

ORIGINAL ARTICLE

Dynamic contrast enhanced magnetic resonance imaging of bladder cancer and implications for biological image-adapted radiotherapy

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Abstract

Purpose. To assess the role of image parameters derived from dynamic contrast enhanced magnetic resonance imaging (DCEMRI) in bladder cancer staging, and to investigate the potential use of such parameter images in biological image-adapted radiotherapy (RT). **Materials and methods.** High-resolution volumetric interpolated breath-hold (VIBE) DCEMRI of 26 patients diagnosed with bladder cancer was performed. DCEMRI parameters derived from tumor and muscle contrast uptake curves were extracted and subjected to correlation analysis with tumor volume as well as clinical, pathological, histological and T2-weighted MR tumor stage. For parameters showing a significant correlation with tumor stage, 3D malignancy maps were generated. As an initial step towards delivery of biologically adapted intensity modulated radiotherapy (IMRT) it was hypothesized that the malignancy map could be used as a RT dose prescription map. Simulating IMRT delivery with multi-leaf collimators (MLCs), idealized dose distributions, constituted by dose cubes, were adapted to the prescription map. The size of the dose cubes were varied to mimic MLCs of varying leaf width. The difference between the adapted and prescribed dose distributions was quantified by the root mean square deviation (RMSD). **Results.** No significant relationships were found between tumor volume and extracted DCEMRI parameters. The normalized area between tumor and muscle contrast uptake curves ($nABC$) evaluated from 0–180 seconds ($nABC_{180}$) and 0–480 s ($nABC_{480}$) correlated significantly with tumor stage ($p = 0.047$ and $p = 0.035$, respectively). Dose prescription maps for 10 patients were generated from the $nABC_{480}$. The RMSD between the prescribed and adapted dose distribution decreased with decreasing size of the dose cubes. Large interpatient variations in the RMSD and in the dependence of the RMSD on different dose cube sizes were found. **Conclusions.** The $nABC_{180}$ and $nABC_{480}$ may provide added value in staging of bladder cancer. High-resolution IMRT is required for some patients for optimal adapted RT.

Non-invasive three-dimensional imaging using magnetic resonance tomography may provide high resolution images revealing structural, functional and molecular tissue properties. The potential use of such images is still not fully exploited, neither for diagnostic purposes nor for designing novel therapeutic strategies.

In dynamic contrast enhanced magnetic resonance imaging (DCEMRI), an intravenous bolus injection of a paramagnetic contrast agent is used to increase the signal intensity on T1-weighted MR images. Via

the vascular network, the contrast agent permeates into the extravascular extracellular space (EES) and is subsequently cleared by renal excretion. Analysis of the temporal signal intensity pattern can be used to derive a variety of descriptive parameters such as peak enhancement, initial enhancement rate, and area under curve (AUC). These parameters reflect the underlying permeability and perfusion of the tumor microenvironment, and composition of the extravascular extracellular space. A voxel-by-voxel quantification of image parameters allows assessment

of tumor heterogeneity and may provide localization of e.g. well-perfused regions.

The signal enhancement in DCEMRI is dependent on tissue vasculature. Therefore, the average enhancement might be expected to be poor in large tumors, as compared to small lesions, because they tend to outgrow their vascular supply and develop large areas of hypoxia and necrosis. However, studies have reported that the enhancement characteristics are independent of tumor volume [1,2]. This indicates a higher prognostic role of DCEMRI, as derived image parameters provide biological intra-tumoral information not available using standard investigations.

Tumors are heterogeneous entities expected to present spatial variations in radiosensitivity. However, the current standard practice in radiotherapy (RT) is to deliver a homogeneous radiation dose to the entire tumor, thus ignoring biological variations. Tumor oxygenation is an important factor in determining the response to RT, where hypoxic tumors are more resistant to RT [3]. Three-dimensional hypoxia mapping could therefore be useful, both for identifying radioresistant patients and for designing focal dose escalation strategies. Studies have demonstrated that selective boosting of radioresistant regions to increase the overall tumor cell kill is feasible with the recent technological advances in intensity modulated RT (IMRT) [4–9]. Such strategies may be termed biologically adapted RT.

