow to consider hetherogeneity across patients.

AIM



New approach to include patient-specific factors in VBA, allowing Odds Ratios at a patient level.

As a first application, we analyse bladder and rectum dose-surface maps (DSMs) incorporating a polygenic risk score with interactions (PRSi)

Patient-specific risk factors modulate NTCP curves

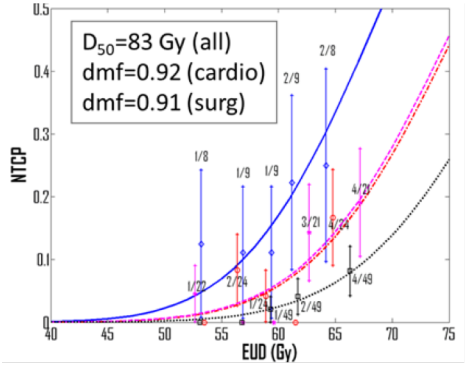
Radiosensitive patients exhibit side effects earlier, i.e. at lower doses

→ The same physical dose results in different effective doses due to different intrinsic radiosensitivity

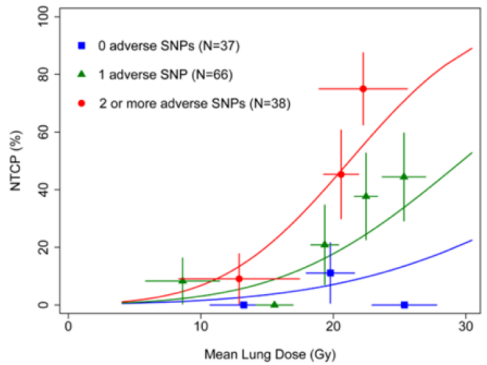
A possible alternative view

Presence of a risk feature ≈ a «pre-existing» dose

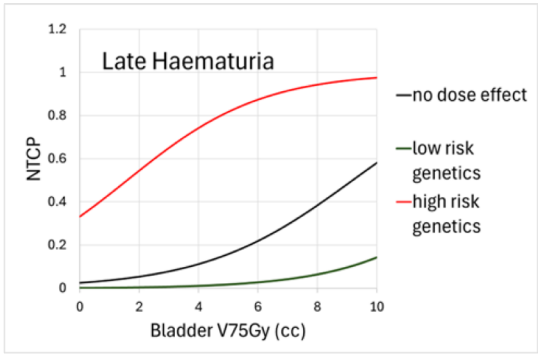
Cicchetti IJROBP 2018 – Jacovacci Phys Med 2023



Defraene IJROBP 2011



Tucker IJROBP 2013



De Langhe RO 2014

Population

- ~700 prostate cancer patients from REQUITE/RADprecise study
- Conventional (1.8-2Gy/fr) or hypofractionated (2.35-2.7Gy/fr) radical radiotherapy

Follow-up to 8 years (min 1 yr, median 2 yrs, 75th percentile 5 yrs)

TOXICITY ENDPOINTS:

