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Original article

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

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ABSTRACT

Purpose: To evaluate the influence of radioresistance and intrafractional movement on the tumour control probability (TCP) in IMRT prostate treatments using simultaneous integrated boosts to PSMA-PET/CT-delineated GTVs.

Materials and methods: 13 patients had PSMA-PET/CT prior to prostatectomy and histopathological examination. Two GTVs were available: GTV-PET and GTV-histo, which is the true cancer volume. Focused IMRT plans delivering 77 Gy in 35 fractions to the prostate and 95 Gy to PTV-PET were produced. For random portions of the true cancer volume, α and α/β were uniformly changed to represent different radiosensitivity reductions. TCP was calculated (linear quadratic model) for the true cancer volume with and without simulated intrafractional movement.

Results: Intrafractional movement increased the TCP by up to 10.2% in individual cases and 1.2% averaged over all cases for medium radiosensitivity levels. At lower levels of radiosensitivity, movement decreased the TCP. Radiosensitivity reductions of 10–20% led to TCP reductions of 1–24% and 10–68% for 1% and 5% affected cancer volume, respectively. There is no linear correlation but a sudden breakdown of TCPs within a small range of radiosensitivity levels.

Conclusion: TCP drops significantly within a narrow range of radiosensitivity levels. Intrafractional movement can increase TCP when the boost volume is surrounded by a sufficiently high dose plateau.

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Modern intensity modulated radiotherapy (IMRT) treatment of prostate cancer (PCa) is often characterised by a homogeneous dose distribution within the prostate. Additionally, a simultaneous integrated boost (SIB) can provide a homogeneous dose escalation within a tumour boost volume (focused IMRT). However, the radiosensitivity of cancer cells can vary on an intercellular and intertumoural level and the maximum dose, which can be prescribed uniformly to the entire prostate or tumour volume, might not be sufficient to eradicate tumour cells with decreased radiosensitivity.

The number of radioresistant cells (RCs) as well as their specific levels of radiosensitivity correlate inversely with the tumour control probability (TCP). Studies have shown both intertumoural [1] and intratumoural [2–5] variations in density and radiosensitivity distributions of RCs within prostate tumours. There is growing evidence for an increased radioresistance of cancer stem cells (CSCs) compared to the mass of non-CSCs within the tumour [5]. Due to the possibility of repopulating the whole tumour, CSCs could play a crucial role in PCa recurrence after radiotherapy.

RCs can be identified using specific markers such as hypoxia [6], the related factor HIF1α [7,8] and aldehyde dehydrogenase (ALDH) [9]. A study by Li et al. showed that 20% of the patients had an increased ALDH1A1 expression in more than 10% of PCa cells [3]. Carnell et al. reported hypoxic subvolumes above 20% of the tumour volume in 36% of the patients [4]. Rao et al. defined 2–25% of the tumour cells in 3D cell cultures as CSCs [10]. Investigating the degree of radioresistance, studies found a 2.5-fold higher surviving fraction at 2 Gy for RCs compared to regular tumour cells [9,11]. Oike et al. [12] reported surviving fractions of cancer cells after radiation with 2 Gy of 0.55 ± 0.14 for normoxic conditions and 0.79 ± 0.20 for hypoxic conditions. All available data indicate that various portions of prostate tumour cells may have radiosensitivity levels significantly below the average.

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Imaging based tumour localisation techniques, e.g. PSMA-PET or multiparametric MRI, have shown limitations in their sensitivity [13,14], potentially leaving parts of the tumour uncovered by the imaging defined boost volume, despite internal margins for its delineation. Especially in cases with a mismatch between planning boost volume and actual tumour volume, intrafractional movement of the prostate could change the TCP. The extent of intrafractional movement differs for the three anatomical dimensions left–right (LR), anterior-posterior (AP) and cranial-caudal (CC) [15–17]. Langen et al. reported average prostate displacements above 3 mm for 0.1% (LR), 5.9% (AP) and 5.1% (CC) of the treatment time and above 5 mm for 0.0% (LR), 1.1% (AP) and 1.0% (CC) of the treatment time [15]. Overall, motions above 3 mm were reported for 47% of all treatment sessions.

Based on our previously published material [13,14,18,19], the true tumour locations are known due to histopathological specimens. In this study, we followed the introduced methodology [14], where focused IMRT treatment plans were optimised for PET-delineated boost volumes and the TCP was calculated for the histologically proven, true tumour volume. We investigate the influence of simulated intratumoural radiosensitivity variations and intrafractional prostate movement on the TCP and hereby estimate the robustness of imaging-based focused IMRT for prostate cancer.

Materials and methods

The utilised data are part of a larger retrospective study on PCa patients. Detailed descriptions of the imaging, registration and contouring protocols were previously published [13,14,18,19] and only basic information on these protocols is given in this section. Please see these references for further details.

Case description

The previously published planning study cohort [14] of 10 patients with intermediate to high risk PCa [20,21] has been increased to 13 cases in this study. All patients had ^{68}Ga-HBED-CC-PSMA-PET/CT imaging followed by a radical prostatectomy.

