University of Strathclyde Glasgow

The validation of a tumour control probability (TCP) model for supporting radiotherapy treatment planning.

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Outline

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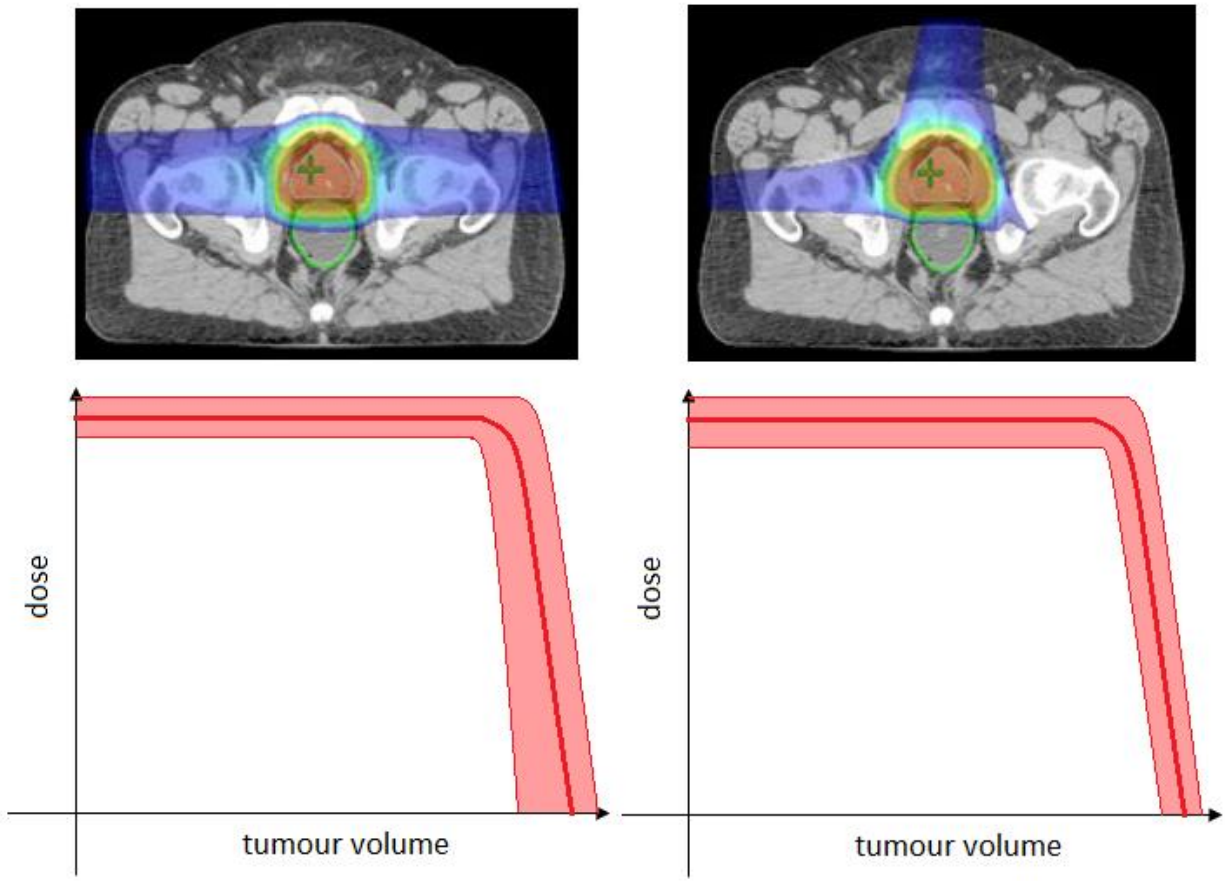
Project aims

The project is focused on the validation of the radiobiological model for radiotherapy outcome through an identification of the impact of changes (uncertainties) in various model components on model outcome. This aims at:

- estimating the accuracy of radiobiological parameters and the robustness of the model
- adopting the biologically optimized plans in radiotherapy treatment planning
- moving towards personalised treatment planning

Robustness analysis in radiotherapy



In radiotherapy the treatment plan robustness is tested through geometric verification.

Different plans may result in the same physical dose distribution but with a different level of uncertainties in relation to the uncertainties in positioning.

