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Correlation between quantitative and semiquantitative parameters in DCE-MRI with a blood pool agent in rectal cancer: can semiquantitative parameters be used as a surrogate for quantitative parameters?

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Abstract

Purpose: The aim of this study was to assess correlation between quantitative and semiquantitative parameters in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in rectal cancer patients, both in a primary staging and restaging setting.
Materials and methods: Nineteen patients were included with DCE-MRI before and/or after neoadjuvant therapy. DCE-MRI was performed with gadofosveset trisodium (Ablavar®, Lantheus Medical Imaging, North Billerica, Massachusetts, USA). Regions of interest were placed in the tumor and quantitative parameters were extracted with Olea Sphere 2.2 software permeability module using the extended Tofts model. Semiquantitative parameters were calculated on a pixel-by-pixel basis. Spearman rank correlation tests were used for assessment of correlation between parameters. A p value ≤0.05 was considered statistically significant.
Results: Strong positive correlations were found between mean peak enhancement and mean K_{trans}: 0.79 (all patients, $p<0.0001$), 0.83 (primary staging, $p = 0.003$), and 0.81 (restaging, $p = 0.054$). Mean wash-in correlated significantly with mean V_p and K_{ep} (0.79 and 0.58, respectively, $p<0.0001$ and $p = 0.009$) in all patients. Mean wash-in showed a significant correlation with mean K_{ep} (0.67, $p = 0.033$) in the primary staging group. On the restaging MRI, mean wash-in only strongly correlated with mean V_p (0.81, $p = 0.054$).
Conclusion: This study shows a strong correlation between quantitative and semiquantitative parameters in DCE-MRI for rectal cancer. Peak enhancement correlates strongly with K_{trans} and wash-in showed strong correlation with V_p and K_{ep}. These parameters have been reported to predict tumor aggressiveness and response in rectal cancer. Therefore, semiquantitative analyses might be a surrogate for quantitative analyses.

Key words: Rectal cancer—Dynamic contrast-enhanced MRI—Correlation—Semiquantitative—Quantitative

MRI has evolved from a modality that provides morphological information only to a tool that can provide functional information. To date, many have focused on biological properties including tumor cell density which can be assessed with diffusion weighted imaging (DWI) MRI, and tumor perfusion assessable with dynamic contrast-enhanced MRI (DCE- MRI) [1]. DCE-MRI is an upcoming technique in rectal cancer for the assess-

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ment of tumor aggressiveness and response prediction after neoadjuvant treatment. DCE-MRI is an imaging technique where T1-weighted sequences are rapidly repeated before, during and after intravenous contrast injection to study signal intensity changes induced by passage of the contrast bolus through tissues. DCE-MRI measures tumor perfusion by providing information on tumor vascularity, permeability and blood volume [2]. Contrast enhancement on DCE-MRI can be assessed either quantitatively or semiquantitatively. Quantitative parameters such as K_{trans}, K_{ep} and V_e reflect tumor permeability and extracellular space volume, and are assessed with DCE-MRI according to the Tofts model [3, 4]. These parameters are relevant as they are known to correlate with neoangiogenesis, which leads to immature and unstable vessels with increased leakiness, which is known to be an important factor in malignant tumor development [5–7]. Quantitative analysis of DCE data is relatively time-consuming and requires specific software and interpretative expertise, likely at least in part explaining its limited adoption in clinical practice [8].

The semiquantitative approach also assumes early and intense enhancement and early wash-out as a predictor of malignancy. The software for semiquantitative analysis creates dynamic curves representing intensity of tumor enhancement over time. Several parameters that characterize the shape of the signal intensity time curve (SITC) can be obtained from the curve, including curve shape, gradient of the upslope, and wash-in/-out gradient [8, 9]. SITCs require less complicated software algorithms and radiologists can readily assess the curves. Also, semiquantitative parameters are easier to obtain and reproduce than quantitative parameters. As a result, semiquantitative DCE analyses are already advocated for clinical use, for example in the characterization of breast lesions [10–13] and prostate cancer [14]. Only a small number of studies evaluated the correlation between quantitative and semiquantitative analysis of DCE-MRI imaging to assess malignancy or therapy response in patients with either breast or prostate cancer [8, 14, 15]. These studies showed a strong positive correlation between quantitative and semiquantitative parameters, such as SITCs with K_{trans} and initial enhancement with K_{ep} [8, 15]. However, the relationship between quantitative parameters and semiquantitative parameters has not yet been studied in rectal cancer, and it therefore remains unclear whether semiquantitative analysis can be used as a surrogate for quantitative analyses in rectal cancer assessment, which would have obvious advantages in terms of time needed for exam interpretation and complexity of exam interpretation [16]. Therefore, the objective of this study was to assess the correlation between semiquantitative and quantitative DCE-MRI parameters in rectal cancer.