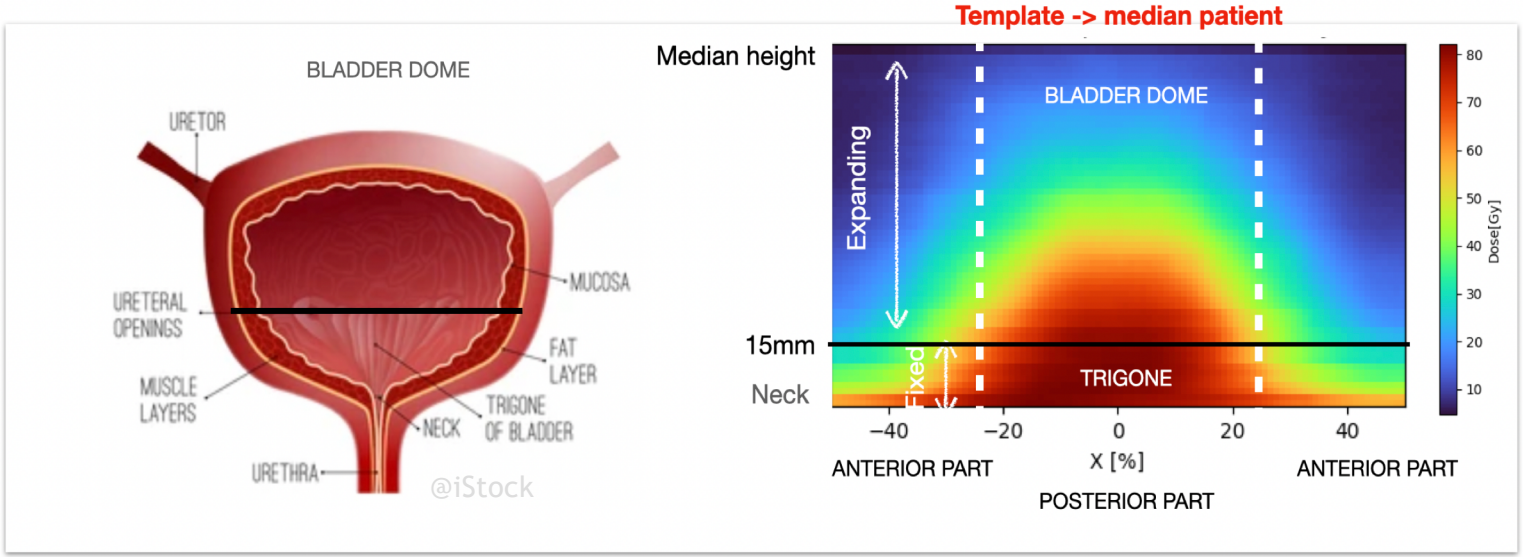
- Grade ≥ 2 late urinary frequency (G0/G1 at baseline) → 4.8%
- Grade ≥ 1 late haematuria (G0 at baseline)) → 7.5%
- Grade ≥ 2 late rectal bleeding (G0/G1 at baseline) → 6.9%

PRSi included 13 validated SNPs and incorporated SNP-SNP interactions

Massi Front Oncol 2020
Franco RO 2021

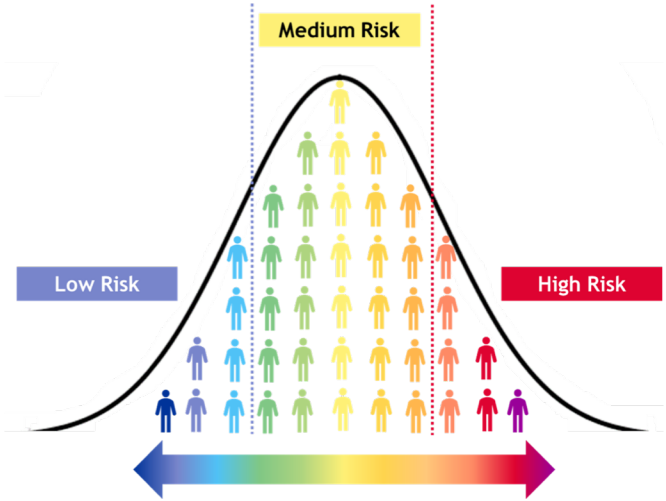
Dose-surface maps generation

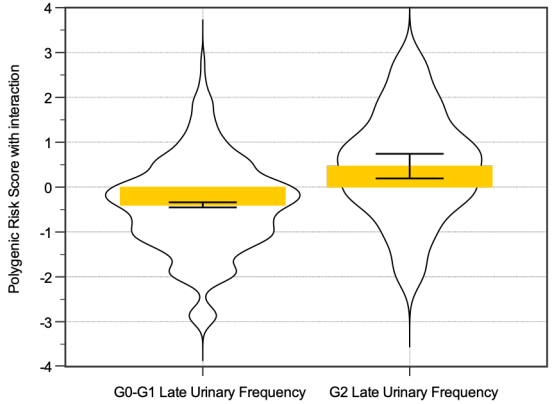
Maps were generated with an in-house software and corrected for fractionation.