Non-invasive biological imaging modalities like MRI and positron emission tomography (PET) have shown a potential for depicting three-dimensional distributions of tumor radiosensitivity. Among them is DCEMRI, where studies have shown correlations between invasive measurements of interstitial oxygen pressure with extracted DCEMRI parameters [1,10]. The present study was performed to (1) assess potential correlations between extracted DCEMR image parameters and bladder cancer staging and tumor volume, and (2) to investigate the potential use of derived parameter images in biological image adapted RT.

Materials and methods

Patients

Twenty-six patients with clinically localized biopsy-proven bladder cancer underwent MRI prior to radical radiotherapy between August 2002 and February 2005. Patient median age was 72 years (range: 55–83 years). The institutional ethics review board approved the study and informed consent was obtained from all patients.

Staging

Pathological staging was performed using the TNM classification system [11]. Clinical, pathological, histological and T2-weighted MR tumor staging was performed for all patients. The radiological staging was performed by an experienced uro-radiologist (J.R.).

MRI protocol

MRI was performed on a 1.5 T MR scanner (Siemens Symphony, Erlangen, Germany), using a phased-array pelvic coil. Prior to DCEMR imaging, the protocol included standard T1-weighted (slice thickness: 5 mm, TR/TE = 860/12 ms) and T2-weighted (slice thickness: 5 mm, TR/TE = 3600/102 ms) turbo spin-echo imaging to provide tumor stage, volume and nodal status. The dynamic sequence was a fat-saturated three-dimensional volumetric breath-hold examination (VIBE) with scanning parameters: TR/TE = 4.2/1.88 ms, scan time = 24 s, slab thickness = 135 mm, slice thickness = 2.5 mm, number of partitions = 54, FOV = 320 mm³, giving a voxel size of 1.25 × 1.25 × 2.5 mm. Images were acquired prior to and 30, 90, 180 and 480 s after an intravenous bolus injection of 20 ml of gadolinium-DTPA (Omniscan, GE Healthcare, UK) using a power injector, followed by a saline flush of 20 ml NaCl (0.9%).

Image analysis

The tumor was traced in the DCEMR images using the enhancement pattern and T2-weighted images by the involved uro-radiologist (J.R.). The delineated tumor was transferred to IDL (Interactive Data Language v6.2, Research Systems Inc., Boulder, CO), where all further image analyses were performed. In IDL, an additional region-of-interest (ROI) was drawn in three axial slices of the gluteal muscle, avoiding artefacts and large vessels. The tumor volumes were calculated on the basis of voxel dimensions in the DCEMR images and the tumor delineations.

Signal intensity versus time curves were plotted for both tumor and muscle and the time dependence of the relative signal intensity, $RSI(t)$, in each voxel was calculated using the equation

$$RSI(t) = \frac{SI(t) - SI(0)}{SI(0)}$$

where $SI(t)$ refers to the signal intensity in a post-contrast voxel, which was obtained at four different time points after injection; 30, 90, 180 and 480 s. $SI(0)$ is the signal intensity acquired prior to injection (at time = 0). The area under the $RSI(t)$ curve (AUC) for muscle and tumor was defined as

$$AUC(t) = \int_0^t RSI(t') dt'$$

where $t = 30, 90, 180$ and 480 s. To account for differences in arterial input between individuals, the normalized area between curves, $nABC(t)$, defined as the area between the tumor and muscle curves divided by the median $AUC(t)$ for muscle, were found.

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Science, Chicago, IL, USA). Extracted DCEMRI parameters were subjected to correlation analysis with tumor volume and clinical, pathological, histological and T2-weighted MR tumor stage using Pearson's correlation test. Significance between variables was assigned at $p < 0.05$.

Malignancy mapping and IMRT

For DCEMRI parameters showing a significant correlation with tumor stage, three-dimensional malignancy maps for 10 selected patients were generated. As an initial step towards delivery of biological adaptive RT, it was hypothesized that these maps could be used as a biological dose prescription map to investigate the potential use of DCEMRI in RT of bladder cancer. The prescribed dose in a given voxel was, for simplicity, taken as the DCEMRI parameter value. By a simplified simulation procedure, idealized dose distributions from segmented IMRT were adapted to the malignancy maps. The dose distributions were constituted by dose cubes varying in size from 2.5 to 10 mm, mimicking multi-leaf collimators (MLCs) of varying leaf width. The dose level in each cube was found by calculating the median value within the cube in the malignancy maps. The influence of the penumbra on the resulting dose distributions were tentatively accounted for by convolving the adapted dose cubes with a three-dimensional Gaussian kernel of $\sigma_x = \sigma_y = \sigma_z = 2$ mm.

