Fitting a tumour control probability model to recurrence data based on MRI-delineated GTVs of radiotherapy of prostate cancer patients

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Purpose

Aim of this study was to fit a tumour control probability (TCP) model to clinical data in terms of PSA relapse after primary radiation therapy for prostate cancer.

Methods and Material

We included 129 intermediate and high-risk prostate cancer patients with primary radiation therapy (21 relapsed, 108 non-relapsed). A GTV was delineated retrospectively based on a pre-treatment multi-parametric MRI imaging (mpMRI), co-registered to the planning CT. The mpMRI-based GTV was considered as the dominant lesion (DIL) defining the response to treatment [1]. The median clinical follow-up was 4 years and the Phoenix definition for PSA relapse has been used. The differential DVHs for the mpMRI-GTV have been used for TCP calculations with the mechanistic Poisson model [2]:

$$TCP(\{D\},V) = \prod_{i=1}^{M}\left[\exp\left(-e^{e\,\gamma-\left(\frac{EQD2_i}{D_{50}}\right)*(e\,\gamma-\ln\ln 2)}\right)\right]^{\Delta v_i} \quad \text{with} \quad EQD2_i = \frac{D_i\left(1+\frac{d_i}{\alpha/\beta}\right)}{1+\frac{2\,Gy}{\alpha/\beta}}$$

D_{50} is the EQD2 resulting to 50% response, and γ is the maximum value of the normalized dose-response gradient. M is the total number of DVH-bins, D_i and d_i are total dose and dose per fraction for the i-th bin. Δv_i is the volume for the i-th dose bin and V the volume of GTV. α/β was 1.93 Gy [3].

The TCP model was fitted using the maximum likelihood estimation technique. The likelihood function L for the binomial model with response r = 1 for relapse-free and 0 for relapse, is:

$$L(P) = L\left(\left(D_{50},\gamma,\frac{\alpha}{\beta}\right),(\{D\},V)\right) = \prod_{j=1}^{N} P_j^{\,r_j}.(1-P_j)^{(1-r_j)}$$

with P_j the TCP prediction, r_j the clinical response for the j-th patient and N the total number of patients in the study.

The best parameter estimation for D_{50} and γ are those maximizing the L(P) estimator or equivalently minimizing the –ln(L(P)):

$$minimize - \ln(L(P)) = minimize \sum_{j=1}^{M}\{r_j \ln(P_j) + (1-r_j)\ln(1-P_j)\}$$

For the minimization we used simulated annealing (SA), a stochastic solver.

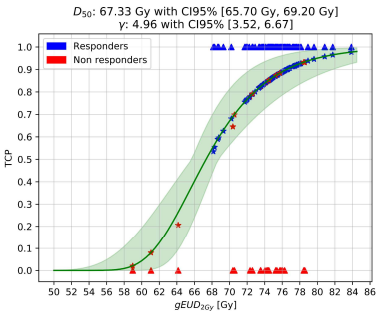

Fig. 1: TCP response curve with 95% confidence interval (CI) (green shadow area). Blue points refer to treatment responder patients and red points refer to non-responder patients. Asterisks denote the calculated TCP according to the mechanistic model.

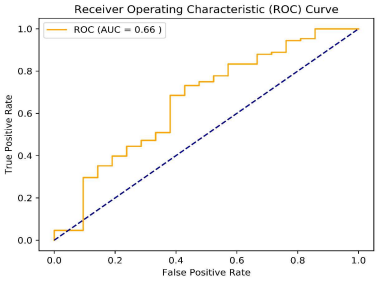

Fig. 2: The ROC curve plots the False Positive Rate (FPR) on the X-axis and the True Positive Rate (TPR) on the Y-axis for all possible thresholds.

Results

The best estimated solution was D_{50} = 67.33 Gy with 95% CI [65.70 Gy, 69.20 Gy] and γ = 4.96 with 95%CI [3.52, 6.67]. α/β was fixed to 1.93 Gy. Parameter ranges for a 68% CI were for D_{50} [66.40 Gy, 67.80 Gy] and γ [4.24, 5.77].

Our estimated D_{50} and γ are in line with previously reported values for similar stages of the prostate carcinoma [4].

The calculated area under curve (AUC) was found to be 0.66. This area represents the ability of the mechanistic model to classify relapsed and relapsed-free patients, which is better than 0.5 (random selection). Some possible explanations for the relative low AUC value are: (i) the known significant underestimation (factor 2) of true GTV by mpMRI [5], (ii) the low number of relapse cases and (iii) the inhomogeneous patients characteristics and of their follow-up period.

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