Variability and Reproducibility of 3rd-generation dual-source dynamic volume perfusion CT Parameters in Comparison to MR-perfusion Parameters in Rectal Cancer

Sonja Sudarski1, Thomas Henzler1, Teresa Floss1, Tanja Gaa2, Mathias Meyer1, Holger Haubenreisser1, Stefan O. Schoenberg1 & Ulrike I. Attenberger1

To compare in patients with untreated rectal cancer quantitative perfusion parameters calculated from 3rd-generation dual-source dynamic volume perfusion CT (dVPCT) with 3-Tesla-MR-perfusion with regard to data variability and tumour differentiation. In MR-perfusion, plasma flow (PF), plasma volume (PV) and mean transit time (MTT) were assessed in two measurements (M1 and M2) by the same reader. In dVPCT, blood flow (BF), blood volume (BV), MTT and permeability (PERM) were assessed respectively. CT dose values were calculated. 20 patients (60 ± 13 years) were analysed. Intra-individual and intra-reader variability of duplicate MR-perfusion measurements was higher compared to duplicate dVPCT measurements. dVPCT-derived BF, BV and PERM could differentiate between tumour and normal rectal wall (significance level for M1 and M2, respectively, regarding BF: p < 0.0001*/0.0001*; BV: p < 0.0001*/0.0001*; MTT: p = 0.93/0.39; PERM: p < 0.0001*/0.0001*), with MR-perfusion this was true for PF and PV (p-values M1/M2 for PF: p = 0.04*/0.01*; PV: p = 0.002*/0.003*; MTT: p = 0.70/0.27*). Mean effective dose of CT-staging incl. dVPCT was 29 ± 6 mSv (20 ± 5 mSv for dVPCT alone). In conclusion, dVPCT has a lower data variability than MR-perfusion while both dVPCT and MR-perfusion could differentiate tumour tissue from normal rectal wall. With 3rd-generation dual-source CT dVPCT could be included in a standard CT-staging without exceeding national dose reference values.

Magnetic resonance imaging (MRI) is the accepted gold standard for local staging of rectal cancer prior to treatment1–4. Despite the infiltration of the mesorectal fascia being to date the most important T-stage criterion for treatment decisions in colorectal carcinoma, it is known, that molecular subtypes of rectal cancer occur even within the same clinical T-stages do result in heterogeneity in terms of treatment response and overall survival5. Therefore new criteria have to be established to better differentiate these patient groups a-priori to treatment as well as during response assessment6. One possibility to further characterize rectal cancer lesions in MR beyond morphologic criteria is functional imaging: Quantitative MR-perfusion values were proven to be reproducible within small variation ranges between readers7. Previous research suggested a role for MR-perfusion as an imaging-based biomarker for the improved assessment and prediction of therapeutic response alone8,9 or together with other parameters as multi-parametric MRI10–13 in the neo-adjuvant setting of locally-advanced rectal cancer.

Computed tomography (CT) perfusion values have shown to be robust and reproducible due to linear signal intensity characteristics of the Hounsfield units scale which is a prerequisite for a technique intended to be used for therapeutic response assessment/prediction. Several studies have investigated the accuracy and the additional value of CT perfusion in therapeutic response assessment/prediction in/of different tumour entities also in rectal cancer14–19. The main disadvantage of CT perfusion has always been the amount of radiation dose the patient was exposed to.

1Institute of Clinical Radiology and Nuclear Medicine, University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. 2Computer Assisted Clinical Medicine, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. Correspondence and requests for materials should be addressed to S.S. (email: sonja.sudarski@medma.uni-heidelberg.de)
In the past few years, with the advent of new dose-saving CT scanner generations featuring e.g. noise-reduction algorithms during post-processing, perfusion analysis by means of CT has become a more practicable alternative to perfusion MRI.

To the best of our knowledge, dynamic volume perfusion CT (dVPCT) featuring noise-reduction as well as motion-correction algorithms by means of 3rd generation dual-source CT scanner systems was not yet evaluated in direct comparison to MR-perfusion performed on a 3 Tesla MR scanner system in the same patients with primary and untreated rectal cancer. Our study goals were therefore to prospectively investigate quantitative perfusion parameters derived from 3rd generation dual-source dVPCT with regard to intra-individual variability of measurements, intra-reader variability, accurate differentiation of tumour from normal rectal wall and with regard to the possibility to include the perfusion scan in a CT (re-)staging protocol without exceeding radiation dose recommendations for the CT staging.