The difference between the prescribed and adapted dose distributions was quantified by the relative root mean square deviation, *RMSD*, defined as

$$RMSD = \frac{\sqrt{\frac{1}{N} \sum_{i=1}^N (D_{p,i} - D_{a,i})^2}}{\bar{D}_p}$$

where $D_{p,i}$ is the prescribed dose in voxel i , $D_{a,i}$ is the adapted dose, and N is the number of voxels in the tumor. $\bar{D}_p$ is the median of the prescribed dose in the tumor.

Results

Tumor volume

Tumor volumes ranged from 0.4 to 139.6 cm^3 (median; 8.5, mean $\pm$ SD; 24.3 ± 34.5). No significant relationships were found either between tumor volume and extracted DCEMRI parameters or between tumor volume and staging (Figure 1).

DCEMRI

Among the estimated image parameters, significant correlations were found between tumor stage assessed in T2-weighted MR images and the normalized area between the tumor and muscle *RSI* curve evaluated from 0–180 s ($nABC_{180}$) and 0–480 s ($nABC_{480}$) ($p = 0.047$ and $p = 0.035$, respectively) (Figure 2). $nABC_{90}$ was close to being significant ($p = 0.111$). Clinical, pathological and histological staging did not correlate significantly with any of the DCEMRI derived parameters (data not shown). In Table I, the median $nABC_{480}$, together with the 2.5 and the 97.5 percentile, is shown for each of the 26 patients. The median $nABC_{480}$ varied from -0.4 to 16.5 , where a positive $nABC_{480}$ corresponds to a tumor with a higher contrast agent uptake than in the gluteal muscle. Figure 3 shows a pre-contrast image set through the centre of one bladder tumor in all three planes (axial, coronal and sagittal) with a parametrical overlay of $nABC_{480}$. The figure illustrates the heterogeneous composition of the tumor.

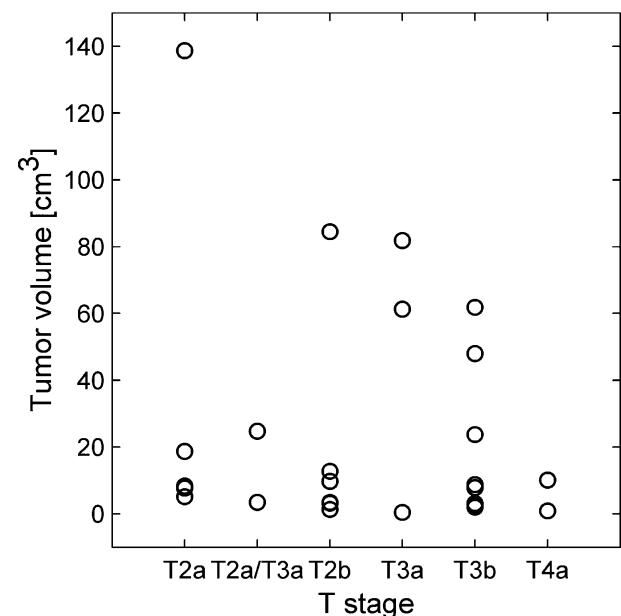


Figure 1. Relationship between tumor volume and T stage assessed in T2-weighted MR images ($r = -0.147$, $p = 0.472$).

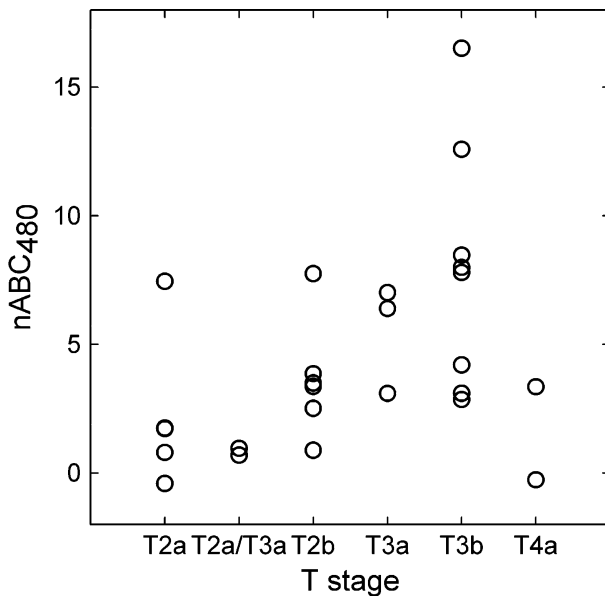


Figure 2. Normalized area between the tumor and muscle contrast uptake curve from 0–480 s, $nABC_{480}$ correlated significantly with T stage assessed in T2-weighted MR images ($r = 0.416$, $p = 0.035$).

