Original Investigation

Usefulness of Perfusion CT to Assess Response to Neoadjuvant Combined Chemoradiotherapy in Patients with Locally Advanced Rectal Cancer

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Rationale and Objectives: To prospectively evaluate perfusion computed tomography (CT) for assessment of changes in tumor vascularity after chemoradiation therapy (CRT) in locally advanced rectal cancer and to analyze the correlation between baseline perfusion parameters and tumor response.

Materials and Methods: Twenty patients with rectal cancer underwent baseline perfusion CT before CRT, and in 11 an examination after CRT was also performed. For each tumor, blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability-surface area product (PS) were quantified. The Mann-Whitney U test compared baseline perfusion parameters of responders and nonresponders and pre- and post-CRT measurements were compared by the Wilcoxon signed-rank test ($P < .05$ statistically significant for both tests).

Results: Baseline BF was significantly lower ($P = .013$) and MTT was significantly higher ($P = .006$) in responders. Both were able to discriminate responders from nonresponders with a sensitivity of 80% and 100% and a specificity of 73.3% and 86.7%, respectively, for BF and MTT. Baseline BV and PS were not significantly different in responders and nonresponders. Perfusion parameters changed significantly in post-CRT scans compared to baseline: BF ($P = .003$), BV ($P = .003$), and PS ($P = .008$) decreased, whereas MTT increased ($P = .006$).

Conclusion: Baseline BF and MTT can discriminate patients with a favorable response from those that fail to respond to CRT, potentially selecting high-risk patients with resistant tumors that may benefit from an aggressive preoperative treatment approach.

Key Words: Computed tomography; perfusion; rectal cancer; prognosis.

The multidisciplinary management of rectal cancer patients has been witnessing a progressive change in the therapeutic approach of locally advanced tumors toward preoperative chemoradiation therapy (CRT), which is useful for tumor downsizing and downstaging, facilitating curative resection, decreasing the local recurrence rate, and improving patient survival (1–7). Tumor downstaging may lead to a partial or complete tumor regression, but in many cases, even if the tumor cell density is significantly decreased, the pathologic stage remains the same. The histological tumor response to the preoperative treatment can be assessed by the tumor regression grade (TRG), which may be determined according to different grading systems. One of them, proposed by Dworak et al, was specifically designed for application in rectal cancer (8).

Predicting which tumors will respond well to this therapeutic approach remains a challenge because morphological imaging criteria are unreliable in this regard (9–11). As it is becoming increasingly important that preoperative imaging may noninvasively select high-risk patients who could truly benefit from more aggressive multimodality treatment approaches in the preoperative setting (12,13), there is a growing interest on functional imaging techniques that can help monitor treatment effects. Both magnetic resonance imaging (MRI) and computed tomography (CT) have shown potential to act as functional biomarkers (14–17). Perfusion CT is able to assess vascular physiology within tumors retrieving information about tumor blood flow (BF), blood volume (BV), mean transit time (MTT), and vascular permeability-surface area product (PS) (18–20). These parameters reflect vascular changes occurring in neoplastic tissue, ultimately related to the angiogenic process: BF reflects vascular supply to the lesion, BV reflects functional vascular volume, MTT reflects the time of blood

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through the tumor bed under the influence of vascular density, morphology and shunting, as well as interstitial pressure, and PS reflects leakiness of the microvasculature (21,22).

Two landmark articles have evaluated perfusion CT in the context of rectal cancer assessment before CRT, with good response defined as tumor downstaging (21,23), but to our knowledge there are no published data about its use as a biomarker for treatment monitoring using TRG as endpoint of response to CRT. Thus the purpose of this study was to prospectively evaluate perfusion CT to assess tumor vascularity changes in locally advanced rectal cancer after neoadjuvant CRT and to analyze the correlation between baseline perfusion parameters and tumor response to CRT, as defined by the TRG.

MATERIALS AND METHODS

Patients

Between November 2007 and September 2010, 26 consecutive patients met the inclusion criteria of this prospective study, consisting of: 1) histologically (biopsy) proven nonmucinous rectal carcinoma; 2) locally advanced disease (staged by MRI as T3-4 and/or N positive); and 3) neoadjuvant treatment consisting of long-course CRT followed by surgical resection of the tumor. Patients with a history of allergy to iodinated contrast agents were excluded, as were patients locally nonresectable tumors and/or metastatic disease. These tumors were excluded based on: 1) the assumption that it would be impossible to foresee their downstaging and downsizing after CRT, thus precluding surgery within the time frame defined in the study design, and therefore introducing heterogeneity in the study population and 2) the fact that metastatic tumors would not receive the same combined CRT before an eventual surgical excision. The study received approval from the local institutional ethical review board, and after the procedure had been fully explained, all patients provided written informed consent. Six patients were excluded: two died before surgery, in three the CRT protocol was interrupted because of complications, and one developed metastatic disease during CRT, forcing a change in the therapeutic regimen. The final study population consisted of 20 patients (12 male, 8 female; median age: 57 years, range: 42–78), staged at baseline MRI as follows: T3N0 (n = 1), T3N1 (n = 13), T3N2 (n = 5), and T4N1 (n = 1).

Treatment

All patients were submitted to three-dimensional CRT with a total dose of 5040 cGy, delivered in 180 cGy fractions, five fractions a week, over a period of 5.5 weeks. Chemotherapeutic agents used concomitantly during the radiotherapy were oral capecitabine (1650 mg/m^2/day, in two divided doses) or oral tegafur-uracil (UFT) + calcium folinate (300 mg/m^2/day + 90 mg/day, in three divided doses on weekdays). Surgery was performed 6–8 weeks after completion of CRT in all patients.

CT Technique

All patients underwent baseline perfusion CT the week before the beginning of therapy. Of these, 11 were submitted to a second perfusion CT study within 2 weeks before surgery (median days after baseline examination: 81; range: 74–96). Regarding the remaining nine patients, one was unavailable for follow-up, two were excluded owing to technical problems (related to peristalsis in the rectum, introducing motion artifacts that may have interfered with the perfusion measurements), and six refused the second examination. Immediately before imaging, patients received intravenous spasmolytic medication (1 mL of hyoscine butylbromide). Patients did not receive oral contrast, bowel preparation, or rectal distention before the CT examinations. They were imaged in the supine position, in a 64-section multidetector CT scanner (Lightspeed 64, GE Healthcare Technologies, Waukesha, WI). A preliminary nonenhanced scan of the pelvic region (2.5-mm section thickness) was performed to localize the tumor. Then, a board-certified radiologist (with 8 years of experience in gastrointestinal imaging) selected a 40-mm scanning range for dynamic CT, chosen to include the maximum area of visible tumor. Dynamic study of the imaging volume, with an acquisition in cine mode, was performed as follows: eight contiguous 2.5-mm reconstructed sections obtained at the same table position, 1-second gantry rotation time, 120 kVp, 300 mA. Scanning was started 5 seconds after intravenous injection of 100 mL of nonionic iodinated contrast agent (370 mg of iodine/mL), followed by 40 mL of saline solution, via a pump injector at a fixed rate of 4–5 mL/second through a 18–20-G catheter in the antecubital vein. A set of eight images per second during 60 seconds was obtained, corresponding to a total of 480 images.

