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Short Communication

Uncertainty evaluation of image-based tumour control probability models in radiotherapy of prostate cancer using a visual analytic tool

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ABSTRACT

Functional imaging techniques provide radiobiological information that can be included into tumour control probability (TCP) models to enable individualized outcome predictions in radiotherapy. However, functional imaging and the derived radiobiological information are influenced by uncertainties, translating into variations in individual TCP predictions. In this study we applied a previously developed analytical tool to quantify dose and TCP uncertainty bands when initial cell density is estimated from MRI-based apparent diffusion coefficient maps of eleven patients. TCP uncertainty bands of 16% were observed at patient level, while dose variations bands up to 8 Gy were found at voxel level for an *iso*-TCP approach.

1. Introduction

Tumour control probability (TCP) models are developed to predict radiotherapy (RT) outcomes, both across populations and on a patient-specific level [1,2]. Initial TCP modelling studies assumed spatially uniform distributions of radiobiological characteristics, both within and between patients [3]. There is currently considerable interest in integrating and adapting RT according to biological information acquired during all stages of the treatment process [4]. In recent TCP studies, patient-specific tumour information including features related to inter- and intra-tumour heterogeneities have been incorporated into the models, while also considering different dose distributions patterns within the tumour for maximum tumour control [5]. Some of these models exploit the benefit of functional imaging that non-invasively provides information on tumour characteristics [6]. However, this information may be influenced by inherent inaccuracies in the image acquisition process, which in turn leads to uncertainties in the TCP model.

Uncertainty in the TCP models, as well as the underlying tumour information may be difficult to explore and analyse. Methods from the field of Visual Analytics (VA) – a discipline that combines visualization with semi-automatic methods of data analysis [7] – could be used to explore and analyse the TCP models. The particular application of VA to TCP models may facilitate the inclusion of uncertainties associated with biological information and the visualization of patient-specific TCP uncertainty bands.

The aim of the present work was therefore to quantify uncertainty bands by using a previously developed VA tool [8], built to include Apparent Diffusion Coefficient (ADC)-induced uncertainties in the TCP calculation, when ADC maps were used to calculate the initial number of clonogens [9]. The study was based on ADC maps of patients with prostate cancer and explored the uncertainties associated with two different approaches to relate ADC values to cell densities.

2. Materials and methods

2.1. Patient information

Magnetic Resonance Imaging (MRI)-based ADC maps derived from diffusion weighted imaging (DWI) together with index-volume contours of eleven prostate cancer patients were included in this study. Image data sets were acquired using an integrated endorectal and pelvic

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[2] Dr. Ludvig Muren, a co-author of this paper, is Editor-in-Chief of Physics & Imaging in Radiation Oncology. A member of the Editorial Board managed the editorial process for this manuscript independently from Dr. Muren and the manuscript was subject to the Journal's usual peer-review process.

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Table 1
Dose and TCP bands, and voxel dose variability for all the patients, assuming the ADC uncertainties inside the index lesion at the two different levels of total TCP, 0.7 and 0.9 ($TCP_{0.7}$ and $TCP_{0.9}$ respectively), and for the two cell density approaches.

Patient (N)	Index Volume (%)	Voxel Dose Variability (Gy)				Dose Uncertainty (Gy, mean ± SD)			
		Linear $TCP_{0.7}$	Linear $TCP_{0.9}$	Sigmoid $TCP_{0.7}$	Sigmoid $TCP_{0.9}$	Linear $TCP_{0.7}$	Linear $TCP_{0.9}$	Sigmoid $TCP_{0.7}$	Sigmoid $TCP_{0.9}$
1	5	0.94	0.96	4.23	4.32	1.1 ± 0.3	1.00 ± 0.0	1.6 ± 0.7	1.1 ± 0.3
2	3	1.28	1.30	1.34	1.47				
3	8	1.05	1.07	2.57	2.60	TCP Uncertainty (%, mean ± SD)			
4	6	1.00	1.05	2.56	2.57	Linear $TCP_{0.7}$	Linear $TCP_{0.9}$	Sigmoid $TCP_{0.7}$	Sigmoid $TCP_{0.9}$
5	11	1.10	1.14	1.92	1.99				
6	5	0.88	0.93	0.95	0.97	3.2 ± 0.4	2.2 ± 0.4	6.5 ± 4.7	4.7 ± 3.4
7	17	1.13	1.17	2.58	2.62				
8	8	0.93	0.95	3.56	3.63	Mean Dose for Iso-TCP (Gy, mean ± SD)			
9	20	0.92	0.96	0.74	0.57	Linear $TCP_{0.7}$	Linear $TCP_{0.9}$	Sigmoid $TCP_{0.7}$	Sigmoid $TCP_{0.9}$
10	1	1.63	1.74	4.50	4.68				
11	2	1.06	1.05	1.32	1.25	109.9±7.7	117.9±7.9	92.4±6.5	100.1±6.5

phased-array coil in a 1.5 T whole body MRI unit Siemens Avanto (Siemens Medical Systems, Erlangen, Germany). Further information on image acquisition, post-processing and patient characteristics were described by Reisæter et al. [10].