Biological dose maps

Three-dimensional dose prescription maps and simulated adapted IMRT dose maps were generated based on the parametric $nABC_{480}$ maps for 10 of the patients. A single axial slice of $nABC_{480}$ (the dose prescription map) and the corresponding adapted dose maps for three of the tumors are shown in Figure 4. As apparent, the adapted dose distributions using small dose cubes appear to reflect the prescription map quite well, although penumbra effects tend to dilute the simulated segmented dose delivery. Figure 5 shows the dependence of the $RMSD$ between the prescribed and the adapted dose distributions on the size of the dose cubes. A

perfect match corresponds to zero $RMSD$. For the highest cube resolution (2.5 mm), the $RMSD$ ranged from 0.05 to 0.22. A clear reduction in $RMSD$ is seen when the size of dose cubes is reduced from 10 mm to 2.5 mm. A cube size of 2.5 mm reduces the median $RMSD$ with on average 35% as compared to a cube size of 10 mm. The reduction in $RMSD$ with cube size ranged from 13 to 65%, reflecting large intertumor variations.

Discussion

To our knowledge, this is the first report relating DCEMRI parameters of bladder cancer to tumor volume and staging. In this study, no significant relationship was found between tumor volume and any of the extracted DCEMRI parameters. This could potentially be due to the relatively small cohort of patients included in the study. However, lack of such a correlation has also been reported in other studies, among them in patients with cervical cancer [1,2,12]. This indicates an improved diagnostic role of DCEMRI since these parameters indicate biologically related intratumoral information not available in standard, anatomical MRI investigations.

The area under the enhancement curve (AUC) is considered to be independent of alterations in bolus duration and noise and is thought to be related to a combination of blood inflow, perfusion and fraction of tumor interstitial space [13,14]. AUC is a model-free parameter often used due to its improved robustness and lack of assumptions as compared to more physiologically related pharmacokinetic models. In addition, unlike pharmacokinetic modelling, AUC may be used to derive parameters that relate more directly to the microvasculature [16]. In the well-known Tofts and Kermode pharmacokinetic model [15], AUC results from a combination of the vascular transfer rate (K^{trans}) and extravascular extracellular space (v_e). Model-based approaches such as the Tofts and Kermode model are generally thought to be more susceptible to noise and fitting errors, and may be less robust. Especially in multicenter clinical trials, there might be large variations in data acquisitions likely to produce differences in pharmacokinetic parameter estimates [13], possibly obscuring the clinical interpretation of DCEMRI data. A model-free approach, such as the AUC , can more easily be implemented across institutions and be successfully compared.

The area between the tumor and muscle enhancement curves normalized to the median uptake in gluteal muscle ($nABC$) is expected to be a very robust estimate where uncertainties due to differences in both bolus duration and bolus size between individuals are minimized [13,14]. The use of

Table I. Median normalized area between the tumor and muscle contrast uptake curve for 0–480 s, $nABC_{480}$, together with the 2.5 and 97.5 percentiles for the 26 bladder cancer patients.

Patient	$nABC_{480}$	Patient	$nABC_{480}$
1	−0.4 (−0.9, 0.9)	14	0.7 (−1.1, 7.0)
2	7.4 (2.4, 21.5)	15	6.4 (−0.7, 24.2)
3	3.1 (0.3, 7.7)	16	0.9 (−1.0, 9.3)
4	3.1 (0.3, 5.9)	17	16.5 (0.4, 77.1)
5	1.7 (−1.0, 18.1)	18	2.5 (−0.7, 8.0)
6	12.6 (−0.6, 35.5)	19	3.5 (0.0, 18.1)
7	7.0 (0.3, 15.9)	20	0.9 (−0.1, 2.3)
8	4.2 (−0.7, 17.1)	21	3.4 (−0.7, 21.5)
9	8.5 (0.2, 53.2)	22	7.7 (−0.1, 27.2)
10	1.7 (−1.0, 12.9)	23	3.9 (−0.8, 13.3)
11	−0.3 (−1.1, 0.1)	24	8.0 (0.8, 46.0)
12	0.8 (−1.0, 12.8)	25	2.8 (−0.9, 16.1)
13	7.8 (1.8, 25.7)	26	3.3 (−0.6, 24.3)