Target volume definition

For the focused IMRT technique, GTV-PET was identified by PSMA-PET using a threshold value of 30% of SUVmax within the prostate [19]. The true tumour volume GTV-histo, considered for the TCP calculations, was defined by a histopathological analysis introduced by Zamboglou et al. [19]. GTV-histo included all histologically visible cancer foci and is not necessarily one single, connected volume. Clinical target volume 1 (CTV-1) included the prostate and the seminal vesicles. CTV-2 included the prostate and half of the seminal vesicles for high risk patients or the prostate and the basis of the vesicles for intermediate risk patients. CTV-1, CTV-2 and GTV-PET were enlarged by an isotropic margin of 4 mm to generate the respective planning target volumes: PTV-1, PTV-2 and PTV-SIB.

IMRT planning

IMRT treatment plans were created in Eclipse v13.5 (Varian, USA) with a calculation grid size of 1 mm. Pursuant to the FLAME trial protocol [22], dose prescriptions were 52.8 Gy in 24 fractions for PTV-1 and 24.2 Gy in 11 fractions for PTV-2, resulting in 77 Gy for PTV-2, with a SIB up to 95 Gy for PTV-SIB over all 35 fractions. Minimum dose objective for PTV-2 was 70 Gy and $D_{2\%}$ constraint for PTV-SIB was 99.75 Gy (105% of prescription dose). Organ at risk (OAR) constraints were taken from the FLAME protocol [22] or from the QUANTEC review [23–25] and adapted to the FLAME protocol. Compliance with the OAR constraints had the highest priority. The attained dose parameters of the treatment plans are illustrated in Supplementary Material A.

Plan evaluation and TCP calculation

Structure sets and calculated dose matrices of the IMRT plans were transferred to MATLAB R2017a (The MathWorks, USA) and the research version of BIOTOP/BIOSPOT (Pi-medical, Greece). The 3D structure and dose matrices were given in voxels of 1 mm^3, defined by the highest possible resolution of the calculation grid in Eclipse. Using the linear quadratic (LQ) Poisson model [26–33], TCP was calculated at voxel level for the true tumour volume [14]. The biologically equieffective dose EQD0 [34], calculated individually for each voxel within the tumour, was used for the TCP calculation at voxel level. As previously deducted and published [14], the LQ model parameters were $\alpha = 0.1335\ \mathrm{Gy}^{-1}$, $\alpha/\beta = 1.93$ Gy [35] and $\rho = 2.8 \cdot 10^8\ \mathrm{cells/cm}^3$ for the tumour cell density [36–38]. The parameter α was chosen to lead to an average TCP of 70% across all cases for a fractionation scheme of 77 Gy over 35 fractions, which is consistent with clinical observations [39,40].

Radiosensitivity distribution

The level of radiosensitivity R can be defined as the ratio of the surviving fraction S_R of cells with decreased radiosensitivity and the fraction of surviving cells S with initial radiosensitivity after receiving a dose of 2 Gy, respectively.

$$R = \frac{S_R(2\ \mathrm{Gy})}{S(2\ \mathrm{Gy})}$$

In the following, we always refer to R as the expression of radiosensitivity of a voxel or a group of voxels. For example, a decrease in radiosensitivity of 15% compared to baseline is equivalent to $R = 1.15$. To apply any particular radiosensitivity level R to a voxel, further calculations are necessary. According to the LQ model, the surviving fraction $S(D)$ in a cell population after receiving a dose D is:

$$S(D) = \exp[-\alpha D + \beta D^2]$$

with radiosensitivity parameters α and β. Changes in radiosensitivity can be implemented by modifying α and β with a factor f_R [41,42].

$$\alpha_R = \frac{\alpha}{f_R}, \beta_R = \frac{\beta}{f_R^2} \text{ and thus } \left(\frac{\alpha}{\beta}\right)_R = \left(\frac{\alpha}{\beta}\right) \cdot f_R$$

Using these equations, f_R is given by the following expression and can be used to apply any level of radiosensitivity R [41,42], relative to a baseline scenario with known values for α and β.

$$f_R = -\frac{\alpha}{\ln(R \cdot S(2\ \mathrm{Gy}))} + \sqrt{\left(\frac{\alpha}{\ln(R \cdot S(2\ \mathrm{Gy}))}\right)^2 - \frac{4\alpha}{(\alpha/\beta)\ln(R \cdot S(2\ \mathrm{Gy}))}}$$

In this study, we used rather moderate R values [9,11,12] ranging from 1.01 to 1.30 (1% and 30% decrease of radiosensitivity, respectively) in steps of 0.01. The number of resistant voxels ranged from 1% to 50% (in 1%-steps) of all voxels within the true tumour volume. Affected voxels were determined randomly, an assumption supported by a publication by De-Colle et al., indicating a homogeneous, hence random distribution of γH2AX foci [43]. In total, this led to 1500 possible combinations of resistant voxels and levels of radiosensitivity, each with a corresponding TCP. During any calculation, there were always two different levels of radiosensitivity: the one given by the baseline α and β and the

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