Robustness analysis in radiotherapy

The errors might effect dose distribution and healthy tissues. Therefore the robustness protocol is defined to:

- allow an identification of a specific patient that may benefit from a more individual way of approaching the radiotherapy goals, and
- select the best plans which carry minimum variation in the dose distribution for the largest uncertainties.

There is a lot of interest in including the biological effectiveness as this will improve the treatment and it would also allow to account for individual patient sensitivity. A way to do this is to evaluate the treatment plans using radiobiological models.

Robustness analysis for radiobiological models

The robustness analysis, in terms of radiobiological models, aims at defining the changes in the output of a model as a function of uncertainties in the input parameters. In the next step the values of various inputs of the model are varied (as if they were subjected to uncertainties) and the resultant change in the output variable is monitored.

Large changes in the output variable imply the particular input varied is important in controlling model behaviour. However the model is not suitable for clinical adoption as its predictions are subjected to large uncertainties.

Project plan

1. Literature review
2. Selection of the clinical endpoint
3. Extraction of the reported values of radiobiological parameters
4. Preparation of the clinical data (dose volume histograms)
5. The BioSuite software learning and testing
6. Calculation of the model outcome for different sets of parameters
7. Data analysis – defining the outcome of the model as a function of the variation of the input parameter

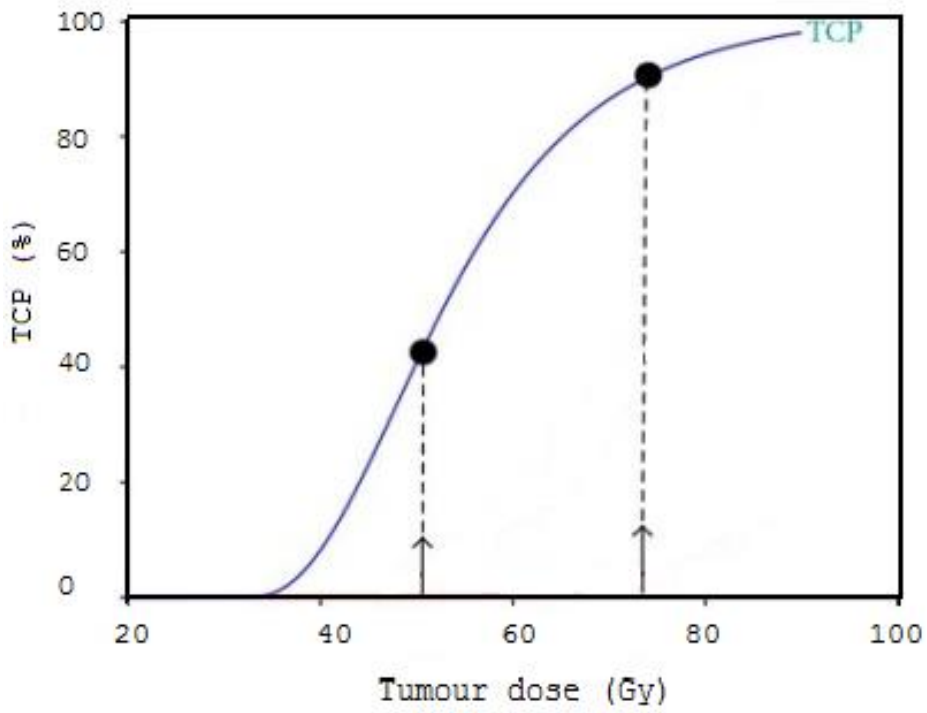
Tumour Control Probability Model

The probability of killing all tumour cells is expressed by the Tumour Control Probability (TCP) model.

$$TCP = \exp\{-\rho v \exp[-\alpha D_{tot} - \frac{\beta d^2}{f} + \gamma(T - T_k)]\}$$

Where:

ρ – density of tumour cells
v - tumour volume
α - the initial slope of the surviving curve
β - the degree of the survival curve
d - dose per fraction
D_{tot} - total dose
f - the number of fractions
T - overall treatment time
T_k - time at which the cells start to repopulate
γ - repopulation constant



