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In silico model of radiotherapy treatment outcome for different fractionation schemes considering dynamic biological processes

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Introduction: Observational clinical studies of radiotherapy (RT) outcome for different fractionation schemes are a very costly and demanding task. Therefore, the development of computational tools that simulate tumour and normal tissue response under scenarios can be enormously useful for trials design. This work presents a model for treatment outcome evaluation of different fractionation schemes considering tumour characteristics and normal tissue tolerances.

Methodology: Tumour response is simulated with a previously published *in silico* model (Tumour Response Model, TRM), which considers a representative virtual tumour created from the volumetric information of real tumours. This model can also import clinical information about tumour oxygenation and real inhomogeneous dose distributions and considers the following biological processes: tumour growth, accelerated proliferation, hypoxia-induced angiogenesis, oxygen-dependent cell killing, resorption of dead cells and shrinkage. Moreover, the response of normal tissues (NTCP) is calculated from the clinical DVH by using the empirical Lyman-Kutcher-Burman (LKB) model.

As an example, two head & neck (HN) IMRT plans with a conventional fractionation scheme were chosen to show the capabilities of the model. Both virtual tumours were created with hypoxic cores, which are commonly observed in these type of tumours.

For each virtual HN tumour, three fractionation schemes were simulated: conventional (2Gy/fx, 1fx/ day, 5 days/week), hyperfractionated (1.2 Gy/fx, 2 fx/day, 5 days/week) and CHART (1.5 Gy/fx, 3 fx/day, every day). The radiobiological parameters for the simulation were $\rho = 10^4$ tumour cells per mm^3, α/β =10 Gy, α =0.37 Gy^{-1} and σ_α=0.06 Gy^{-1}. Simulated tumour control probability (TCP) curves were compared to those calculated with a DVH-based Poisson Model for the same tumour cell density.

Regarding normal tissue, DVHs corresponding to the altered (i.e., non conventional) fractionation schemes were generated by re-escalation and redistribution of the original DVH, keeping constant the relative dose distribution for different fractionation schemes.

NTCP curves were generated for parotid glands (endpoint xerostomia) as a function of biological effective dose (BED) considering α/β values of 3 and 10 Gy.

The Uncomplicated Control Probability (UCP) was calculated from TCP and NTCP curves, considering both parotid glands. For each fractionation scheme, the optimum prescription dose was defined as the maximum dose to the tumour fulfilling the constraint that NTCP remained equal or below 10% for the less irradiated parotid gland (D_{NTCP10}).

Results and discussion: The radiosensitivity parameters in the TCP Poisson Model leading to a match with the TRM simulated TCP curves resulted α/β =10 Gy, α =0.295 Gy^{-1} and σ_α=0.04 Gy^{-}1. TRM considers an intrinsic oxic α value, modified by oxygen enhancement ratios and tumour reoxygenation, while the Poisson model does not consider hypoxia explicitly. An effective α value in the Poisson model is thus needed to match both TCP curves.

The results for the simulated TCP and the resulting value of UCP at the prescription dose D_{NTCP10}, for each patient and fractionation scheme, are shown in Table I for the case of $\alpha/\beta = 3$ Gy, as an example. It can be observed that, for the same patient, the analysed fractionation schemes lead to different prescription doses (fulfilling the same NTCP constraint) and to different UCP values.

Conclusion: A tool for calculating TCP, NTCP and UCP under different fractionation schemes for representative clinical cases has been developed. Dynamic biological processes, volumetric information and clinical

dose distributions are considered for the simulation of the response of tumour and normal tissue. As an example, this tool was applied to two IMRT HN patients under three different fractionation schemes. Results shown that our simulation, with α values commonly assigned to HN tumours, properly describe a realistic clinical outcome. The proposed *in silico* model could be used for any type of tumour, OARs and clinical dose distribution. A thorough validation of the model with a large number of clinical cases is still needed to use the model as a clinical tool.

Country

Chile

Institution

Pontificia Universidad Católica de Chile

Primary author: ASTABURUAGA, Rosario (Pontificia Universidad Católica de Chile)

Co-authors: LÓPEZ-MEDINA, Antonio (Medical Physics Department, Complexo Hospitalario Universitario de Vigo (CHUVI)); GAGO-ARIAS, Araceli (Pontificia Universidad Católica de Chile); SÁNCHEZ-NIETO, Beatriz (Pontificia Universidad Católica de Chile); KARGER, Christian P. (Department of Medical Physics in Radiation Oncology, German Cancer Research Center (DKFZ)); FABRI, Daniella (Pontificia Universidad Católica de Chile); ESPINOZA, Ignacio (Pontificia Universidad Católica de Chile); PARDO-MONTERO, Juan (Grupo de Imaxe Molecular, Instituto de Investigación Sanitaria (IDIS) and Servizio de Radiofísica e Protección Radiolóxica); GUERRERO-URBANO, Teresa (Department of Clinical Oncology, Guys and St. Thomas, NHS Foundation)

Presenters: FABRI, Daniella (Pontificia Universidad Católica de Chile); ASTABURUAGA, Rosario (Pontificia Universidad Católica de Chile)

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