Image and Data Analysis

The image datasets were transferred to an image-processing workstation (Advantage Windows 4.3, GE Healthcare Technologies). Commercially available software (CT Perfusion 3.0, GE Healthcare Technologies) was used to calculate perfusion parameters. This software uses a deconvolution algorithm and is based on a mathematical model (24) that describes the distribution of iodinated contrast material in tissue. Assumptions made within the model (23,25) include the following: the extracapillary interstitial space is a well-mixed and uniform compartment, and by considering the interstitial space as a well-stirred compartment, the concentration of solute within this space is a function of time. An adiabatic approximation of the mathematical model (26) is used in the perfusion software to yield perfusion parameters for a tissue region of interest (ROI). These parameters result from time-contrast enhancement curves of the tissue ROI and the tissue ROI's arterial input. Thus, the resultant perfusion parameters represent mean values for the tissue ROI over the period of the time-contrast enhancement curves.

CT perfusion analysis was independently performed by a board-certified radiologist (with 4 years of experience in

perfusion CT studies) and a senior resident (with no previous experience in perfusion CT), both blinded to each other's measurements, the pathology results, and the patient's clinical response to treatment. The arterial input was obtained by drawing a circular ROI (maximum of 10 pixels) placed in the external iliac artery. An arterial enhancement time curve was automatically generated as well as functional parametric maps, representing in a color scale pixel values of the following perfusion parameters: BF (in milliliters per 100 g of wet tissue per minute), BV (in milliliters per 100 g of wet tissue), MTT (in seconds), and PS (in milliliters per 100 g of wet tissue per minute). To quantify the baseline perfusion parameters of a neoplasm, a free-hand ROI encompassing as much of the tumor area as possible (pre-CRT area range: 292–1355 mm^2; post-CRT area range: 193–1099 mm^2) was drawn along the visible margins of the lesion at a single table position (where the solid tumor area was largest) and then automatically copied to each functional map (Fig 1). For patients without visible tumor burden after CRT, a ROI was placed over the rectal wall, in the former location of the neoplasm. This methodology was chosen because a previous work demonstrated that even if no residual tumor burden is visible macroscopically, viable tumor cells persist in the tumor bed in up to 50% of the cases (27). The variation rate of each perfusion parameter after CRT was calculated as follows: ([pre-CRT value] – [post-CRT value]) × 100/(pre-CRT value).

Standard of Reference

For the histological examination of the surgical specimen, its circumferential resection plane was inked, and it was opened anteriorly and fixed in formalin for 24 hours. The whole specimen was then sectioned transversely, every 0.3 cm. The extent of lateral spread in the mesorectum was assessed on each slice, and the shortest distance between the tumor or lymph node and the circumferential resection plane was measured. Specimens were assessed by a semiquantitative determination of the TRG as proposed by Dworak et al (8) as the standard of reference. According to the proposed grading system, the tumor response to CRT was defined as follows: grade 0, no regression; grade 1, dominant tumor mass with obvious fibrosis and/or vasculopathy; grade 2, dominantly fibrotic changes with few tumor cells or groups (easy to find); grade 3, very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; and grade 4, no tumor cells, only fibrotic mass (total regression or response). Tumor response after CRT was based on the presence of gross residual tumor: tumors with TRG 0-2 scoring were non-responders, whereas neoplasms with TRG 3-4 scores were considered responders.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 17.0, Inc., Chicago, IL). Interobserver variability between measurements of the two readers for pre- and post-CRT perfusion parameters was analyzed by calculating the intraclass correlation coefficient (ICC) (0–0.20, poor correlation; 0.21–0.40, fair correlation; 0.41–0.60, moderate correlation; 0.61–0.80, good correlation; and 0.81–1.00, excellent correlation). Values of perfusion parameters were averaged between the two observers for further analysis. Because most data were not normally distributed, nonparametric tests were used. The median BF, BV, MTT, and PS on pre- and post-CRT examinations were compared by means of the Wilcoxon signed-rank test to investigate changes in the perfusion parameters after CRT. The Mann-Whitney U test was used to compare the variation rates in the perfusion parameters after CRT in responders and nonresponders and also to compare baseline ROI areas and median BF, BV, MTT, and PS of responders and nonresponders. For all of these analyses, a two-tailed P value of less than .05 was considered statistically significant. Receiver operator characteristics (ROC) curves were generated to evaluate the diagnostic performance for baseline perfusion parameters in detecting a favorable response (TRG 3-4). Corresponding areas under the ROC curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated. For these analyses, cutoff values were determined according to the point nearest to the upper left corner in the ROC curves.

RESULTS

Treatment Characteristics

According to the above mentioned protocols, 10 patients were treated with capecitabine, whereas UFT was given to the remaining 10. Surgery consisted of low anterior resection (n = 15), abdominoperineal resection (n = 4), or extended resection (n = 1). The median interval between the baseline perfusion scan and surgery was 101 days (range, 73–112).

Histopathological Findings

After histological analysis of the surgical specimens and application of the Dworak scoring system there were 15 nonresponders (two patients with TRG 0, four patients with TRG 1, and nine patients with TRG 2) and 5 responders (three patients with TRG 3 and two patients with TRG 4). Regarding pathological staging, the results showed 2 patients with a ypT0N0, 1 a ypT1N0, 10 a ypT2N0, 4 a ypT3N0, 1 a ypT3N1, 1 a ypT3N2, and 1 a ypT4N1 tumor.