Methods

Study protocol. This prospective single-centre study was performed according to standards of the Health Insurance Portability and Accountability Act (HIPAA) and the Declaration of Helsinki and in accordance with the guidelines of our institutional ethics committee, the “Medizinische Ethikkommission II of the Heidelberg University at the University Medical Centre Mannheim”, which was the committee having approved the study design and study sequences acquired with MRI and CT in the study participants. All study participants gave written informed consent before inclusion in the study. Patients with clinically indicated MR of the pelvis at a 3 Tesla MR scanner system for local staging and clinically indicated staging CT of the chest and abdomen to screen for distant metastases were prospectively and consecutively enrolled. All patients that were asked to participate in the study had undergone colorectal (re-)staging CT and had suspected rectal cancer.

In case of consent to participate, they underwent a standard staging protocol for rectal cancer including MR-perfusion sequence as reference standard and within 14 days in the framework of their staging for distant metastases by means of contrast-enhanced CT scan of the chest and abdomen, they underwent the additional study CT perfusion sequence over the region of their tumour including a second i.v. contrast bolus.

Inclusion criteria were age >18, and capability of giving consent.

A-priori exclusion criteria were CT contrast media allergic reaction history, renal insufficiency, pregnancy. A-posteriori exclusion criteria were >14 days between MR and CT examination, missing or non-diagnostic MR-or CT perfusion sequence e.g. due to insufficient rectal filling because of stenotic tumour or artefacts due to hip implants. 28 consecutive patients were prospectively enrolled. Final analysis could be performed with 20 patients (60 ± 13 years; 14 men; 6 women), see Fig. 1 for study patient selection. According to TNM-classification the investigated tumours were distributed as follows: T1 tumours: 0, T2: 4, T3: 15, T4: 1. All patients were revealed to suffer from adenocarcinoma; 3 patients did not undergo surgery. In these 3 patients, histopathological diagnosis was reached by punch biopsy in the course of coloscopy/recto-sigmoidoscopy.

Data acquisition. MR-Data was acquired on a 3 Tesla scanner system (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany). A 6-element-body-matrix-coil was used and patients got rectal filling with 100 mL of ultrasound gel. They underwent their distinct examination protocol including a 3D TWIST MR-perfusion sequence with the following parameters TR/TE/FA = 3.6 ms/1.44 ms/15°, matrix-size = 192×117, FOV = 259 mm×158 mm, 20 slices. Temporal resolution was 5 s and in total 70 volumes were acquired (Video 1). Gadolinium based contrast agent (Dotarem, Guerbert, France) was injected at a dose of 0.1 mmol/kg after the 10th volume at a flow rate of 1.5 mL/s.

dVPCT was acquired on a 2 × 192 slice dual-source CT system (Somatom Force, Siemens Healthineers, Erlangen, Germany). Patients got rectal filling with 100 mL of ultrasound gel a-priori to CT data acquisition. Depending on patient’s body weight, tube voltage was set to 80, 90 or 100 kVp. A dynamic shuttle-mode perfusion protocol was planned on the a-priori performed CT staging exam of chest and abdomen with the following acquisition protocol in dual-energy technique: tube voltage 90/150 Sn (Sn = use of a tin filter for spectral shaping); tube current time product (ref.) 10/85 mAs; 80 mL (Iodine concentration 400 mg iodine/mL) of i.v. contrast (Imeron, Bracco Imaging, Germany); monophasic chest exam performed during arterial phase; biphasic upper abdomen exam performed during arterial phase and portal-venous phase monophasic portal-venous phase pelvic exam). The dVPCT scan was performed 15 minutes after the portal-venous phase abdominal scan was completed. 50 mL (Iodine concentration 400 mg iodine/mL) of i.v. contrast (Imeron, Bracco Imaging, Germany) were applied via an 18 G peripheral catheter. Highest temporal resolution during arterial phase was 1.5 s and in total 19 scans were acquired (Video 2). See Table 1 for the detailed CT perfusion protocol.

Post-processing was performed on a dedicated work-station a-priori to the perfusion analysis on the dVPCT data stack, consisting of a noise-reduction algorithm as well as a motion correction algorithm (Siemens syngo.via CT Body Perfusion VA30, Siemens Healthineers, Erlangen, Germany).

