Influence of inhomogeneous radiosensitivity distributions and intrafractional organ movement on the tumour control probability of focused IMRT in prostate cancer

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Purpose

To evaluate the influence of inhomogeneous radiosensitivity distributions and intrafractional organ movement on the tumour control probability (TCP) for prostate IMRT with simultaneous integrated boosts (SIBs) to PSMA-PET/CT-delineated target volumes and to assess the robustness of such treatment plans.

Materials and Methods

13 prostate cancer patients with PSMA PET/CT **and** prostatectomy

PSMA PET/CT	Prostatectomy
Automated segmentation based on SUV	Histopathology Cutting into 4mm slices
GTV-PET for treatment planning	GTV-histo for TCP calculation

Treatment planning + Export of structure and dose matrices

Randomly choose proportions of voxels within GTV-histo (1% - 50% in 1%-steps)

Adjust α and α/β of the chosen voxels to decrease radiosensitivity (by 1% - 30% in 1%-steps) regarding S_{2Gy}

Calculate TCP with and without intrafractional movement for all combinations of proportions and radiosensitivity levels (as the mean result of 10^5 iterations)

- **Case Description[1-4]**
  13 patients with PSMA PET/CT prior to prostatectomy.
- **Dosimetry Protocol (FLAME trial)[5]**
  77 Gy to the whole prostate, up to 95 Gy to PTV-PET in a SIB, 2.2 Gy per fraction, 35 fractions.
- **TCP Calculation[3]**
  Linear quadratic (LQ) model with Poisson distribution.
- **Radiosensitivity**
  Baseline level is defined in a calibration procedure for the LQ model parameters α and α/β, so that the mean TCP over all cases is 70% for a uniform dose of 77 Gy (α = 0.1335 Gy^{-1}, α/β = 1.93 Gy, $\rho = 2.8 \cdot 10^8$ cells/cm^3). Reductions of this radiosensitivity level are simulated by increasing the cell survival probability at a 2 Gy fraction (S_{2Gy}) by adjusting α and α/β for randomly chosen proportions of voxels within GTV-histo.
- **Intrafractional Movement**
  Implementation by asymmetrical 3D Gaussian Filtering of the dose matrix, simulating prostate movement up to 3 mm for the anterior-posterior and cranial-caudal directions and up to 1 mm for the left-right direction.

Fig. 1 Mean TCP results of all 13 cases with baseline radiosensitivity after individual normalization to 100% TCP (without movement).

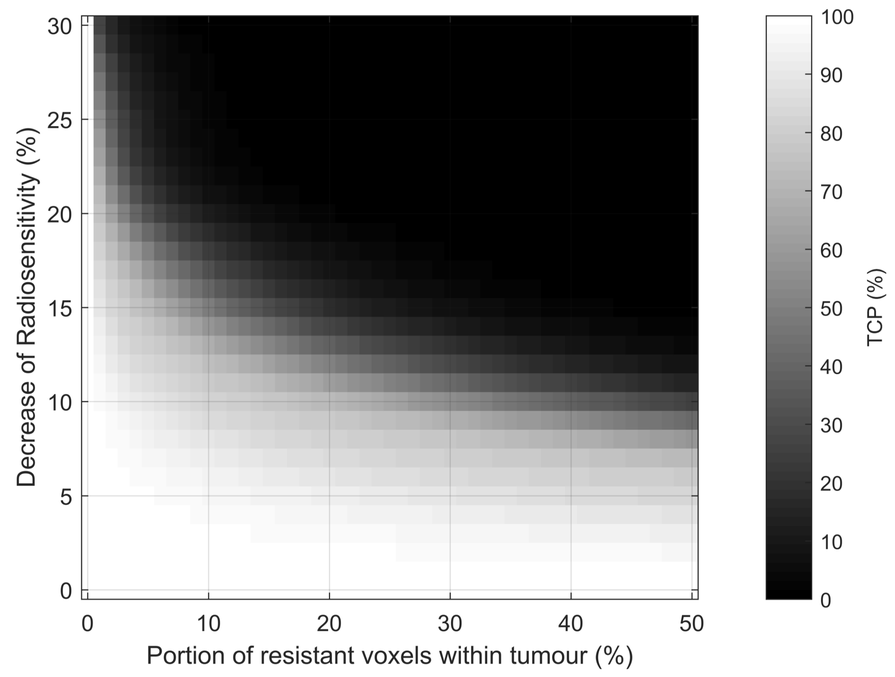
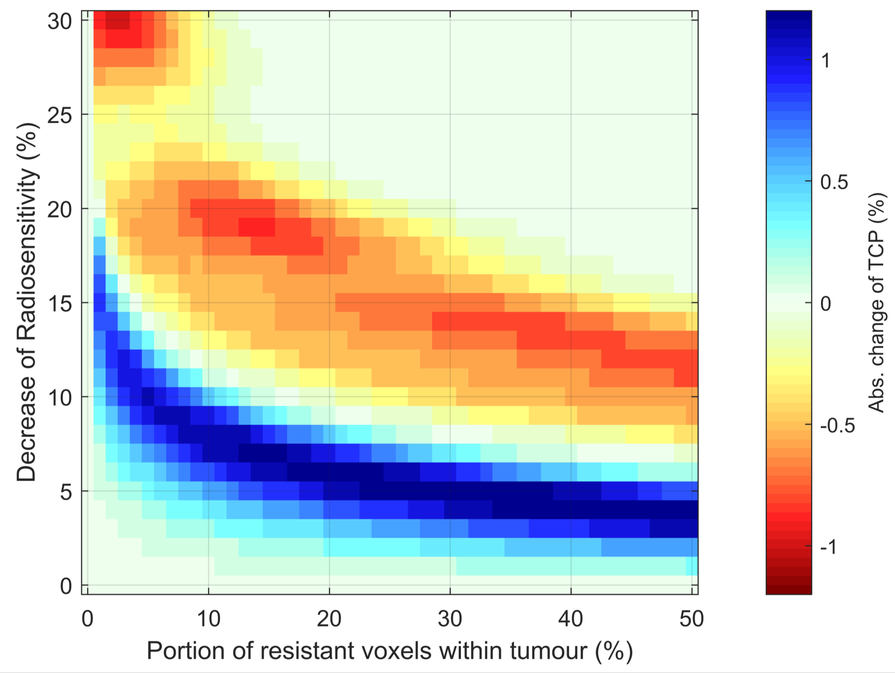