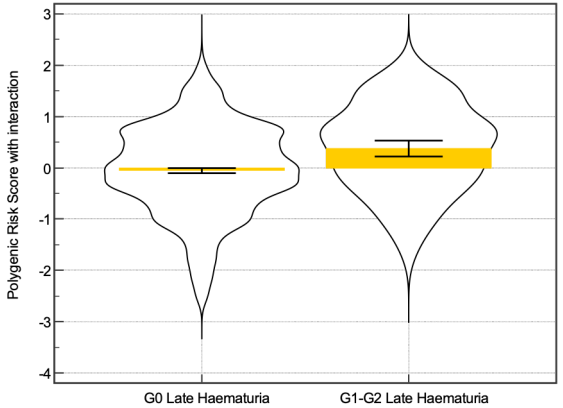


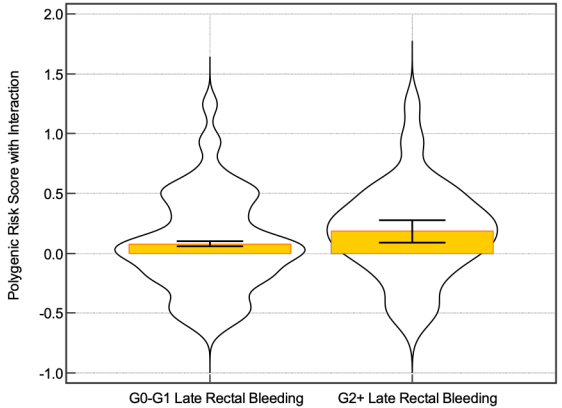
α/β=3Gy, γ=0.7Gy/day, fixed

Association between PRSi and side-effects



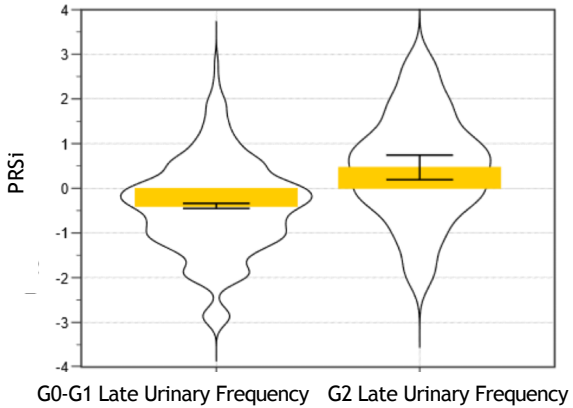


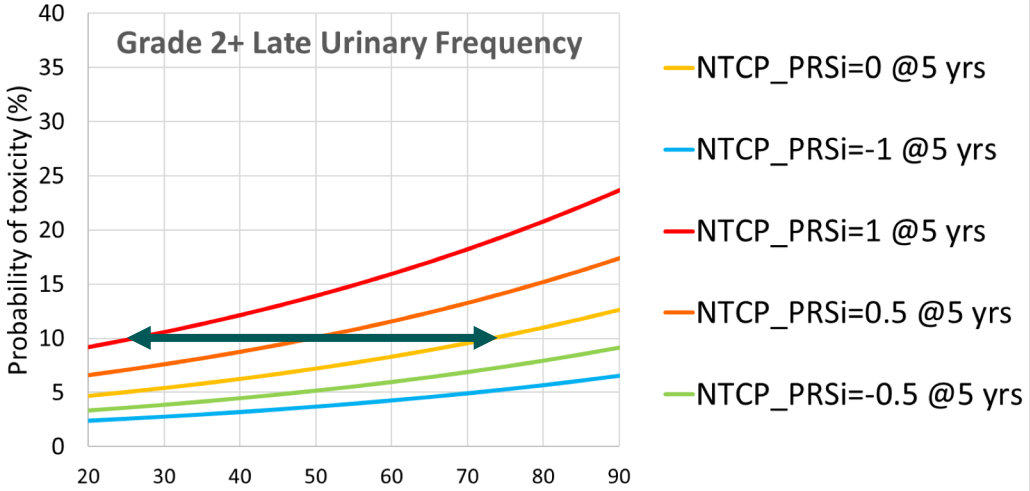




Contribution of the PRSi at the patient level

$$NTCP_j(EUD_j, PRSI_j, @T_{years}) = 1 - e^{-H_0(T_{years} * e^{\beta_{EUD} * EUD_j + \beta_{PRSi} * PRSi_j})}$$