Interobserver Variability

The correlation between pre-CRT measurements of both readers was excellent, with ICCs of 0.86 (0.67–0.94), 0.83 (0.62–0.93), 0.92 (0.80–0.97), and 0.95 (0.87–0.98), respectively for the BF, BV, MTT, and PS. As for post-CRT measurements, the correlation was good to excellent, with ICCs of 0.77 (0.32–0.94), 0.74 (0.51–0.88), 0.89 (0.63–0.97), and 0.75 (0.52–0.84), respectively, for the same

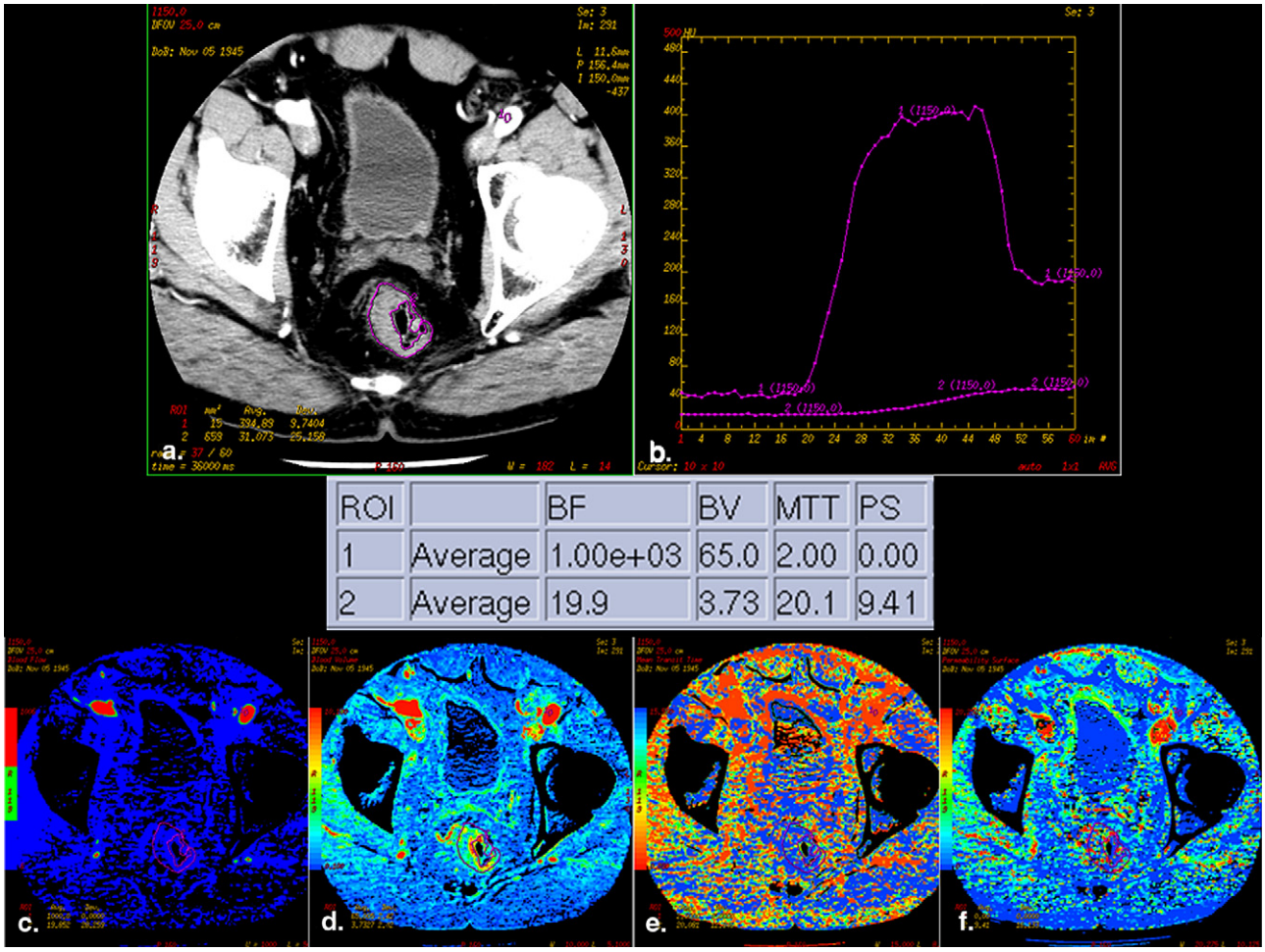


Figure 1. **(a)** Hand-drawn regions of interest (ROIs) along the visible margins of the tumor on axial images. **(b)** A time-enhancement curve corresponding to the tumor ROI is also generated. Perfusion parameters are computed and values can be presented in a table or in each one of the functional parametric maps: **(c)** blood flow (BF); **(d)** blood volume (BV); **(e)** mean transit time (MTT); **(f)** permeability-surface area product (PS).

perfusion parameters mentioned previously. Median differences between readers were the following: for BF, difference on pre-CRT images was 3.75 mL/100 g/minute and on post-CRT CT was 1.45 mL/100 g/minute; for pre-CRT BV was 0.10 mL/100 g and on post-CRT CT was 0.33 mL/100 g; for MTT on pre-CRT scans was 0.55 seconds and on post-CRT images was 1.70 seconds; for pre-CRT PS was 0.95 mL/100 g/minute and for post-CRT examinations was 1.01 mL/100 g/minute.

ROI Areas

The median baseline ROI area was not significantly different between tumors that responded well (495 mm^2; range, 344–723 mm^2) and poorly responding lesions (625 mm^2; range, 292–1355 mm^2) ($P = .257$).

Perfusion Parameters for Assessment of Response

Differences between medians of baseline perfusion parameters across all levels of TRG and in responders and nonresponders are summarized in Table 1. BF was significantly lower and MTT was significantly higher in responders than in nonresponders. No significant difference was found for BV and PS of responders and nonresponders. The AUCs for the perfusion parameters were the following: 0.88 for BF, 0.67 for BV, 0.92 for MTT, and 0.63 for PS (Fig 2). Corresponding sensitivities, specificities, PPV, and NPV for each perfusion parameter are provided in Table 2. Figure 3 shows box-and-whisker plots for BF and MTT, with depiction of the threshold value for discrimination between responders and nonresponders. A combination of these two perfusion parameters yielded a sensitivity of 80% (95% CI, 28–99) and a specificity of 66.7% (95% CI, 38–88) for characterization of response.

Perfusion Parameters before and after CRT

In the 11 patients who underwent pre- and post-CRT perfusion CT, the median BF on pre-CRT images was 61.00 mL/100 g/minute (range, 20.10–86.60) and on post-CRT CT was 20.10 mL/100 g/minute (range, 7.73–60.80) ($P = .003$). For pre-CRT median BV was 4.84 mL/100 g (range, 3.05–5.23) versus 2.80 mL/100 g (range, 1.64–4.26) for post-CRT CT

TABLE 1. Baseline Perfusion Parameters Across All Levels of TRG and in Responders and Nonresponders to Combined Chemoradiation Therapy

	TRG	BF (mL/100 g/minute)	BV (mL/100 g)	MTT (s)	PS (mL/100 g/minute)
Nonresponders (n = 15)	0	94.50 (50.00–139.00)	5.63 (4.65–6.60)	8.09 (4.28–11.90)	6.59 (6.57–6.61)
	1	82.95 (68.00–109.00)	4.85 (4.21–5.92)	5.11 (4.88–5.62)	12.10 (10.70–18.00)
	2	63.70 (41.10–118.00)	5.05 (3.05–9.14)	8.33 (5.72–11.50)	12.50 (6.36–41.40)
	Total	68.00 (41.10–139.00)	5.00 (3.05–9.14)	6.82 (4.28–11.90)	11.40 (6.36–41.40)
Responders (n = 5)	3	38.60 (25.00–58.00)	4.65 (3.58–4.76)	11.10 (10.20–22.50)	13.70 (4.70–20.30)
	4	40.55 (20.10–61.00)	4.73 (4.28–5.17)	15.65 (11.40–20.90)	14.80 (11.90–17.70)
	Total	38.60 (20.10–61.00)	4.65 (3.58–5.17)	11.10 (10.20–22.50)	13.70 (4.70–20.30)
P value (nonresponders vs. responders)		0.013	0.256	0.006	0.407

BF, blood flow; BV, blood volume; MTT, mean transit time; PS, permeability-surface area product; TRG, tumor regression grade.
Minimum and maximum values are provided between parentheses.