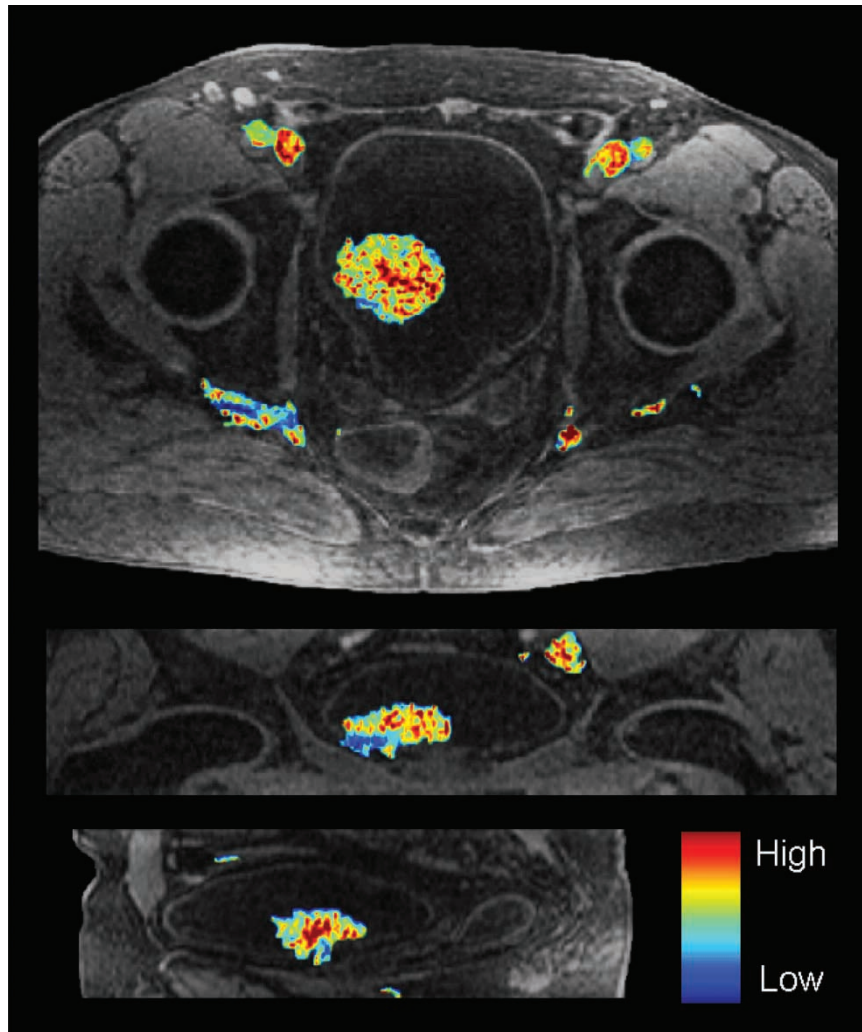


Figure 3. Representative axial (upper), coronal (middle) and sagittal (lower) pre-contrast T1-weighted MR images for one bladder cancer patient with parametrical overlay of $nABC_{480}$.

muscle as a reference tissue has been advocated by others as a true vascular input function since the arterial circulation of contrast agent to tumor is difficult to obtain [17]. In this study, it is shown that $nABC_{180}$ and $nABC_{480}$ correlated significantly with tumor stage assessed in T2-weighted MR images. As no other imaging parameters correlated with staging, the current findings indicate the potential of $nABC$ as a predictor of tumor stage.