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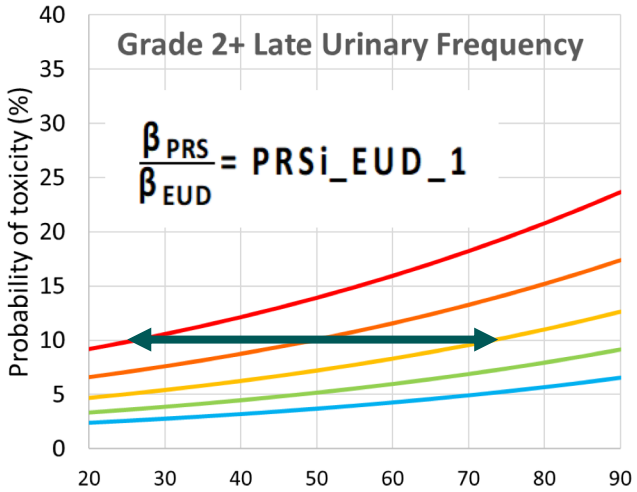
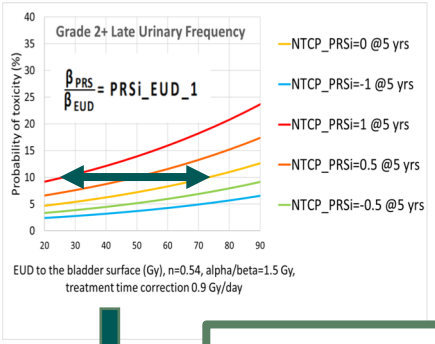


EUD to the bladder surface (Gy), n=0.54, alpha/beta=1.5 Gy, treatment time correction 0.9 Gy/day

$$PRSi\_EUD_j = \frac{\beta_{PRS}}{\beta_{EUD}} * PRSi_j$$

Additional "Effective-Genetics" Dose



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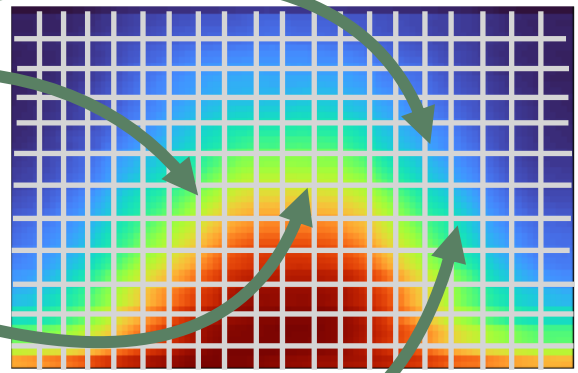


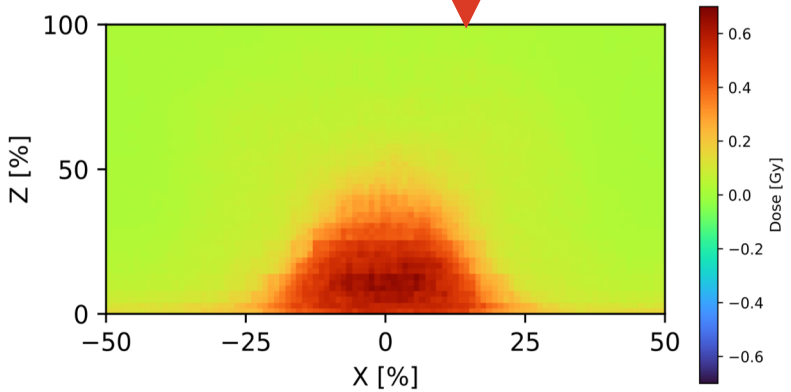
Modulation of Dose-Surface Maps

(algebraic) addition to each voxel of a dose proportionally to that voxel contribution to the total EUD

