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Dynamic contrast enhanced magnetic resonance imaging for hypoxia mapping and potential for brachytherapy targeting

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ABSTRACT

Background and purpose: Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) may be used to visualize tumor hypoxia, and was in this work explored in treatment planning of hypoxia-guided brachytherapy of patients with locally advanced cervical cancer (LACC).
Materials and methods: Pharmacokinetic A_{Brix} maps were derived from DCE-MR images taken prior to chemoradiotherapy of 78 patients with LACC. A logistic regression procedure was used to segment the tumor volume fraction from the A_{Brix} maps that showed the strongest association with patient survival, denoted biological target volume (BTV) fraction. A hypoxia gene score was calculated from a biopsy-based gene signature and correlated against the BTV fraction. Brachytherapy planning based on the A_{Brix} maps was performed, for 23 patients. A general planning aim was a minimum D_{90} dose of 7.5 Gy to the tumor per brachytherapy fraction. Two planning approaches were explored: (1) a conventional uniform and (2) a non-uniform approach targeting the BTV to the highest dose possible.
Results: The segmented BTV fraction was significantly associated local and locoregional control ($P = 0.025$) and the hypoxia gene score ($P = 0.002$). Comparing brachytherapy approaches 1 and 2, it was possible to dose escalate the BTV with 0.4 Gy per fraction in median (D_{90}; cohort range [0, 3.8]). Some tumors could not be dose escalated without violating the dose constraints to the organs at risk.
Conclusions: Tumor regions associated with hypoxia may be targeted with brachytherapy. The presented methodology may become useful in future strategies to improve cure probability of resistant tumors.

1. Introduction

Radiotherapy (RT) is the treatment of choice for patients with locally advanced cervical cancer (LACC), and is normally given as a combination of external- and internal RT (brachytherapy). Despite improvements in radiotherapy imaging and delivery, patients still experience relapse and/or radiation-induced toxicity in critical organs within the pelvis [1]. It is therefore important to investigate new treatment strategies, especially for high-risk patients. One possible strategy is to give patients with resistant disease a higher dose to the entire tumor, also called uniform dose escalation. Another approach would be to only boost the radioresistant regions within the tumor while giving the rest of the tumor a lower (conventional) dose; a non-uniform dose escalation or dose painting [2]. This could potentially give a higher tumor control and at the same time an acceptable level of radiotoxicity compared to the uniform approach.

The tumor oxygen level has a large influence on tumor cells' radiosensitivity [3], and hypoxia (oxygen deficiency) is one of the most important biological factors that impact radiotherapy outcome [4]. In order to escalate the dose to hypoxic tumor regions, a clinically feasible method to identify these regions must be developed. Functional medical imaging like DCE-MRI may potentially be used for this purpose. In DCE-MRI a contrast agent is injected into the patient's blood stream and the temporal uptake of the agent is depicted. Through pharmacokinetic analysis of the

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contrast uptake curves, biological information can be extracted from the images. The pharmacokinetic parameter A_{Brix} in the so-called 'Brix' pharmacokinetic model has been shown to reflect tumor hypoxia measured invasively by Eppendorf histography [5]. Furthermore, we have shown that A_{Brix} is associated with chemoradiotherapy outcome and a hypoxia gene signature in cervical tumors [6–8], suggesting that A_{Brix} maps can be used to visualize radioresistant, hypoxic regions. Moreover, the straightforwardness of the 'Brix' modelling approach makes A_{Brix} an appealing parameter for clinical use [8]. Still, methods to extract hypoxic regions from the A_{Brix} maps and strategies to combat these hypoxic areas with radiation are lacking.

In the current work, the purpose was to explore an approach where A_{Brix} maps were segmented using a center/width segmentation procedure. The relationship between the segmented volume fraction and a previously published hypoxia gene signature was investigated. We further carried out brachytherapy planning where two treatment plans were created; one with uniform dose escalation to the entire tumor and another with non-uniform dose escalation to the segmented hypoxic regions. Lastly, the resulting dose distributions to tumor and organs at risk were compared for the two plans.

2. Materials and methods

2.1. Patients, MRI and pharmacokinetic analysis

The included cohort of 78 women with LACC and the MR imaging protocol have been described in detail in a previous study [9]. Briefly, all patients received radiotherapy with concomitant cisplatin. Radiotherapy was given over 5 weeks by external beam radiotherapy (EBRT) (25 fractions; 2 Gy/fr to tumor, 1.8 Gy/fr to pelvis) and intracavitary brachytherapy (6–7 fractions; 4.2 Gy/fr). The patients were followed up by clinical examinations every 3–6 months, and median follow up time was 56 months. Endpoints were local control (LC; control with the gross tumor volume), locoregional control (LRC; control within the irradiated pelvic volume including regional lymph nodes except the paraaortal nodes) and progression-free survival (PFS; survival without locoregional and/or distant relapse). The study was approved by the national health ethics board, and written informed consent was obtained from all patients.