A high local $nABC$ may indicate a well-vascularized region of high oxygen pressure (pO_2), most likely with proliferating cells, which also has been argued previously for comparable parameters derived from DCEMRI [1,10,18,19]. Thus, it may be that low levels of $nABC$ indicate hypoxia, and that $nABC$ maps may be employed in biological image adapted radiotherapy. However, tumor stage is a negative predictor for disease-specific survival following radiotherapy of bladder cancer [20]. As well-oxygenated tumors (suggested to have a high $nABC$

in the current work) are more radiosensitive, it may seem like a paradox that $nABC$ correlated positively with tumor stage in the current work. Nevertheless, a high $nABC$ is likely to reflect an extensive vascular network caused by a high degree of vascular recruitment, thus resulting in an invasive, high stage tumor. This apparent paradox is well illustrated in the work by Lancaster et al. [1], where both descriptive and pharmacokinetic parameters were obtained from DCEMRI of cervix carcinomas. Common to these parameters is that high levels imply high contrast enhancement (as is the case with $nABC$), and three of the parameters correlated positively with pO_2 ($p < 0.01$). Also, tumor stage was close to being significantly correlated with the 'A' pharmacokinetic parameter ($p = 0.08$). Furthermore, this parameter was correlated with radiotherapy outcome ($p = 0.02$). Thus, in addition to being positively correlated with tumor stage, it is not unlikely that $nABC$ is positively correlated with both pO_2 and patient

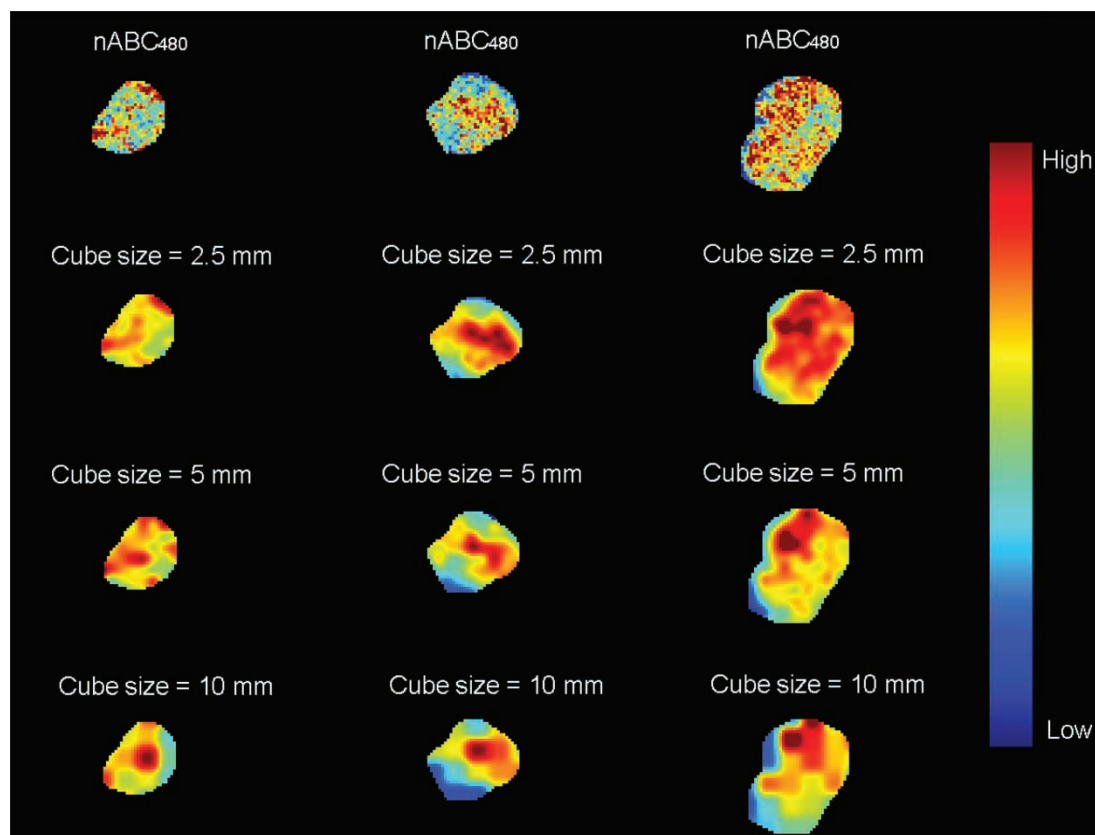


Figure 4. Axial $nABC_{480}$ maps and simulated, adapted dose maps for cube sizes of 2.5, 5 and 10 mm for three different bladder tumors.

survival. A controlled clinical study is required to reveal the predictive potential of $nABC$ for radiotherapy outcome of bladder cancer patients.