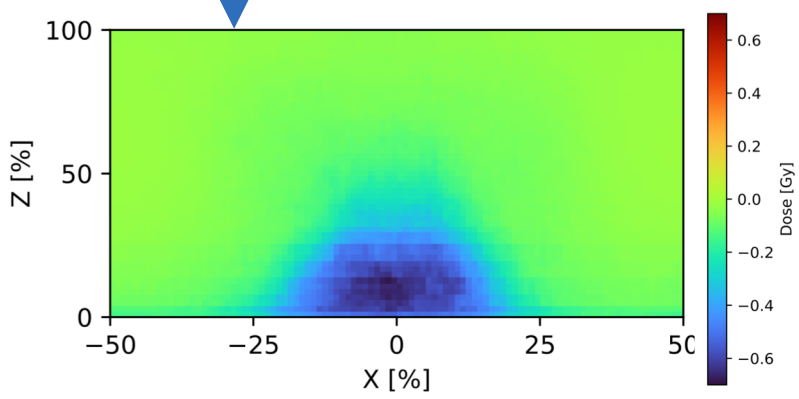
$$EUD = \left(\sum_{i=0}^{N} v_i \cdot D_i^n \right)^{1/n}$$

DSMs are (non-uniformly) shifted towards higher doses for PRSi>0, towards lower doses for PRSi<0 and not changed for PRSi=0

PRSi> 0



PRSi<0



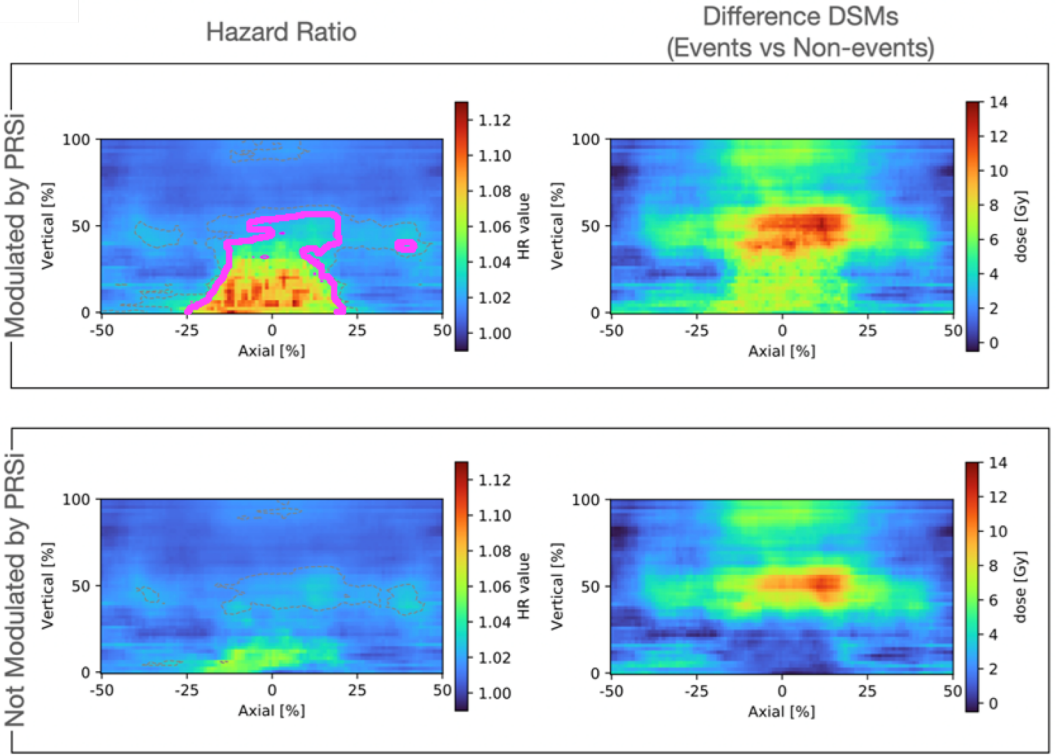
Results: Late Urinary Frequency

- Toxicity rate -> 4.8%;
- Mean PRSi -> 0.61/-0.40
  in patients with/without toxicity (p<0.0001)
- “Effective-Genetics” Dose = 47 Gy (n=0.54)