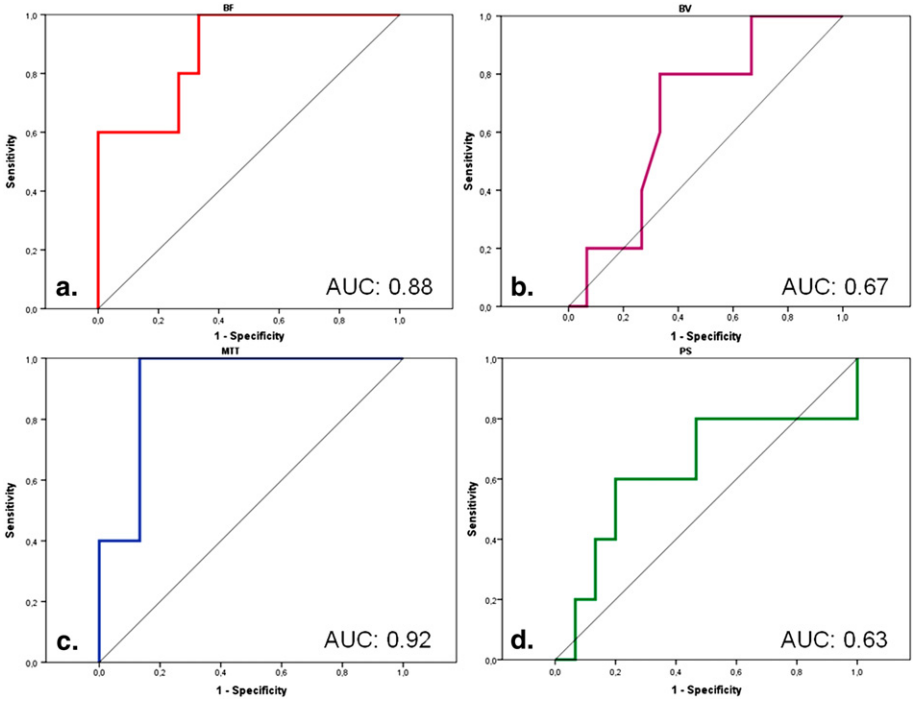


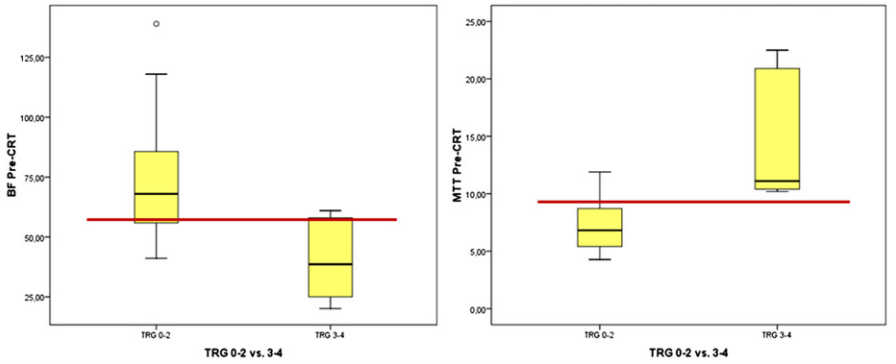
Figure 2. Comparison of receiver operating characteristic curves displaying the diagnostic performance for baseline measurements: **(a)** blood flow (BF); **(b)** blood volume (BV); **(c)** mean transit time (MTT); **(d)** permeability-surface area product (PS) in the evaluation of good response to chemoradiation therapy (tumor regression grades 3 and 4). AUC, area under the curve.

TABLE 2. Diagnostic Performance of Baseline Perfusion Measurements in Detecting a Good Response to CRT

Perfusion Parameters	Sensitivity	Specificity	PPV	NPV	Cutoff Point
BF	80.0% [4/5] (28–99)	73.3% [11/15] (44–92)	50.0% [4/8] (15–84)	91.7% [11/12] (61–99)	59.25 mL/100 g/minute
BV	80.0% [4/5] (28–99)	66.7% [10/15] (38–88)	44.4% [4/9] (13–78)	90.9% [10/11] (58–99)	4.80 mL/100 g
MTT	100% [5/5] (47–100)	86.7% [13/15] (59–98)	71,4% [5/7] (29–96)	100% [13/13] (75–100)	9.52 seconds
PS	60.0% [3/5] (14–94)	80.0% [12/15] (51–95)	50.0% [3/6] (11–88)	85.7% [12/14] (57–98)	13.45 mL/100 g/minute