Delivering a uniform radiation dose distribution to the entire tumor may result in treatment failure since radioresistant tumor cells might receive insufficient radiation dose. If biological intratumoral information can be derived from DCEMRI, tumors with radioresistant regions can be identified and treatment planning strategies using IMRT can be employed to improve the treatment outcome. As opposed to current practice, where the enhancement pattern in DCEMR images is used visually with respect to target volume definition, future approaches should aim at exploiting this information to map physiological parameters of relevance for tumor radiosensitivity.

Based on $nABC_{480}$, theoretical dose prescription maps were generated for 10 of the bladder cancer patients to evaluate the potential of using segmented IMRT for biologically adapted radiotherapy. In Table I, the intratumoral variation in $nABC_{480}$, indicated by the 2.5 and 97.5 percentiles, deviated markedly between the tumors, suggesting that some patients (presenting heterogeneous tumors) may benefit from local dose escalation. The dose cubes were introduced in order to simulate varying resolution of multi-leaf collimators in adapted radiotherapy. As apparent

from Figure 4, rather large voxel-to-voxel variations in the dose prescription map ($nABC_{480}$) were seen. Using the root mean square deviation ($RMSD$) to evaluate the simulated delivery, a clear reduction in the patient averaged $RMSD$ when using dose cubes of

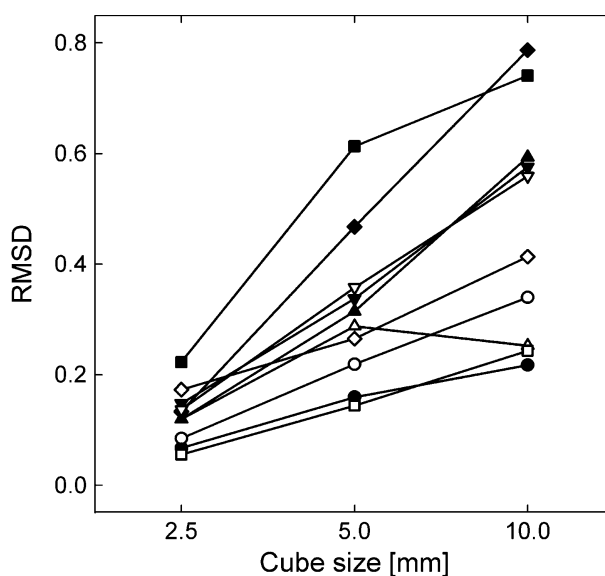


Figure 5. Relative root mean square deviation ($RMSD$) between the prescribed and the adapted dose distribution as function of varying dose cube size.

2.5 mm compared to cubes of 5 and 10 mm was found (Figure 5). In a previous study, where non-uniform tumor dose distributions using IMRT with 2.5 mm multi-leaf collimators were investigated [5], *RMSD* and the estimated tumor control probability (*TCP*) were highly correlated quantities. Thus, *RMSD* appears to be a suitable metric for evaluating the quality of adapted treatments. The current work indicates that *RMSD* may be reduced by, on average, 35% by choosing 2.5 over 10 mm MLC resolution. However, heterogeneous tumors presenting scattered, small and radioresistant foci may not be optimally treated even with high resolution adapted radiotherapy.

Current advances in IMRT technology has allowed for realization of dose distributions based on parameters extracted from biologically related images, but controlled patient studies are needed to evaluate the potential benefit of biologically adapted treatments. High spatial resolution of the intensity modulated beams is needed to provide the irregular dose distributions required. It may also be relevant to evaluate the temporal evolution of image parameters during the course of treatment [9,21], as this may have an impact on the dose prescription map. The situation is further complicated by the considerable geometrical uncertainties taking place during RT (bladder/tumor motion) for the present patient group [22]. Methods to account for such uncertainties [23] would also need to be included to realize the full potential of a biological adaptive RT approach.

In summary, the present study has shown that staging and parameters extracted from DCEMRI of bladder cancer are independent of tumor volume. Furthermore, the normalized area between the tumor and muscle contrast uptake curve (*nABC*) from 0–180 s and 0–480 s derived from the DCEMRI data correlated significantly with tumor stage. The underlying biological information may be useful for improved radiotherapy planning. Simulations of adapted IMRT based on DCEMR image parameters indicate that the treatment outcome might be increased with high-resolution IMRT for patients showing large intratumoral variations.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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