MRI was performed on a 1.5 T Signa Horizon LX tomograph (GE Medical Systems, Milwaukee, Wisconsin). The patients had DCE-MRI prior to treatment. The imaging protocol also included axial T2-weighted fast spin echo images. DCE-MRI was recorded with an axial T1-weighted fast spoiled gradient recalled (FSPGR) sequence, with the entire tumor volume in the field of view. A fast manual bolus injection of gadopentetate dimeglumine (Gd-DTPA) (Magnevist®; Schering, Berlin, Germany) with a dose of 0.1 mmol/kg body weight was used. The DCE-MRI sequence comprised 14 image series during a time period of 5 min; one series recorded before the bolus injection and 13 after. The temporal resolution varied from 15 s (early time points) to 1 min (late time points). The previously defined gross tumor volume (GTV) [9] was transferred to the DCEMRI series. The *Brix* pharmacokinetic model was fitted to the time-enhancement characteristics voxel-by-voxel using least squares minimization, producing A_{Brix} (amplitude) maps for each patient [8].

2.2. Image segmentation

Assume that the tumor is composed of a set voxels, where each voxel has a given image value. The center (C) and width (W) defines the image value interval considered for display of an image. The volume fraction *VF* of the tumor for a given center/width thus corresponds to the relative number of voxels found within that interval of values;

$$VF = \frac{N_{[C-W/2,C+W/2]}}{N_{TOT}} \quad (1)$$

Here, $N_{[C-W/2,C+W/2]}$ is the number of tumor voxels within a given center/width, and N_{TOT} is the total number of tumor voxels (proportional to the tumor volume). If VF is negatively associated with treatment outcome, tumors with large fractions may be interpreted as predominantly having treatment resistant cells. For instance, tumors with a high hypoxic fraction are known to be less radiosensitive. Furthermore, associations between chemoradiotherapy outcome and VF may be explored using logistic regression:

$$p(VF) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 VF)}} \quad (2)$$

where p is the probability of treatment failure and β_0 and β_1 are regression coefficients. Treatment outcome was defined from progression free survival (PFS), giving zero for cancer-free patients and unity for patients with relapse. PFS was used, as this provided a balanced set of responders and non-responders (46 and 32 patients, respectively). Repeating this procedure systematically for many center/width permutations allows the identification of the center/width giving the highest β_1, i.e. the strongest association with outcome. This specific center/width thus points at the region (s) within the tumor of highest relevance with respect to treatment resistance and was used for segmentation of a new treatment volume within the GTV; the biological target volume (BTV).

To confirm that the relationship to outcome was retained for the segmented fractions, the BTV fractions were included in a Kaplan-Meier analysis, where patients were divided into two equally sized groups and differences in outcome between the groups were assessed by log-rank test. Here, local and locoregional control were considered.

2.3. Hypoxia gene signature

To investigate whether BTV reflected tumor hypoxia, the BTV fraction was analyzed against the hypoxia gene signature which was identified in previous work on the present patient cohort [6]. In brief, gene expression profiles of pretreatment biopsies from 46 of the tumors were measured by Illumina bead arrays human WG-6 v3 (Illumina Inc.). A relationship between the gene expressions and hypoxia was shown by gene set and ontology analyses. A gene expression signature of 31 key hypoxia responsive genes was created [6]. As a measure of the signature a hypoxia gene score was calculated for each tumor by averaging the median centered expression levels for the 31 genes. The association between the hypoxia gene score and the BTV fraction was estimated by first order linear regression.

2.4. Brachytherapy treatment planning

To investigate the feasibility of increasing the dose to the BTV using brachytherapy, 23 patients were randomly selected from the total cohort of 78 patients. Oncentra Planning (Nucletron, an Elekta company, Veenendaal) was used for treatment planning. The T2-weighted axial image series including the GTV and the BTV were imported into the treatment planning system using the DICOM standard. The bladder, rectum, and sigmoid colon were delineated for all the patients.

For locally advanced cervical cancer, brachytherapy is typically carried out 3–5 weeks after start of EBRT. Since the MR image acquisition was performed prior to EBRT there was no applicator present in the patient. To simulate a brachytherapy situation a