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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 ($0.36 \pm 0.11 \text{ (min}^{-1}\text{)}$) to the post-scan ($0.44 \pm 0.13 \text{ (min}^{-1}\text{)}$) ($p < 0.001$). 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 ($0.10 \pm 0.05 \text{ (min}^{-1}\text{)}$, $p < 0.001$) and the post-scan ($0.10 \pm 0.04 \text{ (min}^{-1}\text{)}$, $p < 0.001$). 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.

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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 ($5 \times 5 \text{ Gy}$) 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.

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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

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]^{0.15} × 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 se-

lected. 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]:

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

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.

Fig. 2. Scatterplots showing the median K^{trans} , v_e and v_p values within tumor and muscle tissues at the perfusion-CT-scans before (pre) and after (post) radiotherapy treatment. Each dot represents the median value of the pharmacokinetic parameter of one patient. Note the increase of K^{trans} within the tumor after treatment, whereas the median K^{trans} values of muscle tissue outside of the irradiated volume remained stable.

pCT-data on a voxel-by-voxel basis and on a tumor uptake curve based on the average of all tumor voxels (Fig. 2). Pharmacokinetic analysis was performed using in-house developed software in MATLAB (R2008b, The Mathworks Inc., Natick, USA). The concentration time curves from pCT-data were fitted to the pharmacokinetic model, with the pharmacokinetic parameters being calculated using the Levenberg–Marquardt algorithm, with boundaries set to $0 \leq K^{trans} \leq 5 \text{ min}^{-1}$, $0 \leq v_e \leq 1$ and $0 \leq v_p \leq 1$ [21–23].

Statistical analysis

All data are expressed as means $\pm$ standard deviation (SD) and range. Statistical differences between the parameters were evalu-

ated in SPSS (version 15.0, SPSS Inc., Chicago, IL, USA), performing a Wilcoxon-signed-rank test for the comparison of related measurements. Differences were considered to be significant when the p -value was less than 0.05.

Results

Perfusion of tumor and muscle tissues

To study differences in the perfusion of tumor and normal tissue, 23 patients diagnosed with rectal cancer underwent sequential pCT-imaging before and after treatment. From these scans, the pharmacokinetic parameters of tumor and normal tissue were calculated at both imaging time-points. In Fig. 1, CT-images of a

representative patient are shown with the perfusion K^{trans} maps of both tumor and muscle tissues at both time-points. Visual interpretation of the K^{trans} maps showed a higher and more heterogeneous uptake in tumor tissue compared to muscle tissue on both scans. Note the increased K^{trans} in tumor tissue on the post-treatment scan compared to the pre-treatment scan, whereas K^{trans} in muscle tissue presented similar patterns at both imaging time-points.

Perfusion parameters before and after short-course radiotherapy

For the quantification of the pharmacokinetic parameters, the median K^{trans} , v_e and v_p values of tumor and muscle tissues were calculated at both time-points. Fig. 2 shows scatterplots of the median parameter values for tumor and muscle tissues. After RT, an increase of the median K^{trans} within the tumor was found for all patient except one, resulting in an average increase of K^{trans} of $25.4 \pm 28.7\%$ (range: -3.8 – 113.1%) ($p < 0.001$). However, the median K^{trans} values within the muscle tissue was not significantly different between the two imaging time-points ($p = 0.554$). The other two pharmacokinetic parameters, v_e and v_p , showed no significantly different values between the two time-points and between tumor and muscle tissues. In Table 1, an overview of all median parameter values is shown with the corresponding statistics.

In Fig. 3, the average histogram of the K^{trans} values within the tumor is shown for all patients. As can be seen from the histogram, pre-operative treatment with short-course hypofractionated RT resulted in an increased tumor perfusion for the included patients.

For the bins of the histogram presenting the number of voxels with a relatively high K^{trans} value, an increase of the number of voxels was observed between the pre- and post-treatment pCT-scan. In contradiction, a decrease was found for the number of voxels in the bins with a lower K^{trans} value. The shift of the histogram towards increased bins with relatively higher K^{trans} indicates an increase of tumor perfusion due to pre-operative treatment with short-course hypofractionated RT.