Dose-length-product of the dVPCT study sequence and of the total CT examination consisting of the staging CT scan and the dVPCT scan were assessed. The total CT examination was designed to adhere to national diagnostic reference values by the German Federal Office for Radiation Protection for standard a CT chest scan and biphasic abdominal scan valid at the time-point of patient enrolment.

Image analysis. As morphological gold standard to accurately choose the tumour region and normal rectal wall, high-resolution para-axial T2 TSE MR images were used.

MR: Perfusion quantification was performed as follows: a region-of-interest (ROI) was carefully manually drawn to delineate the tumour in a representative slice within the maximum area of circumferential tumour burden (see Figs 2 and 3), as well within normal rectal wall distant from the tumour. To estimate the arterial input function (AIF), another ROI was drawn in one of the iliac arteries (common or external) or femoral superficial artery visible (see Fig. 3) depending on the specific tumour position within the rectum using the Osirix DICOM
Figure 1. Study patient selection.

| Parameter                        | Value                          |
|----------------------------------|--------------------------------|
| Scan area                        | Pelvis                         |
| Scan mode                        | VPCT                           |
| Scan length                      | 11.4 mm                        |
| Scan direction                   | Adaptive 4D spiral             |
| Tube voltage                     | 80, 90 or 100 kVp              |
| Tube current                     | 220, 150 or 100 mA.s, respectively |
| Dose modulation                  | —                              |
| Rotation time                    | 0.33 s                         |
| Cycle protocol                   | 2 × 3 s; 10 × 1.5 s; 3 × 4.5 s; 4 × 9 s |
| Max. temporal resolution         | 1.5 s                          |
| Total cycle time                 | 64 s                           |
| Slice collimation                | 48 × 1.2 mm                    |
| Slice width                      | 1.5 mm                         |
| Reconstruction increment         | 1.0 mm                         |
| Reconstruction kernel            | Br36                            |
| Contrast osmolality              | 400 mg/mL                      |
| Volume                           | 50 mL + 50 mL Saline           |
| Flow rate                        | 5 mL/s                         |
| Start delay of scan              | 5 s after start of contrast injection |

Table 1. Acquisition parameters of the study CT perfusion sequence. kVp = peak kilovoltage; VPCT = volume perfusion CT.
viewer (Pixmeo, Geneva, Switzerland). Perfusion parameters were calculated employing the fast deconvolution algorithm using an in-house developed established perfusion plugin tool (UMMPerfusion)\textsuperscript{23}. Plasma flow (PF) [mL/100 mL/min], plasma volume (PV) [mL/100 mL] and mean transit time (MTT) [s] were estimated in tumour tissue and normal rectal wall.

CT: The noise-reduced and motion-corrected dVPCT data stack was evaluated as follows: ROIs delineating the tumour tissue and normal rectal wall as well as the AIF were drawn in the identical regions and the identical vessel (see Fig. 3) using dedicated software (Siemens syngo.via CT Body Perfusion VA30, Siemens Healthineers, Erlangen, Germany). A variant of the deconvolution algorithm was applied to calculate dVPCT values. Blood flow (BF) [mL/100 mL/min], blood volume (BV) [mL/100 mL], MTT [s] and Permeability (PERM) [mL/100 mL/min] were estimated in tumour tissue and normal rectal wall.

**Figure 2.** Example of corresponding rectal cancer tumour areas in MR and CT and localization of the investigated tumour area within the pelvis: (a) Sagittal view of the rectal carcinoma and localization of the the representative tumour area investigated with perfusion analysis. (b) Coronal view of the rectal carcinoma and localization of the representative tumour area investigated with perfusion analysis. (c) Paraxial MR image from the T1 weighted TWIST angiographic stack perpendicular to the rectum lumen, with representative semicircular tumour area at 3 to 9 o'clock suitable for tumour perfusion analysis. (d) Paraxial CT image from the dVPCT stack perpendicular to the rectum lumen, with the corresponding representative semicircular tumour area at 3 to 9 o'clock suitable for tumour perfusion analysis.