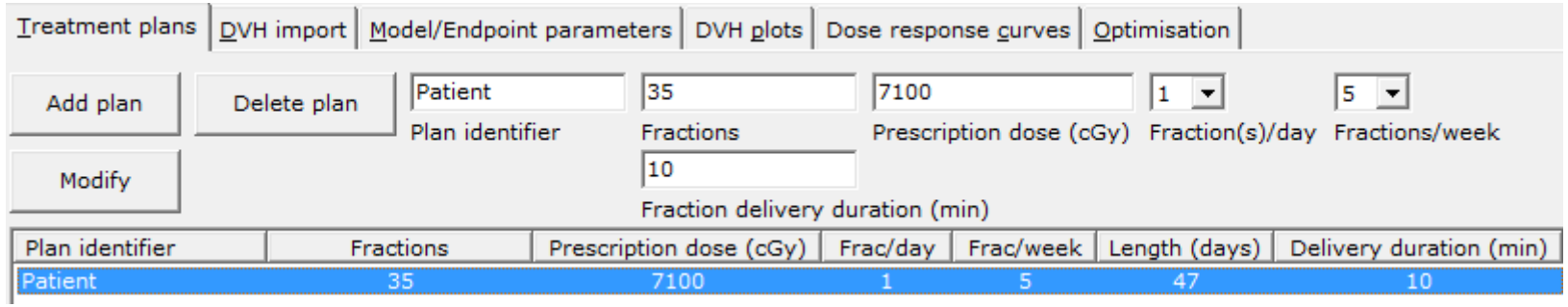
The role of TCP in Radiotherapy

The role of TCP model in radiotherapy is to:

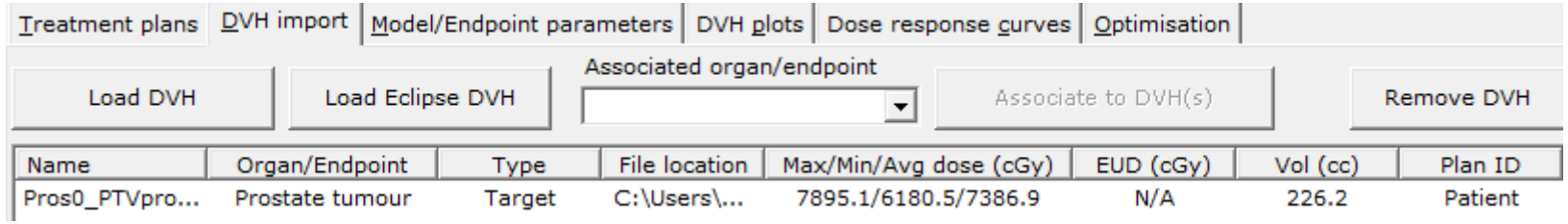
- provide information on the biological equivalent of dose delivery
- quantify the effect of radiation quality
- guide biologically-based optimization algorithms

Input data and BioSuite program

BioSuite is a software developed to calculate the outcome of tumour control probability model as well as to perform treatment optimisation (the calculation of the optimal number of fractions and dose per fraction).



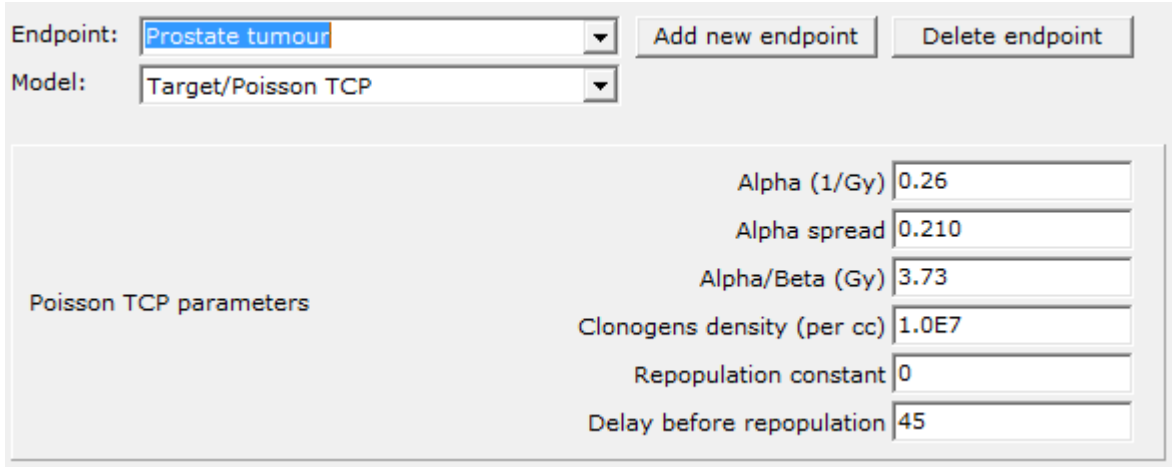
Treatment plan constrains



Patient dose volume histogram

Input data and BioSuite program

Input parameters:



Set	α/β [Gy]	α [Gy^{-1}]	σ_α [Gy^{-1}]	N (per cc)	Ref.
1	1.5	0.04	0.02	15.3	[22]
2	3.1	0.15	0.04	$1 \cdot 10^6$	[31]
3	8.3	0.26	0.06	$3 \cdot 10^6$	[33]
4	50.3	0.15	0.03	$5 \cdot 10^6$	[34]

N - number of clonogenic cells.

22. *D. Brenner, E. Hall, Fractionation and protraction for radiotherapy of prostate carcinoma, Int. J. Radiat. Oncol., Biol., Phys., 1999, Vol. 43, No. 5: 1095-1101.*

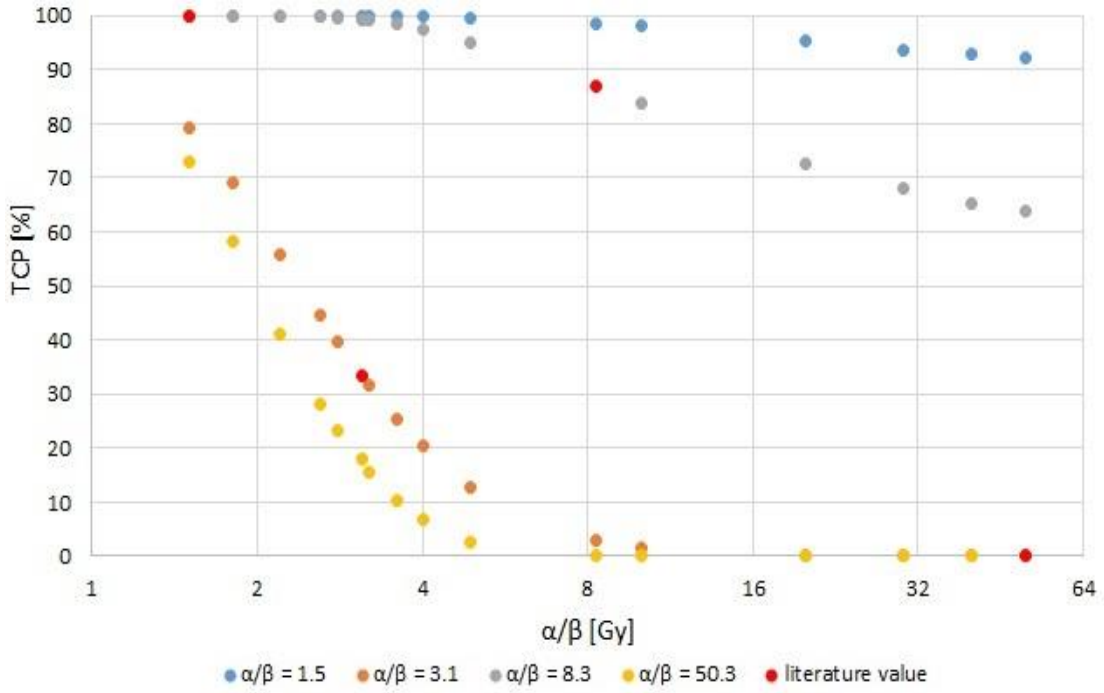
31. *J. Wang, X. Li, C. Yu, S. DiBiase, The low alpha/beta ratio for prostate cancer: What does the clinical outcome of HDR brachytherapy tell us?, Int. J. Radiat. Oncol., Biol., Phys., 2003, 57: 1101-8.*