Discussion

The purpose of this study was to characterize changes of tumor perfusion after short-course hypofractionated radiotherapy treatment. The pharmacokinetic parameters of rectal tumors revealed significant higher K^{trans} values compared to muscle tissue at both the pre- and post-treatment pCT-scan. Short-course RT resulted in a significant increase of the median K^{trans} in tumor tissue, indicating an early increase in tumor perfusion already on the last day of pre-operative RT. The significant increase of tumor perfusion during the rather short time interval between the pre- and post-treatment pCT-scan could be explained by first endothelial cell death within the irradiated volumes, resulting in endothelial cell leakage which in turn results in increased values of K^{trans} within

Fig. 3. Histogram of the K^{trans} values within the tumor for all of the included patients on the pre-treatment scan (dark boxes) and post-treatment scan (light boxes). The bars represent the mean and the error-bars the standard deviation of the K^{trans} estimates within the bin. Note the increase of the number of voxels within the bins with a higher K^{trans} value (>0.4) after pre-operative treatment with short-course hypofractionated radiotherapy, indicating an increase of tumor perfusion after radiotherapy treatment.

the tumor. The VOI manually selected within muscle tissue was chosen outside of the irradiated volume, so no endothelial cell death was expected to occur within the VOIs of muscle tissue. An increase in tumor perfusion early during pre-operative treatment might improve the availability of cytotoxic agents of chemotherapy to the tumor, often administered after finishing the radiotherapy treatment. The data as presented within this study could serve as reference data of perfusion changes within the tumor during RT-treatment for future studies combining a short-course hypofractionated radiotherapy course with anti-angiogenic agents (e.g., rapamycin).

In general, perfusion measurements are intrinsically variable due to internal and external factors, including day-to-day physiological variations, technical variability, observer variability and intra-tissue heterogeneity [24]. The used acquisition time of 100 s was long enough to perform measurements of K^{trans} , whereas measurements of v_e require imaging times which incorporate the maximal signal enhancement in the tumor tissue, about 120–180 s after injection of the contrast agent [25,26]. For this reason, the relatively short imaging time used within this study might bias the v_e values measured within this study. The used sampling time of 1 s was expected to be sufficient for reliable estimations of both K^{trans} and v_p [15,26].

One of the major limitations of this study was the relatively small dimension of the FOV of the pCT-scan in craniocaudal direction. The craniocaudal coverage of the pCT FOV of only 2.88 cm resulted for some patients in an incomplete coverage of the rectal tumor. For these patients, pCT-measurements were obtained from the tumor region showing the highest FDG-uptake, as assessed from the static PET-CT scan. Due to incomplete tumor coverage, the calculated median values of the three investigated pharmacokinetic parameters only represent the perfusion of the tumor region covered by the FOV. However, Goh et al. presented a study showing that an increased FOV in craniocaudal direction does not improve the reproducibility of perfusion measurements [27]. Another limitation was that day-to-day differences in bladder and rectum filling, hampering a voxel-wise comparison of the pharmacokinetic parameter maps of the pre- and post-treatment pCT-scans within this study. Due to large differences in bladder or rectum filling for some of the included patients, a rigid registration was not sufficient to enable a correct registration of the pre- and post-treatment pCT-scans. However, available non-rigid registration algorithms are not yet properly validated for rectal cancer.

In conclusion, perfusion-CT measurements of rectal tumors enable the assessment of changes of tumor perfusion resulting from

Table 1

Overview of the median pharmacokinetic parameters, K^{trans} , v_e and v_p , in tumor and muscle tissues both pre- and post-treatment.

		Pre-RT	Post-RT	p-value
K^{trans} (min ⁻¹)	Tumor tissue	0.36 ± 0.11	0.44 ± 0.13	<0.001
	Muscle tissue	0.10 ± 0.05	0.10 ± 0.05	0.554
	p-value	<0.001	<0.001	
v_e (–)	Tumor tissue	0.31 ± 0.10	0.32 ± 0.09	0.795
	Muscle tissue	0.28 ± 0.05	0.29 ± 0.03	0.381
	p-value	0.356	0.344	
v_p (–)	Tumor tissue	0.04 ± 0.02	0.04 ± 0.02	0.124
	Muscle tissue	0.03 ± 0.01	0.03 ± 0.01	0.098
	p-value	0.266	0.266	

radiotherapy treatment. Short-course hypofractionated radiotherapy of rectal cancer significantly increased tumor perfusion (K^{trans}), which might improve the bioavailability of cytotoxic agents in rectal tumors, often administered to the patient after radiotherapy treatments.

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