**Figure 3.** Example of corresponding rectal cancer tumour areas and positioning of ROIs for the assessment of arterial input function (AIF) for perfusion: (a) Example of a manually drawn ROI for assessment of AIF over the right superficial femoral artery and a manually drawn ROI for perfusion analysis over a representative slice of tumour area on MR perfusion images. (b) Example of the manually drawn ROI for assessment of the arterial input function (AIF) over the right superficial femoral artery in analogy to (a) and a manually drawn ROI for perfusion analysis in the identical representative slice of tumour area on dVPCT images corresponding to (a).
Deconvolution approaches in general assume that the tissue time concentration curve \( C(t) \) can mathematically be described as convolution of an AIF \( C_a(t) \) with an unknown impulse residue/response function (IRF)\(^{20} \). In this equation, the IRF defines the probability that a molecule of the agent entering the tissue voxel at time-point \( t' \) is still there at time-point \( t \).

\[
C(t) = \int_{-\infty}^{t} C_a(t') \times IRF(t - t') \times dt'
\]  

(1)

In the CT software used in this study a variant of the deconvolution algorithm, namely the AATH model (short for adiabatic approximation to the tissue homogeneity model) including determination of the arterial arrival delay \( \Delta t \) in equation 1 was applied\(^{20} \). In this form it has 6 free parameters: baseline attenuation and arrival delay \( \Delta t \), blood flow \( F \), mean transit time \( MTT \), flow extraction product \( FE \) and a decay parameter containing the extravascular distribution volume\(^{20} \). In the equation of the impulse residue function IRF of the AATH model, the blood volume \( BV \) is calculated from the central volume principle as \( BV = F \times MTT \). PS - or PERM as it is called in our study - (permeability surface area product) is calculated from E (extraction fraction) = \( FE/F \) using the Renkin-Crone equation\(^{20} \). For MR perfusion analysis on the other hand, a fast (model-free) deconvolution algorithm was applied in our study:

\[
f = \text{max} \left[ C_a(t) \otimes^{-1} C_a(t) \right]
\]  

(2)

here, \( C_a(t) \) and \( C_a(t) \) are the contrast material concentrations as the function of time in a region-of-interest (ROI) in the tissue and inside the artery feeding the region of interest (arterial input function), respectively\(^{24} \). The perfusion \( f \) is the maximum value of the tissue impulse response function, i.e. the deconvolution \((\otimes^{-1})\) of the two concentration functions\(^{24} \). Eq. 2 is solved by singular value decomposition (SVD) using a regularization of 0.15 times the maximal singular value\(^{24} \).

The reading was performed by one radiologist (T.H.) with 7 years of experience in abdominal MRI and CT. The complete analysis was performed two times (M1 and M2 with >2 weeks between the 2 time points) to assess intra-reader variability.

**Statistical analysis.** Statistical analysis was performed using dedicated software (SAS, Institute Inc. Software, version 9.4, 2012; Prism Version 7.03 for Windows, GraphPad Software, La Jolla, California, USA, www.graphpad.com; JMP, Version 13.0.0. SAS Institute Inc.; Cary, NC 1989–2007). For the descriptive analysis mean, standard deviation, median, range, skewness and kurtosis of distribution have been assessed for the continuous variables. Variability of measurements is described by the coefficient of variation (CoV) consisting of the percentage of the standard deviation from the means.

Differences between duplicate measurements of the same reader are described by the intra-class correlation coefficient (ICC) and its 95% confidence interval (CI) and results of Bland-Altman analysis. Here, beside the p-value, the arithmetic mean difference of M1 and M2 (95% CI) is given to further describe intra-reader variability of the data. Given the results of d'Agostino-Pearson-tests for the variables, non-parametric testing was further performed: the Wilcoxon sign rank test (for paired data) was used to investigate differences between tumour tissue and non-diseased rectal wall in dVPCT and perfusion MRI parameters. The level of significance was set to \( p = 0.05 \).

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

**Results**

In Table 2 absolute values of the 4 dVPCT parameters and the 3 MR-perfusion parameters, respectively, are listed for measurements M1 and M2 in tumour tissue and normal rectal wall.

| Perfusion Parameter                     | MR-Perfusion M1 | MR-Perfusion M2 | dVPCT M1 | dVPCT M2 |
|----------------------------------------|----------------|----------------|----------|----------|
| Plasma flow/Blood flow [mL/100 mL/min] | 43.9 ± 23.4 (±53%) | 53.9 ± 16.3 (±48%) | 51.7 ± 24.2 (±47%) | 34.8 ± 16.5 (±47%) |
| Plasma volume/Blood volume [mL/100 mL] | 40.9 ± 25.8 (±63%) | 28.5 ± 17.8 (±62%) | 48.0 ± 35.7 (±74%) | 27.6 ± 19.2 (±70%) |
| Mean transit time [s]                  | 60.1 ± 24.6 (±41%) | 50.1 ± 18.2 (±36%) | 56.7 ± 24.3 (±43%) | 40.4 ± 17.2 (±39%) |
| Permeability [mL/100 mL/min]           | 24.1 ± 7.6 (±32%) | 8.3 ± 3.2 (±39%) | 25.0 ± 6.9 (±28%) | 9.0 ± 3.5 (±39%) |