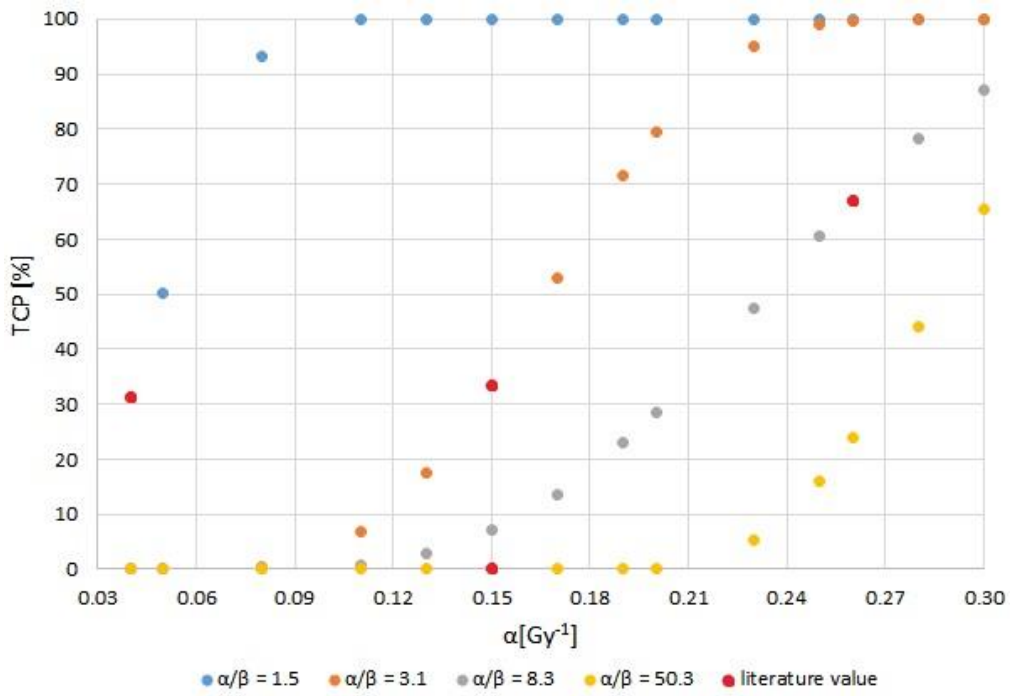
33. *E. Nahum, B. Movsas, E. Horwitz, C. Stobbe, J. Chapman, Incorporating clinical measurements of hypoxia into tumour local control modelling of prostate cancer: implications for the α/β ratio, Int. J. Radiat. Oncol., Biol., Phys., 2003, 57: 391-401.*

34. *A. Nahum and J. Chapman, In response to Dr. Orton, Int. J. Radiat. Oncol., Biol., Phys. 2004, 58: 1637-1639.*