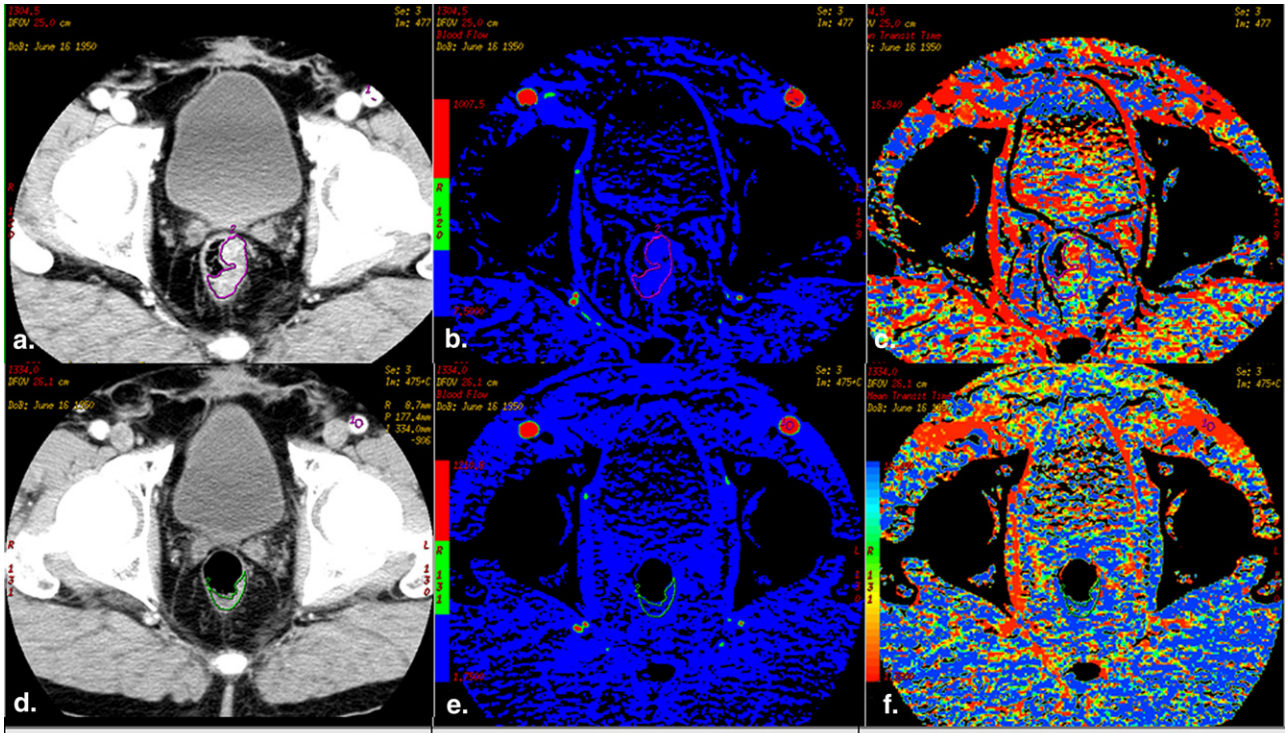
BF, blood flow; BV, blood volume; MTT, mean transit time; NPV, negative predictive value; PPV, positive predictive value; PS, permeability-surface area product.
Absolute numbers are given between brackets and 95% confidence intervals are provided between parentheses. Cutoff values were chosen according to the point nearest to the upper left corner in the receiver operating characteristic curves.

(*P* = .003). The median MTT on pre-CRT scans was 8.63 seconds (range, 4.88–22.50) and on post-CRT images was 15.90 seconds (range, 4.48–26.70) (*P* = .006). For pre-CRT CT, median PS was 12.80 mL/100 g/minute (range, 8.55–20.30) versus 9.51 mL/100 g/minute (range, 3.71–13.50) for post-CRT examination (*P* = .008). Of these 11 patients, 4 were responders and 7 were nonresponders. All responders and four nonresponders showed lower BF, BV and PS and a higher MTT after CRT (Fig 4). Among nonresponders, one showed higher BF and BV (Fig 5), in



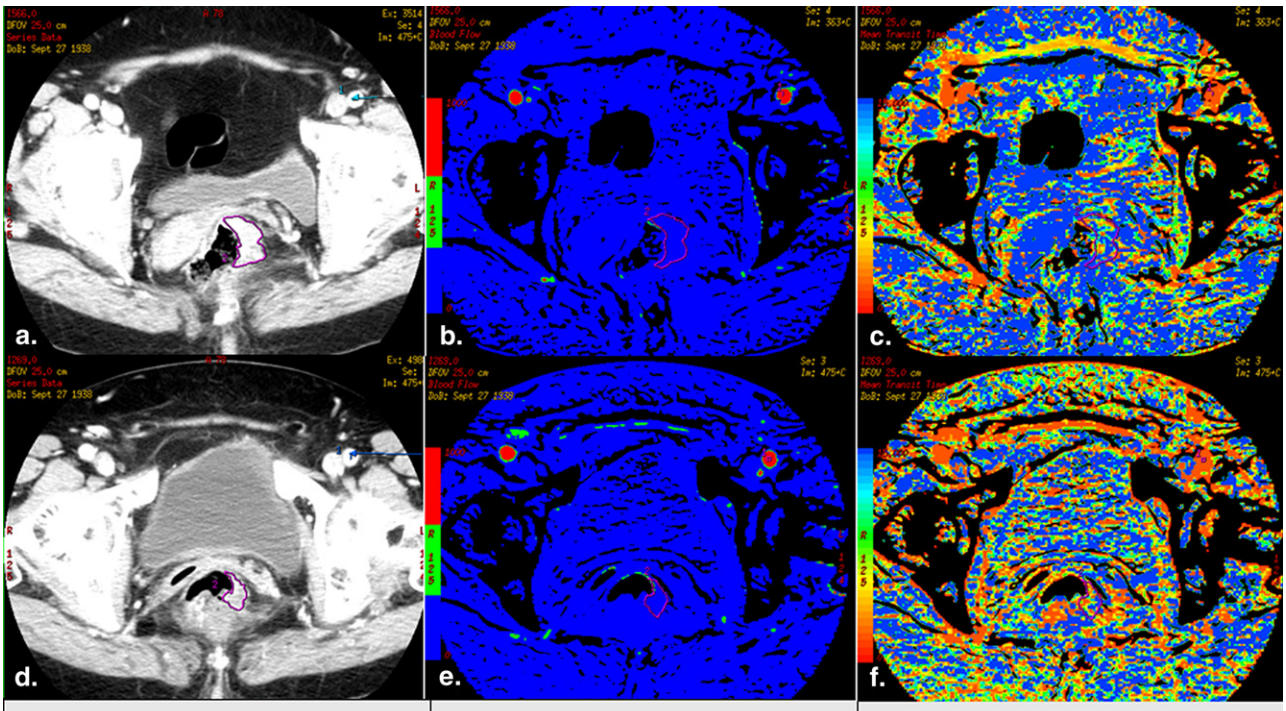
Perfusion parameters	Thresholds
BF (mL/100g/min)	59.25
MTT (s)	9.52

Figure 3. Box-and-whisker plots showing baseline blood flow (BF) and mean transit time (MTT) values of responders (tumor regression grade [TRG] 3-4) and nonresponders (TRG 0-2). Boxes stretch from lower quartile to upper quartile (25th to 75th percentile); median is shown as a line across each bar; whiskers show sample minimum and maximum; O denotes outliers; *red horizontal lines* represent thresholds. Using a threshold value of 59.25 mL/100 g/minute for BF it is possible to differentiate responders from nonresponders with a sensitivity of 80.0% and a specificity of 73.3%. Regarding MTT, a threshold of 9.52 seconds allows distinction between responders and nonresponders with a sensitivity of 100% and a specificity of 86.7%.



