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Functional imaging

Tumor perfusion increases during hypofractionated short-course radiotherapy in rectal cancer: Sequential perfusion-CT findings

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ABSTRACT

Purpose: The purpose of this study was to investigate perfusion of rectal tumors and to determine early responses to short-course hypofractionated radiotherapy (RT).
Material and methods: Twenty-three rectal cancer patients were included, which underwent perfusion-CT imaging before (pre-scan) and after treatment (post-scan). Contrast-enhancement was measured in tumor and muscle tissues and in the external iliac artery. Perfusion was quantified with three pharmacokinetic parameters: K^{trans}, v_e and v_p. Perfusion differences between tumor and normal tissue and changes of the pharmacokinetic parameters between both scans were evaluated.
Results: The median tumors K^{trans} values increased significantly from the pre-scan (0.36 ± 0.11 (min^{-1})) to the post-scan (0.44 ± 0.13 (min^{-1})) ($p < 0.001$). Also, histogram analysis showed a shift of tumor voxels from lower K^{trans} values towards higher K^{trans} values. Furthermore, the median K^{trans} values were significantly higher for tumor than for muscle tissue on both the pre-scan (0.10 ± 0.05 (min^{-1}), $p < 0.001$) and the post-scan (0.10 ± 0.04 (min^{-1}), $p < 0.001$). In contrast, no differences between tumor and muscle tissues were found for v_e and v_p. Also, no significant differences were observed for v_e and v_p between the two pCT-imaging time-points.
Conclusions: Hypofractionated radiotherapy of rectal cancer leads to an increased tumor perfusion as reflected by an elevated K^{trans}, possibly improving the bioavailability of cytotoxic agents in rectal tumors, often administered early after radiotherapy treatment.
 Radiotherapy and Oncology 94 (2010) 156–160

Radiotherapy (RT), alone or with chemotherapy, is an established treatment for patients diagnosed with rectal cancer [1–3]. In tumors judged to be resectable, pre-operative RT is primarily used to lower the risk of local failure [4–6]. For this purpose, short-course hypofractionated RT (5×5 Gy) followed by immediate surgery has been extensively used. However, several trial initiatives are currently ongoing to modulate the schedule of short-course hypofractionated RT from immediate surgery to a planned delay before surgery with the possible advantage of tumor down-sizing. Further knowledge of the biological changes of the tumor during short-course RT would be useful to optimize the treatment management and to improve the development of response predictors, allowing individualized treatment.

Perfusion Computed-Tomography (pCT) imaging is increasingly used in clinical studies as a non-invasive technique to assess the microvascular status of tumor tissue [7–13]. pCT-imaging is a dynamic imaging technique, which can give insight in the uptake kinetics of the administered tracer by pharmacokinetic modeling [14]. A for pCT-imaging commonly applied pharmacokinetic two-compartment model for perfusion imaging is the extended Kety-model, with the following pharmacokinetic parameters: the trans-endothelial volume transfer constant K^{trans}, the fractional volume of the extravascular-extracellular space (EES) (v_e) and the fractional blood plasma volume v_p [14,15]. For cancer research, K^{trans}, describing the transfer rate of the contrast agent from the blood plasma into the EES, is the most valuable pharmacokinetic parameter, related to the microvascular blood flow, vessel wall permeability and vessel density [14].

pCT-measurements have been shown to serve as early markers of treatment response [9–12,16]. Tumors with a high K^{trans} tend to better respond to chemotherapy and/or radiotherapy treatment than tumors with lower values of K^{trans}, blood volume and/or blood flow [9–12,16–18]. However, little is known about therapy-related

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changes of the perfusion parameters of tumor tissue. Wang et al. presented the predictive strength of repeated pCT-imaging, with a decrease of the permeability being predictive for a higher progression-free survival period in non-small cell lung cancer patients treated with chemotherapy [12].

To the best of our knowledge, no study has yet examined early changes in tumor perfusion in response to radiotherapy treatment of rectal cancer.

The purpose of this study was to investigate perfusion of rectal tumors and responses to hypofractionated short-course RT. This could give important insight into early changes in the tumor microcirculation during radiotherapy and might help to better predict tumor response.

Material and methods

Patient characteristics

Twenty-three patients, diagnosed with non-locally advanced rectal cancer (NLARC), were included in this study. Based on pre-treatment magnetic resonance imaging (MRI), the clinical TNM staging was staged as T I–III, N 0–II, M 0–I. All patients were referred to pre-operative treatment with short-course RT, 5 fractions of 5 Gy on five consecutive working days, followed by a total mesorectal excision (TME) within 3 days after the last RT fraction. According to the Dutch law, the medical ethics committee approved the trial and all patients gave written informed consent before entering the study.