The relations between TCP and model parameters

Different sets of parameters the same treatment plan



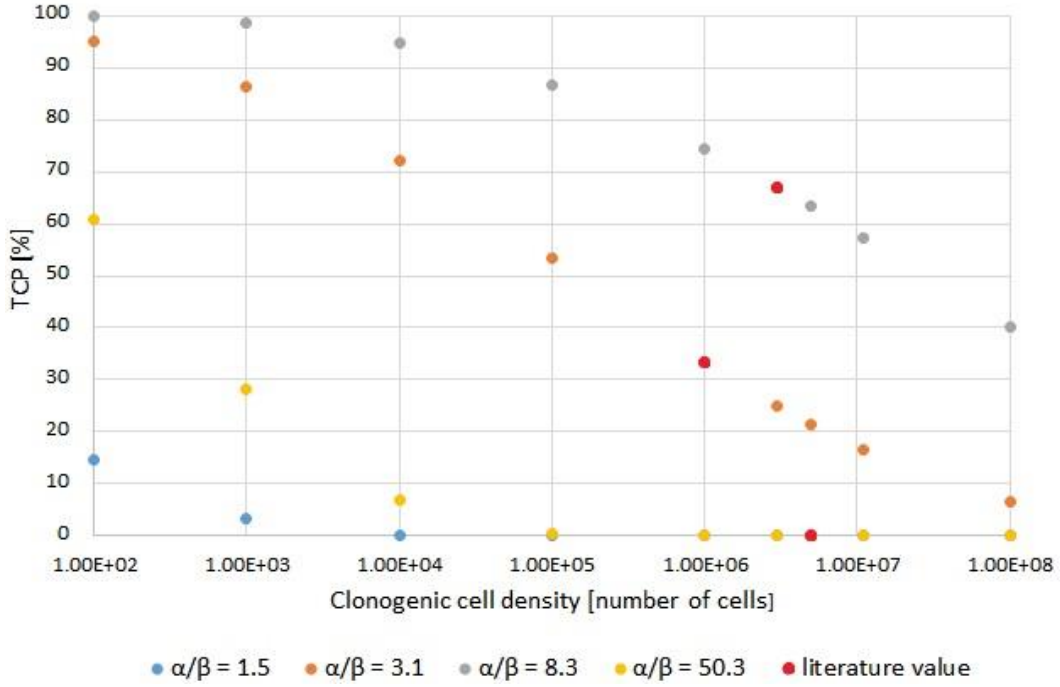


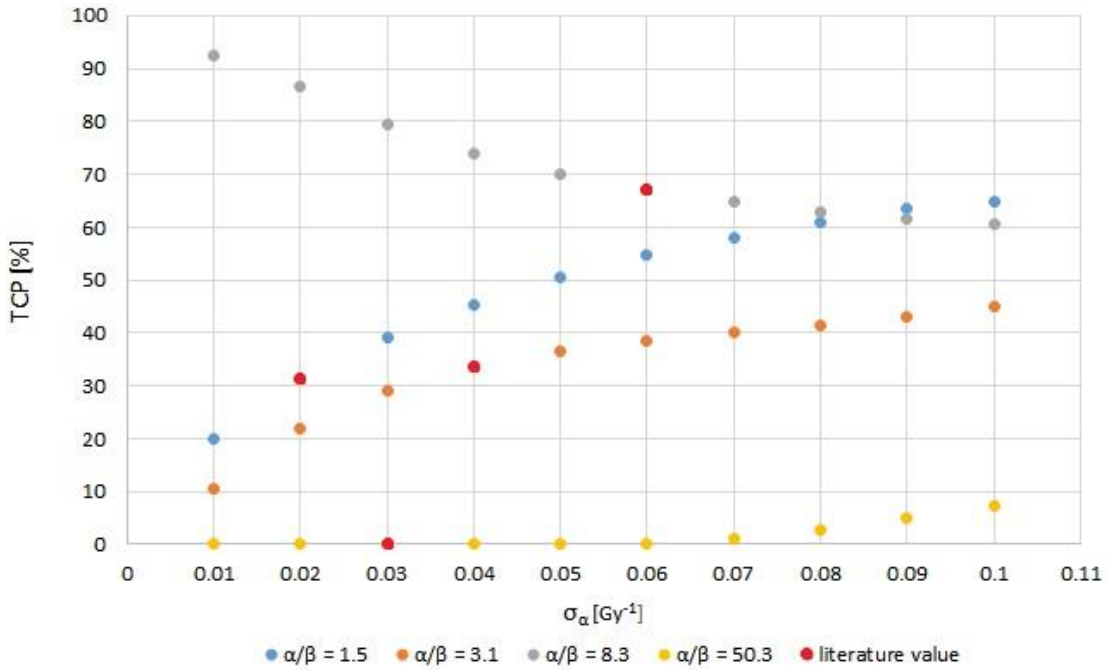
α/β = 1.5 Gy – Brenner and Hall (1999)
α/β = 8.3 – Nahum et al. (2003) - fraction of oxygenated cells

α/β = 3.1 - J. Wang et al. (2003)
α/β = 50.3 - Nahum and Chapman (2004) - fraction of hypoxic cells