2.2. Visual analysis tool

A VA tool was developed [8] to evaluate the propagation of uncertainties into TCP calculations, caused by cell density estimations from MRI-based ADC maps in prostate cancer patients [9]. In brief, the proposed VA framework incorporated the following four main components: (1) It supported quantification and exploration of ADC-induced uncertainty (cell density uncertainties within the index lesion derived from ADC maps) and its propagation to TCP modelling; (2) it facilitated exploration and analysis of the sensitivity of TCP models to different assumptions and parameter variations; (3) it enabled identification and exploration of inter-patient response variability within cohorts; (4) it allowed, given a targeted treatment outcome, to identify the treatment strategies or parameters that would achieve it.

2.3. Cell density, ADC uncertainties and TCP computations

The cell density at each voxel within the index lesion was calculated using two different approaches: (1) A linear relation between ADC and cell density [11]; (2) an inverse sigmoid relation between ADC and cell densities, with cell densities in the range of 10^5–10^7 cell/cm^3. Voxels outside the index lesion were considered to have a constant cell density of 10^5 cell/cm^3 for both cases; further details about the two different approaches to derive cell densities have been described elsewhere [9].

ADC map uncertainties were included in the calculations of voxel cell densities based on the results of a multicentre study previously performed across three different clinical platforms, where ADC maps from a phantom and a volunteer (http://drtherapat.eu/deliverables/reports/) were derived by using the same image sequences. The ADC value at each voxel was then modelled as a Gaussian distribution, assuming a standard deviation (σ) of 3% of the unknown real value. From this, the quantitative real ADC value at each voxel position was estimated by an analytical approximation of the probability that the real value occurred, given the measured ADC value. The uncertainties on ADC values for the experimental data were also considered to compute the linear relation between volumetric cell density and measured ADC values [8].

TCP modelling was based on Linear-Quadratic (LQ) curves, combined with a Poisson dose–response model. The LQ model parameters were set as: $\alpha = 0.18\,Gy^{-1}$ and $\alpha/\beta = 1.93\,Gy$, and considering an intra-tumour normal distribution of both α and β of 15% [12].

2.4. Evaluation of the tool

The eleven patients were loaded into the visualization tool frame, assuming the aforementioned radiobiological parameters, the two different approaches for the relation between cell density and ADC values, and the voxel-wise intrinsic uncertainty bands for the ADC maps.

TCP bands for each patient derived from the uncertainties in the cell density were calculated assuming a prescribed dose of 95 Gy in 2.7 Gy/fraction to the index lesion, while the rest of prostate received concomitantly 77 Gy in 2.2 Gy/fraction, mimicking an integrated boost treatment [13]. The overall patient TCP and dose uncertainty bands were evaluated at two different levels of the mean TCP: 0.7 ($TCP_{0.7}$) and 0.9 ($TCP_{0.9}$). TCP levels and dose uncertainties bands were compared using paired *t*-test.

Additionally, assuming voxel-wise *iso*-TCP distributions across the whole prostatic volumes for the overall patient $TCP_{0.7}$ and $TCP_{0.9}$ levels, mean dose per voxel and the associated dose uncertainty bands were also calculated.

3. Results

The ratio between the index volume and prostate volume ranged from 1% to 20% across the eleven patients. Across the population, the ADC values inside the index lesion (mean ± SD: 1.07 ± 0.17·10^3 mm^2/s) were lower than outside the index (1.22 ± 0.16·10^3 mm^2/s), indicating higher cell density values inside the index lesion (Table 1).

The visualization tool allowed quantification of TCP and dose uncertainty bands at each subject and at different levels of the overall mean TCP. For $TCP_{0.7}$, the individual TCP bands ranged between 3% and 4% across the patients for the linear approach, and between 1% and 16% for the sigmoid approach. At $TCP_{0.9}$, the TCP uncertainty bands ranged from 1% to 3% for the linear approach, and from 1% to 11% using the sigmoid approach.

Mean doses at the index volume needed to achieve the overall patient $TCP_{0.7}$ and $TCP_{0.9}$ levels (*iso*-TCP for all voxels) were 110 Gy and 118 Gy for the linear approach; and 92 Gy and 100 Gy for the sigmoid approach, reflecting the lower cell density values resulting from the