Table 2. Variability of perfusion measurements in tumour tissue and normal rectal wall with MR-Perfusion vs. dVPCT. Legend: Data means ± standard deviation (± coefficient of variation (CoV)).
Table 3. Assessment of Intra-reader variability of MR-Perfusion and dVPCT – Intraclass correlation coefficient analysis. aEstimates the reliability of single ratings. CI = confidence interval.

| Perfusion Parameters | M1 vs. M2 | Rectal wall | M1 vs. M2 | Rectal wall |
|----------------------|-----------|-------------|-----------|-------------|
| Tumour               | Intraclass correlation coefficient* | 95%-CI     | Intraclass correlation coefficient* | 95%-CI     |
| Mean transit time [s] | 0.9240    | 0.8–0.97    | 0.6421    | 0.29–0.84   |
| Blood flow [mL/100 mL/min] | 0.7691    | 0.50–0.90   | 0.6015    | 0.23–0.82   |
| Plasma flow [mL/100 mL] | 0.4638    | 0.04–0.75   | 0.9333    | 0.84–0.97   |
| Blood volume [mL/100 mL] | 0.8912    | 0.75–0.96   | 0.6790    | 0.35–0.86   |
| Plasma volume/ [mL/100 mL] | 0.5773    | 0.19–0.81   | 0.8223    | 0.60–0.93   |
| Mean transit time [s] | 0.8699    | 0.70–0.95   | 0.4963    | 0.08–0.76   |
| Permeability [mL/100 mL/min] | 0.6847    | 0.36–0.86   | 0.1615    | 0.25–0.83   |

Discussion

We found that 3rd generation noise-reduced and motion-corrected dVPCT parameters assessed in patients with rectal cancer have a generally lower intra-individual variability than MR-perfusion parameters, which is true in tumour tissue as well as in normal rectal wall. What is more, dVPCT measurements were found to be reproducible within narrow variation ranges both in rectal cancer tumour tissue and normal rectal wall in the intra-reader variability analysis. We believe that the noise-reduction and motion-correction post-processing algorithms applied before CT perfusion analysis in this study might have added to the observed lower data variability in the first place. If similar post-processing algorithms are going to be established for MR perfusion analysis, the cards will supposedly be reshuffled again.

Our third finding is that dVPCT can differentiate tumour tissue and normal rectal wall by means of BF, PV and PERM measurements. Similar findings were published by Bellomi et al. who found that BF, BV, and permeability-surface area product (PS) were significantly higher in rectal cancer than in normal rectal wall20. Bellomi et al. were using a 16-section multi-detector CT scanner. MTT seems to be rather unhelpful in distinguishing rectal cancer tumour tissue from normal rectal wall. This seems to be true for both dVPCT and MR-perfusion on the basis of our results. Albeit we used similar tracer kinetics models for the calculation of perfusion values in CT and MRI, the deconvolution algorithm-derived (AATH model) absolute dVPCT measurements cannot be directly compared with the fast deconvolution algorithm-derived absolute MR-perfusion measurements as explained in great detail above referring to the publications by Klotz et al.20 and Gaa et al.24. As the approach of the MR perfusion analysis, the fast (model-free) deconvolution algorithm, does not describe two compartments, several perfusion parameters as e.g. permeability surface area product cannot be determined. Therefore, this tracer kinetics model might assumedly not be as interesting for anti-vascular drugs treatment monitoring and response assessment as e.g. two compartment models, where the assumption is made that the tracer in the tissue can distribute in two separate compartments, namely the plasma space and the extracellular extravascular space/interstitial space24. What is more, irrespective of the tracer kinetics model being applied after data acquisition, different contrast bolus application protocols and different lengths as well as differing time-points of data acquisition of the perfusion sequences (also resulting in a different temporal resolution at different time-points) are used in CT compared to MRI. Albeit one study by Kierkels et al.27 that compared absolute values of CT perfusion performed on a 40-slice CT-postion emission tomography system and MR perfusion...
### Table 4. Assessment of Intra-reader variability of MR-Perfusion and dVPCT – Bland-Altman analysis. Arithmetic mean differences are presented as % from the mean of M1 and M2. CI = confidence interval. * indicates statistical significance.