Perfusion parameters	Baseline	Post-CRT
BF (mL/100g/min)	38.60	18.40
MTT (s)	10.40	19.90

Figure 4. Good responder to chemoradiation therapy (CRT): apart from morphological changes between pre- **(a)** and posttherapy **(d)** with a clear lesion downsizing, perfusion computed tomography showed a decrease in blood flow (BF) from pretreatment study **(b)** to posttreatment examination **(e)**. There is also an increase in mean transit time (MTT): **(c)** baseline; **(f)** post-CRT. The blood volume and the permeability-surface area product (data and parametric maps not shown) also decreased.



Perfusion parameters	Baseline	Post-CRT
BF (mL/100g/min)	79.30	61.20
MTT (s)	8.40	11.00

Figure 5. Poor responder to chemoradiation: absence of response to treatment was found with a lack of significant downsizing of the tumor between pre- **(a)** and posttherapy **(d)** images. Perfusion measurements revealed a decrease in the blood flow (BF): **(b)** baseline; **(e)** post-chemoradiation therapy (CRT), and also in the mean transit time (MTT): **(c)** baseline; **(f)** post-CRT. The blood volume and the permeability-surface area product (data and parametric maps not shown) also decreased.

other a higher PS was found and in a third the MTT was lower after CRT. Nevertheless, the median variation rates of the perfusion parameters after CRT were not significantly different in responders and nonresponders: 58.0% versus 63.0% (P = .85) for BF, 29.1% versus 42.2% (P = .70) for BV, 48.3% versus 84.2% (P = .70) for MTT, and 47.7% vs. 23.9% (P = .13) for PS.

Table 3 yields a detailed view of the perfusion measurements on a patient-by-patient basis.

Radiation Dose

The effective radiation dose to the patients ranged from 36.03 mSv to 36.13 mSv. Of this, the cine acquisition was responsible for 20.74 mSv, whereas the remaining effective dose was related to the nonenhanced scans.

DISCUSSION

The results of our study show that baseline BF and MTT were significantly different in responders and nonresponders (BF was significantly lower and MTT significantly higher in responders) and were accurate for predicting a favorable tumor response to CRT, with an AUC of 0.88 and 0.92, respectively. Baseline BV and PS were not significantly different among responders and nonresponders. Comparing the functional perfusion data at baseline with those obtained following CRT conclusion, there was a significant change in all perfusion parameters: BF, BV, and PS decreased, whereas the MTT increased, but these changes were not different in responders and nonresponders.

To our knowledge, assessing response to CRT as defined by the TRG has not been focused in previous studies of perfusion CT of rectal cancer. Former works addressed the diagnostic value of perfusion CT in evaluating response based on morphologic criteria of tumor downstaging (21,23). The use of these criteria as endpoint of response to CRT may be prone to under- or overstaging and requires accurate baseline and post-CRT imaging examinations. However, our study assessed response to CRT based on the TRG, which is an objective criterion as standard of reference to evaluate

TABLE 3. Perfusion Measurements on a Patient-by-patient Basis

	BF (mL/100 g/mm^2)		BV (mL/100 g)		MTT (seconds)		PS (mL/100 g/mm^2)		
Patient Number	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT	TRG
1	86.60	20.20	4.86	2.00	4.88	13.00	18.00	13.50	1
2	84.80	23.60	5.08	1.85	6.15	11.00	8.55	8.99	2
3	38.60	18.40	4.65	3.21	11.10	21.00	20.30	7.89	3
4	51.30	19.00	5.23	2.24	8.63	16.00	12.50	9.51	2
5	41.10	60.80	3.05	3.38	8.80	9.70	10.90	7.20	2
6	65.20	9.22	5.05	3.05	8.33	27.00	16.60	11.10	2
7	79.30	52.90	4.84	2.80	5.62	4.50	12.80	11.90	1
8	25.00	9.08	3.58	2.61	22.50	24.00	13.70	9.00	3
9	68.00	53.00	4.21	3.50	5.19	9.90	11.40	11.10	1
10	20.10	20.10	4.28	4.26	20.90	23.00	11.90	11.80	4
11	47.80	NA	3.75	NA	8.83	NA	41.40	NA	2
12	79.70	NA	5.00	NA	6.82	NA	13.20	NA	2
13	60.50	NA	4.18	NA	7.24	NA	12.50	NA	2
14	118.00	NA	9.14	NA	5.72	NA	6.36	NA	2
15	109.00	NA	5.92	NA	5.02	NA	10.70	NA	1
16	50.00	NA	4.65	NA	11.90	NA	6.57	NA	0
17	139.00	NA	6.60	NA	4.28	NA	6.61	NA	0
18	58.00	NA	4.76	NA	10.20	NA	4.70	NA	3
19	63.70	NA	5.27	NA	11.50	NA	7.62	NA	2
20	61.00	7.73	5.17	1.64	10.40	20.00	17.70	3.71	4

BF, blood flow; BV, blood volume; CRT, chemoradiation therapy; MTT, mean transit time; NA, not applicable; PS, permeability-surface area product; TRG, tumor regression grade.

response. Moreover, grade analysis is a better predictor of outcome after treatment than T downstaging (28). In patients with gross residual tumor (TRG 0-2), the risk of local and distant recurrence is increased and the disease-free survival is statistically poor (29).

Confirming the findings of a previous study (23), our results showed that baseline BF and MTT are different between responders and nonresponders, being respectively significantly higher and significantly lower in poorly responding patients. This can be theoretically explained by the presence of intratumoral arteriovenous shunts with a high perfusion rate and low exchange of oxygen (30). Such arteriovenous shunts were shown to account for up to 30% of total tumor flow of blood (31–33) and in an animal study it was demonstrated that tumoral areas of high BF in perfusion CT images corresponded to sites of shunting of blood flow (20). These shunts have low resistance to flow, resulting in increased BF and shorter MTT. BV, although not significantly different, is also higher in poor responders. It seems therefore logical that high perfusion values, which suggest a high rate of angiogenesis within the tumor, may point toward a poor therapy response and/or a worse prognosis. High perfusion could also be a result of intrinsic high angiogenic activity of tumor (34). Interestingly, our results disagree with those from a previous study that showed baseline BF and BV in poor responders to be significantly lower and MTT significantly higher than in responders (21). Reasons for these discrepancies with our results may reflect the use of a different end point to assess response, different patient selection criteria (we did not use endorectal ultrasound for initial staging) and also differences in the perfusion technique: a shorter scanning time (effective scan duration of about 30 seconds) may be too short to reliably assess PS (35,36), and the use of thicker sections of 10 mm may also influence quantitative perfusion data (21). Table 4 provides a comparison between the methods and findings of our study and those from the two above mentioned works.