PET-CT and pCT acquisition

All patients underwent FDG-PET-CT and pCT-imaging at two time–points: prior to the start of therapy and at the day of the last RT fraction. All PET-CT and pCT examinations were performed on the same dedicated Siemens TruePoint Biograph 40 PET-CT simulator (Siemens Medical, Erlangen, Germany). The patients were positioned equal to the radiotherapy treatment position using a laser alignment system to have minimal variations between imaging and treatment conditions and between the two imaging time-points. For the PET-CT scan, an intravenous injection of FDG (weight [kg] * 4 + 20 MBq) was performed. For PET reconstruction (OSEM2D: four iterations, eight subsets), CT-based attenuation correction; 3D scatter- and decay-correction were performed. After the PET-CT scan, a pCT-scan was performed over 100 s. The volume of interest (VOI) for the pCT-scan was defined by an expert radiation oncologist (J.B. or G.L.) with knowledge of the PET-data. To ensure that the most representative tumor area was chosen, the tumor area with the highest FDG-uptake on the PET-scan was selected. Knowledge of the FOV selected for the first pCT-scan was used to select the identical region for the second pCT-scan.

For the pCT-scan, a volume of 120 of an iodinated contrast agent (300 mg iodine/mL, Xenetix 300, Guerbet, Aulnay-sous-Bois, France) was injected at a rate of 3 mL/s via an automatic injector (Stellant Sx, CT Injection System, MedRad, Warrendale, USA) into the antecubital fossa.

The pCT-scan was performed in a static cine-mode over 12 contiguous slices with a slice thickness of 2.4 mm, a field-of-view of 500 mm and an image size of 512 × 512 pixels. Other acquisition settings were: tube voltage 80 kVp, tube current 140 mAs and a rotation time of 1 s.

Pharmacokinetic analysis

Automatic image-registration between the static PET-CT scan and the pCT-scan was performed based on mutual-information (Focal software, version 4.34, CMS Inc., St. Louis, Missouri). For each PET-CT scan, the tumor was delineated with dedicated software (TrueD VC50, Siemens MI, Erlangen, Germany) using automated SUV-thresholding of the PET-images with the threshold (percentage of SUV_{max} within the tumor) depending on the tumor-to-background signal ratio, with the gluteus muscle selected as relevant background tissue [19,20]. As a reference sample for the pharmacokinetic analysis, an additional VOI was manually selected within the gluteus muscle to check for possible changes of the pharmacokinetic parameters of muscle tissue outside the irradiated volume. When quantifying the pharmacokinetic parameters of muscle tissue, a VOI was manually drawn within both the left and right gluteus muscle. The median values of the pharmacokinetic parameters within both VOIs were averaged to account for intra-tissue heterogeneity of the muscle tissue. The resulting contours of both tumor and muscle tissues were projected on the registered pCT. The pCT-data were down-sampled from a voxel size of 0.98 × 0.98 × 2.4 mm to 3.92 × 3.92 × 4.8 mm to improve the signal-to-noise ratio (SNR). For the quantification of the dynamic pCT-data, the extended Kety-model was used, describing the uptake of a contrast agent from the blood plasma into the tissue by [14]:

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(u) e^{\frac{-K^{trans}}{v_e}(t-u)} du$$

The blood plasma concentration curve (C_p), extracted from the right external iliac artery, was derived from the acquired whole blood tracer concentration (C_b) divided by (1-Hct), with the hematocrit value (Hct) set to 0.45 (Fig. 2) [14]. To improve the SNR, C_p was calculated by averaging the concentration time curves over all voxels selected inside the iliac artery. The tumor and muscle tissue concentration curves (C_t) were extracted from the dynamic

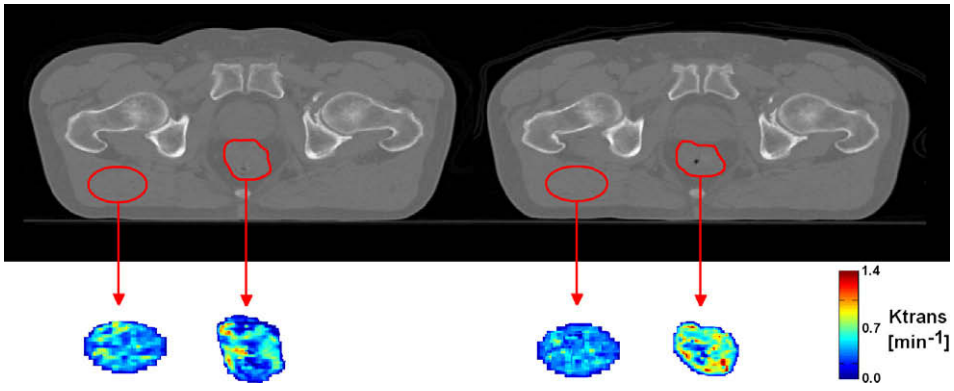

Fig. 1. Comparison between a perfusion-CT-image on a pre-treatment (left) and post-treatment (right) scan for a representative patient. The upper row displays the anatomic pre-contrast CT-images, the lower row the K^{trans} maps of the muscle and tumor tissue regions. Note the increased values of K^{trans} in the tumor tissue on the post-treatment scan compared to the pre-treatment scan. In contrast, muscle tissue presented with similar pattern of K^{trans} at both time-points.