Cox: p-value < 0.05
FDR for cluster: p-adj < 0.05

HRs for the dose ~1.02-1.12 (every 1Gy)

HRs for the dose ~1.01-1.06 (every 1Gy)

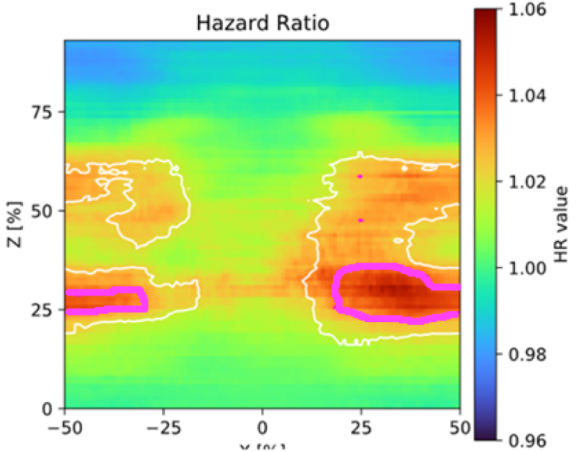


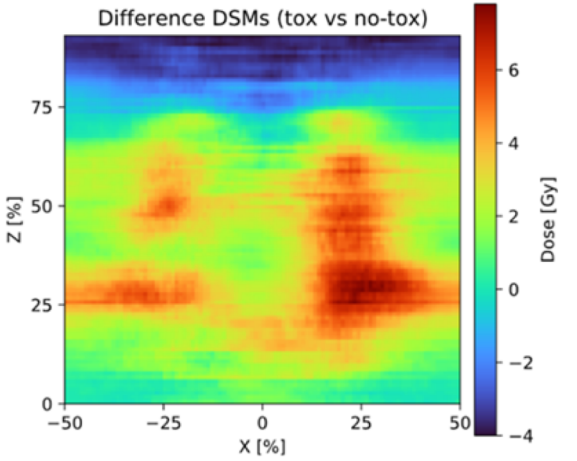
Results: Late Rectal Bleeding

- Toxicity rate -> 6.9 %;
- Mean PRSi -> 0.18/0.08
  in patients with/without toxicity (p=0.03)
- “Effective-Genetics” Dose = 69 Gy (n=0.1)

HRs for the dose ~1.02-1.06 (every 1Gy)

Cox: p-value < 0.05
FDR for cluster: p-adj < 0.05





Conclusion

- We can consider patient-specific risk factors as if they were effective doses.
- The modulation by the risk factors increases the heterogeneity of dose distributions in the patient population, escalating the doses for radiosensitive patients and de-escalating the doses for radioresistant patients.
- The enhanced heterogeneity increases the size of the areas classified as significantly different and re-gains steepness for the dose-response curve at a voxel level

These results suggest the value of clarifying patient-specific risk factors to synergistically clarify dose-response relationships

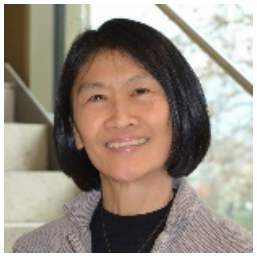
- The method creates risk-factor-modulated dose maps and can be naturally translated and extended into the inclusion of modulation from other patient-specific risk factors, even considering multiple features together.

To all patients participating in the REQUITE study

To all people involved in the REQUITE/RADprecise Consortium

To you all for your kind attention

Catharine West



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Petra Seibold

REQUITE
Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality-of-Life in Cancer Survivors

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RADprecise

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