Both baseline BF and MTT showed respectively AUCs of 0.88 and 0.92 in determining a good response to CRT, thus being able to yield a diagnostically useful threshold value. Therefore, BF values below 59.25 mL/100 g/minute and MTT values over 9.52 seconds were found to have high accuracy for predicting a good response to CRT. Contrarily, baseline BV and PS could not accurately discriminate responders from nonresponders. Again, explanation for poor response is probably related to the opening of a significant number of arteriovenous shunts rather than the acquisition of a new vascular supply. Shunting facilitates the passage of blood directly from the arterial to the venous beds bypassing the exchange capillaries, hence decreasing MTT (37). This would result in a high perfusion rate with minimal or null exchange of nutrients (including oxygen), therefore preventing and limiting the action of chemotherapeutic drugs over the capillary bed, helping to explain an unfavorable response (38). We are aware, however, that this explanation, which is also based on findings from previous reports (20,23,31–33,38) is speculative, because it lacks pathologic confirmation.

The previous studies on perfusion CT for monitoring CRT effects in rectal cancer showed significant changes in perfusion parameters after therapy. Sahani et al reported a significant

TABLE 4. Comparison of Findings from Previous Reports on Perfusion CT of Rectal Cancer with Results from the Present Study

Authors	Year	Number of Patients	Technical Parameters	Criteria for Response	Results	
					Prognostic Information	Monitoring of Treatment Response
Sahani et al	2005	15 (9 repeated after CRT)	4-row MDCT, 5-mm sections, 100–120 kVp, 200–240 mA, 125 mL of contrast (300 mg/mL), 45" acquisition	T downstaging at pathologic analysis compared with pre-CRT endorectal US or MRI	Cancers with high baseline BF and low MTT responded poorly to CRT	Fall in BF and rise in MTT after CRT
Bellomi et al	2007	25 (19 repeated after CRT)	16-row MDCT, 10-mm sections, 120 kVp, 300mA, 40 mL of contrast (370 mg/mL), 50" acquisition	T or N downstaging at pathologic analysis compared with pre-CRT endorectal US	Cancers with high baseline BF and BV showed good response to CRT	Fall in BF, BV, and PS after CRT
Curvo-Semedo et al	2011	20 (11 repeated after CRT)	64-row MDCT, 2.5-mm sections, 120 kVp, 300 mA, 100 mL of contrast (370 mg/mL), 60" acquisition	Dworak's TRG 3 or 4	Cancers with high baseline BF and low MTT responded poorly to CRT	Fall in BF, BV, and PS and rise in MTT after CRT

BF, blood flow; BV, blood volume; CRT, chemoradiation therapy; MDCT, multidetector computed tomography; MTT, mean transit time; PS, permeability-surface area product; TRG, tumor regression grade.

decrease in BF and increase in MTT (23), whereas Bellomi et al showed a significantly lower BF, BV, and PS after CRT (21). In agreement with those results, we demonstrated a significant change in perfusion parameters after CRT compared with the baseline scan: BF, BV, and PS diminished, whereas MTT increased. This may reflect a decreased number of arteriovenous shunts (BF), a reduced volume of the vascular bed (BV) and a reduced leakage from neoplastic vessels (PS). The higher MTT is probably an expression of the sum of changes in the tumor vascular bed itself. However, the median variation rates of the perfusion parameters after CRT were not significantly different in responders and nonresponders. Therefore, our results suggest that a baseline perfusion study alone could discriminate between responders and nonresponders and a post-CRT is not warranted in order to achieve that goal.

Our study has limitations. Results are based on a small patient cohort of a single center and are therefore specific to the methods and software we used, and as such our thresholds may not necessarily apply to other patients. They should be regarded as preliminary data that may stimulate studies on larger populations, especially multicenter trials encompassing standardization of protocols for perfusion CT in this clinical setting.

The use of a large (100 mL) dose of iodinated contrast is not recommended by some authors, who suggest that a smaller (<50 mL) bolus should be administered instead. Nevertheless, it was demonstrated that contrast volumes similar to those applied in clinical practice for abdominopelvic CT imaging are not detrimental to the accuracy of quantitative tumor vascular parameters measured at perfusion CT, with the advantage of obtaining simultaneously morphological (staging) data (39). Restrictions on the administration rates by the caliber of the intravenous cannula usually sited in clinical practice imply that rates above 5 mL/second are not commonly used (39). Moreover, the deconvolution method we applied can tolerate lower injection rates, such as less than 5 mL/second (19). The free-hand drawing of a ROI in a single slice may not fully represent the overall tumor vascular profile and implicates a subjective judgment by the readers of where the tumor margin is located. Therefore, even subtle variations in ROI size and positioning between readers may result in substantial variations in perfusion parameters. However, observer variability is lower for this type of ROI analysis as shown in other studies (40,41) and in concordance with our results with good to excellent interobserver agreement. We did not test reproducibility because of the radiation burden and concerns of contrast-induced nephropathy. A potentially distinct efficacy of the different chemotherapeutic drugs with impact on the results should theoretically be considered. We did not assess baseline tumor volume, which may predict response to therapy (42), nor did we evaluate changes in tumor volume after therapy, because contrast-enhanced scans of the whole pelvis were not performed. A direct correlation with histological markers of angiogenesis, such as microvessel density, was not assessed

because it is not routinely performed in our institution. Furthermore, there are limitations in its routine use as a biomarker: it requires invasive tissue sampling, needs standardization, and suffers from random sampling errors because the entire tumor volume is not examined, which can hamper evaluation because of the heterogeneity of malignant neoplasms (43).

In conclusion, baseline BF was significantly lower and MTT was significantly higher in responders than in nonresponders; both parameters can accurately discriminate patients with a favorable response from the ones that fail to respond to preoperative CRT, potentially selecting high-risk patients with radio- and chemo-resistant tumors that may benefit from a more aggressive preoperative treatment approach.