| Perfusion Parameters | MR perfusion Tumour vs. rectal wall | M1 vs. M2 | Arithmetric mean difference (95%-CI) [%] | p-value (H₂, Mean = 0) | dVPCT Tumour vs. rectal wall | M1 vs. M2 | Arithmetric mean difference (95%-CI) [%] | p-value (H₂, Mean = 0) |
|----------------------|-------------------------------------|-----------|----------------------------------------|------------------------|-------------------------------|-----------|----------------------------------------|------------------------|
| Plasma flow [mL/100 mL/min] | 0.1292 | −15.89 (−36.85–5.08) | 0.8233 | −1.01 (−10.30–8.29) | 0.6439 | −2.09 (−11.41–7.23) | 0.0499 | 0.38 (−15.31–16.07) |
| Plasma volume/ [mL/100 mL] | 0.3435 | −9.12 (−28.73–10.52) | 0.2275 | 9.74 (−6.61–26.09) | 0.4788 | −2.02 (−7.86–3.83) | 0.6616 | −3.35 (−19.10–12.41) |
| Mean transit time [s] | 0.1917 | 7.29 (−3.98–18.56) | 0.0409* | 14.33 (0.65–28.01) | 0.4476 | −4.38 (−10.21–7.44) | 0.3721 | −7.49 (−24.63–9.66) |

### Table 5. Tumour vs. normal rectal wall in MR-perfusion and dVPCT. CI = confidence interval. * indicates statistical significance.

| Perfusion parameters | MR-perfusion Tumour vs. rectal wall | M1 vs. M2 | Est. Median Diff (95%-CI) | p-value (H₂, Mean = 0) | dVPCT Tumour vs. rectal wall | M1 vs. M2 | Est. Median Diff (95%-CI) | p-value (H₂, Mean = 0) |
|----------------------|-------------------------------------|-----------|--------------------------|------------------------|-------------------------------|-----------|--------------------------|------------------------|
| Plasma flow/ Blood flow [mL/100 mL/min] | 0.0400* | 7.895 (−2.31–15.79) | 0.0107* | 11.1 (−0.3–26.3) | <0.0001* | 15.8 (30.57–60.73) | <0.0001* | 53.73 (32.56–65.83) |
| Plasma volume/ Blood volume [mL/100 mL] | 0.0020* | 10.50 (8.615–19.32) | 0.0028* | 13.65 (3.9–28.4) | <0.0001* | 3.525 (2.93–3.95) | <0.0001* | 3.795 (2.54–4.91) |
| Mean transit time [s] | 0.0696 | 11.12 (−0.27–22.31) | 0.0266* | 7.75 (6.0–23.7) | 0.9273 | −0.13 (−0.63–0.53) | 0.3884 | −0.415 (−0.93–0.3) |
| Permeability [mL/100 mL/min] | <0.0001* | 14.09 (10.78–18.25) | <0.0001* | 17.33 (9.56–21.28) |

performed on a 3 T scanner system and found that the values of the transfer constant K(trans) did correlate, while fractional extravascular-extracellular space v(e), and fractional plasma volume v(p) did not, one can generally say that CT and MR rectal cancer perfusion analyses cannot alternatingly be used for assessing therapeutic response in patients. Consequently, it is of great interest to define the modality with the best capability to differentiate tumour tissue, with low variability of the data and good reproducibility.

One disadvantage of CT perfusion for to date is the necessity of an extra i.v. contrast bolus for the perfusion sequence. However, with technical advantage and broader use of scanners where low kV settings at sufficiently high tube current power are available, it would also be possible to add a larger range venous scan (thorax and abdomen) for staging purposes immediately after the perfusion study without the need for a second contrast injection. Although, the total amount of iodine applied to the patient would be lower, future studies will probably show that this can be fully compensated for by the increased iodine contrast at low kV.

The biggest disadvantage of dVPCT is the amount of radiation dose which is still applied despite the noise-reduction and motion-correction post-processing algorithms applied before CT perfusion analysis that have led to the possibility to a-priori reduce the dose of the perfusion scan: even by using the shortest possible noise-reduction and motion-correction post-processing algorithms applied before CT perfusion analysis that at the time of data acquisition for prediction of tumour aggressiveness and response in rectal cancer.