Fig. 2 Influence of intrafractional movement on the TCP (from Fig. 1).



Tab. 1 Representative parameters and results for the 13 cases.

Case	Volume GTV-histo (cm^3)	Volume PTV-SIB (cm^3)	Sensitivity of PET imaging	TCP Baseline	TCP abs. effect** of movement	TCP rel. effect** of radiosensitivity*
1	22.2	37.8	82%	70%	+7%	-100%
2	17.5	43.1	94%	100%	-	-86%
3	13.7	15.7	69%	79%	+8%	-100%
4	5.8	30.6	91%	100%	-	-81%
5	5.5	26.0	100%	100%	-	-59%
6	4.5	19.6	83%	100%	-	-55%
7	2.2	24.9	84%	100%	-	-21%
8	1.8	8.5	73%	98%	-	-83%
9	1.6	8.6	100%	100%	-	-23%
10	1.5	16.8	94%	100%	-	-20%
11	1.1	13.6	90%	100%	-	-29%
12	0.4	21.9	100%	100%	-	-5%
13	0.3	20.5	100%	100%	-	-5%
Mean	6.0	22.1	89%	96%	+1.2%	-51%

* radiosensitivity exemplarily chosen: 15% decrease for 10% voxels.
** effects given with regard to the baseline TCP.

Results

- There is a sudden breakdown of TCP values within a small range of radiosensitivity reduction levels (Fig. 1).
- Even low decreases (15%) of the radiosensitivity for few tumour voxels (10%) may result in a significant TCP reduction (Tab. 1).
- Intrafractional movement in average only has a minor effect on the TCP and can even increase the TCP for medium radiosensitivity levels if the tumour volume is not entirely covered by the PET-delineated SIB volume (Fig. 2, Tab. 1). In these cases, the tumour voxels receiving D_{min} outside of the SIB do not really suffer regarding TCP when moving even further away, due to the dose plateau surrounding the SIB. Moving towards or even into the SIB, however, results in a significant dose increase, increasing also the TCP.
- Mismatches between tumour and SIB volume significantly decrease the TCP (Tab. 1), especially in tumours with low radiosensitivities. When boosting imaging-defined subvolumes, maximizing the imaging sensitivity (tumour coverage by SIB volume) is essential for a robust treatment. This could be achieved by a combined use of PET and multiparametric MRI to identify the tumour volume.

1. Thomann, B., et al., *Influence of inhomogenous radiosensitivity distributions and intrafractional organ movement on the tumour control probability of focused IMRT in prostate cancer.* Radiotherapy and Oncology, 2018, *in press:* doi.org/10.1016/j.radonc.2018.02.006
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3. Zamboglou, C., et al., *Evaluation of intensity modulated radiation therapy dose painting for localized prostate cancer using (68)Ga-HBED-CC PSMA-PET/CT: A planning study based on histopathology reference.* Radiotherapy and Oncology, 2017. **123**(3): p. 472-477.
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5. Lips, I.M., et al., *Single blind randomized Phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial.* Trials, 2011. **12**: p. 255-255.