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REFERENCES

1. Pahlman L, Glimelius B. The value of adjuvant radio(chemo)therapy for rectal cancer. Eur J Cancer 1995; 31A:1347–1350.
2. Kaminsky-Forrett MC, Conroy T, Luporsi E, et al. Prognostic implications of downstaging following preoperative radiation therapy for operable T3-T4 rectal cancer. Int J Radiat Oncol Biol Phys 1998; 42:935–941.
3. Mohiuddin M, Hayne M, Regine WF, et al. Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancers. Int J Radiat Oncol Biol Phys 2000; 48:1075–1080.
4. Medich D, McGinty J, Parda D, et al. Preoperative chemoradiotherapy and radical surgery for locally advanced distal rectal adenocarcinoma. Dis Colon Rectum 2001; 44:1123–1128.
5. Janjan NA, Crane C, Feig BW, et al. Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. Am J Clin Oncol 2001; 24:107–112.
6. Valentini V, Coco C, Picciocchi A, et al. Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 2002; 53:664–674.
7. Theodoropoulos G, Wise WE, Padmanabhan A, et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 2002; 45:895–903.
8. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 1997; 12: 19–23.
9. Chen CC, Lee RC, Lin JK, et al. How accurate is magnetic resonance imaging in restaging rectal cancer in patients receiving preoperative combined chemoradiotherapy? Dis Colon Rectum 2005; 48:722–728.
10. Huh JW, Park YA, Jung EJ, et al. Accuracy of endorectal ultrasonography and computed tomography for restaging rectal cancer after preoperative chemoradiation. J Am Coll Surg 2008; 207:7–12.
11. Barbaro B, Vitale R, Leccisotti L, et al. Restaging locally advanced rectal cancer with MR imaging after chemoradiation therapy. RadioGraphics 2010; 30:699–716.
12. Barrett MW. Chemoradiation for rectal cancer: current methods. Semin Surg Oncol 1998; 15:114–119.
13. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 2001; 358:1291–1304.
14. Brasch RC, Li KC, Husband JE, et al. In vivo monitoring of tumour angiogenesis with MR imaging. Acad Radiol 2000; 7:812–823.
15. Harvey C, Dooher A, Morgan J, et al. Imaging of tumour therapy responses by dynamic CT. Eur J Radiol 1999; 30:221–226.
16. Miles KA, Charnsangavej C, Lee FT, et al. Application of CT in the investigation of angiogenesis in oncology. Acad Radiol 2000; 7:840–850.
17. Dugdale PE, Miles KA, Bunce I, et al. CT measurement of perfusion and permeability within lymphoma masses and its ability to assess grade, activity, and chemotherapeutic response. J Comput Assist Tomogr 1999; 23:540–547.
18. Goh V, Halligan S, Daley F, et al. Colorectal tumor vascularity: quantitative assessment with multidetector CT—do tumor perfusion measurements reflect angiogenesis? Radiology 2008; 249:510–517.
19. Kambadakone AV, Sahani DV. Body perfusion CT: technique, clinical applications, and advances. Radiol Clin N Am 2009; 47:161–178.
20. Kan Z, Phongkitkarun S, Kobayashi S, et al. Functional CT for quantifying tumor perfusion in antiangiogenic therapy in a rat model. Radiology 2005; 237:151–158.
21. Bellomi M, Petralia G, Sonzogni A, et al. CT perfusion for the monitoring of neoadjuvant chemotherapy and radiation therapy in rectal carcinoma: initial experience. Radiology 2007; 244:486–493.
22. Goh V, Halligan S, Wellsted DM, et al. Can perfusion CT assessment of primary colorectal adenocarcinoma blood flow at staging predict for subsequent metastatic disease? A pilot study. Eur Radiol 2009; 19:79–89.
23. Sahani DV, Kalva SP, Hamberg LM, et al. Assessing tumor perfusion and treatment response in rectal cancer with multisection CT: initial observations. Radiology 2005; 234:785–792.
24. Johnson JA, Wilson TA. A model for capillary exchange. Am J Physiol 1966; 210:1299–1303.
25. Lee TY, Purdie TG, Stewart E. CT imaging of angiogenesis. Q J Nucl Med 2003; 47:171–187.
26. St Lawrence KS, Lee TY. An adiabatic approximation to the tissue homogeneity model for water exchange in the brain. I. Theoretical derivation. J Cereb Blood Flow Metab 1998; 18:1365–1377.
27. Vliegen RF, Beets GL, Lammering G, et al. Mesorectal fascia invasion after neoadjuvant chemotherapy and radiation therapy for locally advanced rectal cancer: accuracy of MR imaging for prediction. Radiology 2008; 246:454–462.
28. Bouzourene H, Bosman FT, Seelentag W, et al. Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 2002; 94:1121–1130.
29. Losi L, Luppi G, Gavioli M, et al. Prognostic value of Dworak grade of regression (GR) in patients with rectal carcinoma treated with preoperative radiochemotherapy. Int J Colorectal Dis 2006; 21:645–651.
30. Brown JM, Giaccia AJ. The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. Cancer Res 1998; 58:1408–1416.
31. Eddy HA. Alterations in tumor microvasculature during hyperthermia. Radiology 1980; 137:515–521.
32. Peters W, Teixeira M, Intaglietta M, et al. Microcirculation in rat mammary carcinoma. Proc Am Assoc Cancer Res 1980; 21:38.
33. Wheeler RH, Ziessman HA, Medvec BR, et al. Tumor blood flow and systemic shunting in patients receiving intraarterial chemotherapy for head and neck cancer. Cancer Res 1986; 46:4200–4204.
34. Leek RD, Landers RJ, Harris AL, et al. Necrosis correlates with high vascular density and focal macrophage infiltration in invasive carcinoma of the breast. Br J Cancer 1999; 79:991–995.
35. Miles KA. Perfusion CT for the assessment of tumour vascularity: which protocol? Br J Radiol 2003; 76(spec no 1):S36–S42.
36. Goh V, Halligan S, Hugill JA, et al. Quantitative colorectal cancer perfusion measurement using dynamic contrast-enhanced multidetector-row computed tomography: effect of acquisition time and implications for protocols. J Comput Assist Tomogr 2005; 29:59–63.
37. Chaplin DJ, Trotter MJ, Dougherty GJ. Microregional tumor blood flow: heterogeneity and therapeutic significance. In: Bicknell R, Lewis CE, Ferrara N, eds. Tumor angiogenesis. Oxford, UK: Oxford University Press, 1997; 61–70.
38. De Vries AF, Griebel J, Kremser C, et al. Tumor microcirculation evaluated by dynamic magnetic resonance imaging predicts therapy outcome for primary rectal carcinoma. Cancer Res 2001; 61:2513–2516.
39. Goh V, Bartram C, Halligan S. Effect of intravenous contrast agent volume on colorectal cancer vascular parameters as measured by perfusion computed tomography. Clin Radiol 2009; 64:368–372.
40. Goh V, Halligan S, Hugill JA, et al. Quantitative colorectal cancer perfusion measurements using MDCT: inter and intra-observer agreement. AJR Am J Roentogenol 2005; 185:225–231.

41. Goh V, Halligan S, Gharpuray A, et al. Quantitative assessment of colorectal cancer tumor vascular parameters by using perfusion influence of tumor region of interest. Radiology 2008; 247:726–732.
42. Kim YH, Kim DY, Kim TH, et al. Usefulness of magnetic resonance volumetric evaluation in predicting response to preoperative concurrent chemoradiotherapy in patients with resectable rectal cancer. Int J Radiat Oncol Biol Phys 2005; 62:761–768.
43. Cuenod CA, Fournier L, Balvay D, et al. Tumor angiogenesis: pathophysiology and implications for contrast-enhanced MRI and CT assessment. Abdom Imaging 2006; 31:188–193.