**Limitations**

This analysis was performed with a small patient cohort and further research is needed to verify findings. Multiple publications investigated the diagnostic and prognostic value of CT perfusion with regard to tumour histology, presence of distant metastasis, therapeutic response to chemo-radiation therapy as well as overall survival. We did not correlate perfusion parameters with histo-pathological findings, surgical data or outcome data. Furthermore, this analysis focused on absolute perfusion parameter values. However, recently performed research suggests semi-quantitative analysis of pharmacokinetic curves in MR-perfusion as valuable parameter for prediction of tumour aggressiveness and response in rectal cancer. Yet, semi-quantitative perfusion analysis...
was out of the scope of this paper. A crucial bias that all perfusion examinations in CT and MRI are facing is the calculation of the AIF. The approach of this paper was to keep CT ROI for AIF constant to the ROI chosen for MR-perfusion analysis, namely common or external iliac arteries or superficial femoral artery. However, as the blood supply of the rectum is complex, and iliac arteries are prone to present with plaques and stenosis in patients with atherosclerosis, the authors know, that this method can only be a rough approximation of the real AIF. There are multiple approaches to minimize the bias caused by AIF calculation, e.g. by calculating semi-automated and threshold-based a mean AIF from all vessels visible in the perfusion sequences, yet, this approach was out of the scope of this publication.

What was discussed already in great detail above is that the deconvolution algorithm is only one possibility of many to estimate perfusion. It is known, that perfusion values largely differ between different tracer kinetics models, e.g. if compartment models are applied\(^{24,32}\).

Perfusion analysis results might also vary even within the same imaging modality depending on temporal resolution being dependent on z-axis coverage and on cycle protocols if shuttle mode CT perfusion is applied as well as on acquisition duration\(^{20,33}\). Goh et al. found that increasing the temporal interval from 1 to 4 seconds leads to overestimation of tumour blood flow and underestimation of blood transit in distributed parameter analysis\(^{34}\). Therefore, acquisition interval should be shorter than 3 seconds, which was the case with 1.5 s cycle time during arterial inflow phase in our CT studies. Yet, with regard to radiation dose, cycle time was increased up to 9 s towards the end of the 64 s of the perfusion scan. Finally, it is known that perfusion analysis values might even vary due to different versions of the same perfusion software used\(^{35}\).

We did not include inter-reader variability analysis in this paper, but previous publications have investigated this topic for CT\(^{36}\) and MRI, respectively\(^{7}\).

We did not perform detailed evaluation of subjective or objective image quality.

CT scan protocol was designed to adhere to national diagnostic reference values by the German Federal Office for Radiation Protection\(^{22}\) for standard CT chest and abdomen examinations valid at the time-point of patient enrolment. The possibility to include with new CT scanner systems dose-intensive perfusion sequences in CT staging protocols without exceeding dose reference values is very encouraging given accuracy and validity of the perfusion analysis. Given the fact, that there are even attempts of the CT community to overtake T staging\(^{36}\) which is to date clearly regarded as the holy grail of MR in rectal cancer imaging, the idea of a one-stop-shop CT approach in rectal cancer patients quickly comes to one’s mind. However, as dose recommendations for standard CT examinations are constantly updated and national CT dose reference values have been only recently lowered dramatically\(^{22,37}\), further optimization of perfusion CT protocols taking e.g. acquisition duration for dose reduction into account is mandatory to reach this goal in the future\(^{20,36}\).

Conclusions
Our data show that 3rd generation dual-source deconvolution model-derived dVPCT measurements have a lower intra-individual variability than MR-perfusion measurements in rectal cancer patients and are also highly reproducible between the same reader within narrow variation ranges in rectal cancer tumour tissue as well as in normal rectal wall. dVPCT can differentiate tumour tissue and normal rectal wall by means of BF, BV and PERM measurements. With a 3rd generation dual-source CT scanner system, dVPCT could be included into a chest and abdomen CT staging examination in our study without exceeding national diagnostic reference value recommendations.

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Author Contributions
T.H., U.I.A., and S.O.S. designed the study. S.S., M.M., and H.H. contributed to the sample collection. T.H., S.S. and T.F. performed data and image analysis. S.S., and T.F. drafted the manuscript. T.G., U.I.A., T.H. and S.S. revised the manuscript. All authors reviewed the manuscript.

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