The relations between TCP and model parameters

Different sets of parameters the same treatment plan





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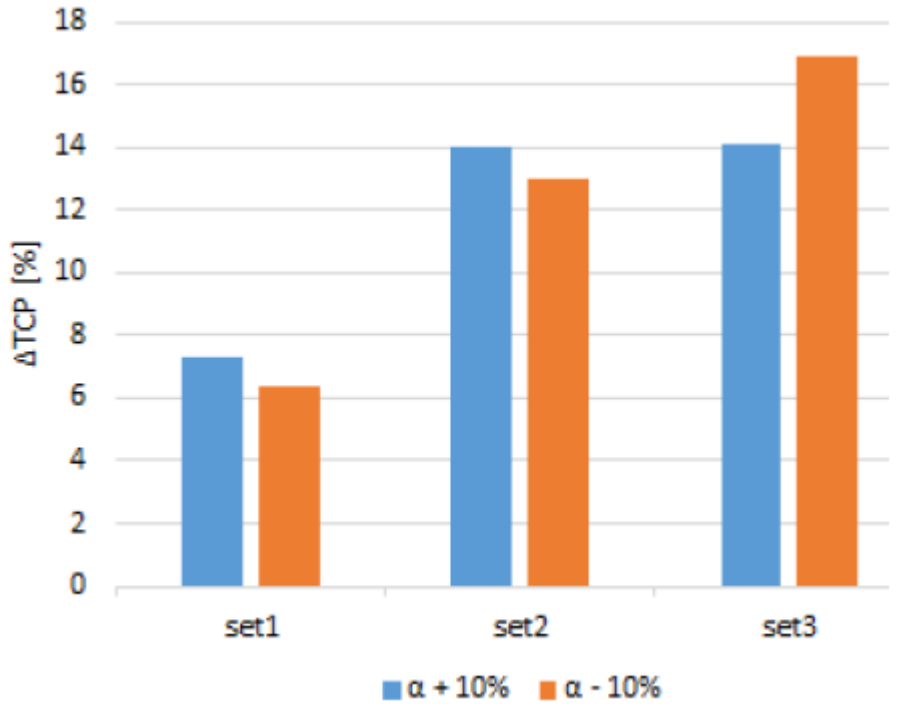
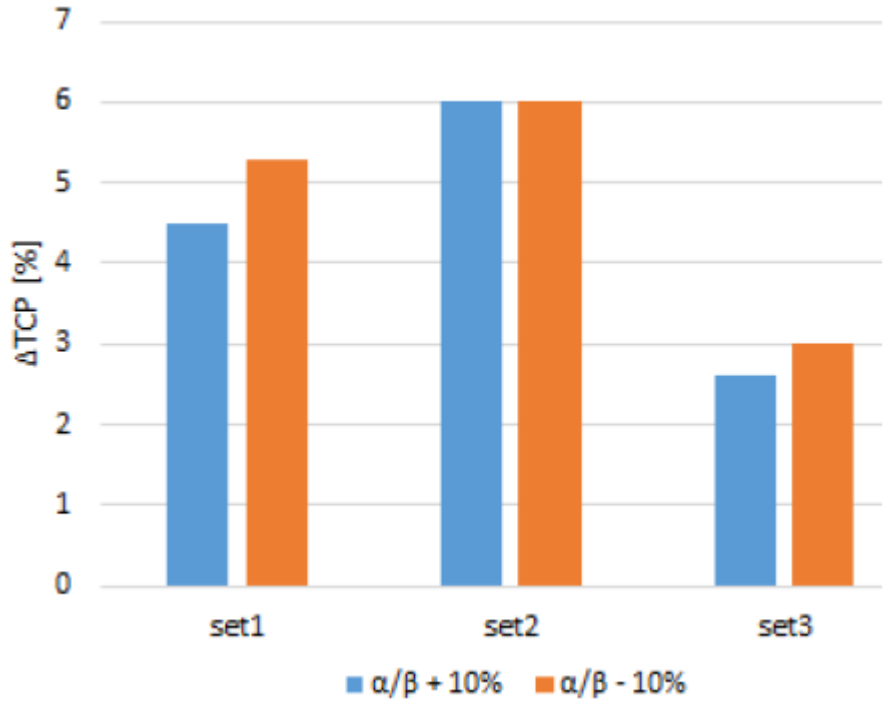
The robustness of TCP model





Conclusions

1. Different literature data presents the self-consistent sets of parameters which give the best possible TCP for the specific case.

2. Sensitivity of the TCP model to uncertainties of its parameters cannot be explicitly defined since each set of parameters is unique and shows individual relation with the model outcome.

3. The results show how a 10% change in α parameter might lead to a 17% change in TCP, whereas in the case of α/β parameter this is just 6% (assuming that in both cases all of the rest parameters were left unchanged).

4. TCP model might be applicable in treatment planning systems introducing a proper adjustment to the clinical case; however it might bring serious consequences when the biological or physical uncertainties will occur. Therefore further investigation has to be carry out to introduce radiobiological models in treatment planning systems.

Future perspectives

1. Performing the multi-dimensional representation of the distribution of TCP using automatically generated sets of parameters to investigate the influence of uncertainties of 6 parameters on TCP.

2. Building a in-home program for calculating TCP.

3. Experimental validation of the model using different dose fractionations.

4. Performing the Monte Carlo simulations for the proton and high energy electron beams in terms of the physical effects (DNA double-strand break).

5. Performing the optimisation for proton and X-ray therapies and developing the new dose fractionation regimes so that the best TCP will be achieved.

Thank you for your attention!