Materials and methods

Patients

This is a retrospective analysis performed as part of a prospective study on contrast-enhanced MRI for staging of rectal cancer lymph nodes, which was approved by the local institutional review board [17]. Between March 2011 and July 2012, nineteen consecutive patients with biopsy-proven rectal cancer were included. All patients underwent DCE-MRI either before treatment and/or after a long course of neoadjuvant chemoradiation (CRT), in case of locally advanced rectal cancer.

MRI acquisition

All MRI examinations were performed at 1.5T (Intera or Achieva, Philips Medical Systems, Best, the Netherlands). In order to reduce bowel movement, an intravenous bolus injection of 20 mg of butylscopolamine (Buscopan®, Boehringer Ingelheim bv, Ingelheim, Germany) was administered. No bowel preparation was administered. The protocol included T2-weighted turbo spin echo sequences in 3 orthogonal planes (sagittal, transverse, and coronal). The transverse plane was angled perpendicular, and the coronal plane parallel to the tumor axis as identified on the sagittal scan. Multiple flip angles (5, 10, 15, 20, 25) spoiled gradient echo sequences with identical TR and TE (TE 4.6 ms, TR 7.9 ms) were acquired with the same geometrical characteristics as the DCE-MRI sequence, to calculate T1 relaxation times on a pixel-by-pixel basis. The DCE sequence consisted of a transverse (identical plane as the transverse T2W sequence) dynamic T1-weighted 3D fast field echo with 10 mm thickness and overcontiguous slices using the following parameters: 8 s temporal resolution, TR/TE 7.9/4.6 ms, 30° flip angle, 11 slices, 5-mm slice thickness, 5-mm interslice distance, with a total acquisition time of 6 min. In plane resolution 0.43×0.34 mm^2, matrix 512×512, and FOV 220×220 mm^2 no view sharing was used. After three series (24 s) of unenhanced baseline measurements, 0.12 ml/kg bodyweight of the blood pool contrast agent gadofosveset trisodium (Ablavar®, Lantheus Medical Imaging, North Billerica, Massachusetts, USA) was injected at a rate of 0.70 ml/s into the brachial vein, followed by a 20-ml saline flush with an MR compatible power injector (Spectris Solaris, MEDRAD, Warrendale, Pennsylvania, USA). Gadofosveset trisodium is approved and used for MRA, but not for use in oncology. It has been proven valuable in the staging of lymph nodes in rectal cancer [17].

Image analysis

The DCE-MRI parameter maps (K_{trans}, K_{ep}, V_e, V_p, Wash-in, Peak enhancement, and Wash-out) were fused

with the T2-weighted axial images by use of OsiriX Medical Imaging Software (Pixmeo, Bernex, Switzerland). Volumes of Interest (VOIs) including the whole tumor volume were generated by a single reader (MHM, blinded to clinical and pathological data, 3 years of experience with rectal cancer MRI) who drew free hand regions of interests (ROI) around all visible tumor based on the anatomical T2-weighted images on each consecutive slice with visible tumor (i.e., intermediate signal intensity mass). ROIs were transferred to the various fusion maps. Any high-signal areas (indicating necrosis) were also included in the ROIs. On the restaging MRIs hypointense areas within the tumor bed (indicating fibrosis) were also included in the ROIs. A representative example of the delineation is shown in Fig. 1.

Quantitative DCE analysis

T1 maps were generated using the five different flip angles (5, 10, 15, 20, 25). A DCE kinetic model analysis of the VOIs was performed using the extended Tofts model [3] in the Olea Sphere 2.2 software permeability module (Olea Medical, La Ciotat, France). The arterial input function (AIF) was obtained from the right femoral artery. Estimated kinetic model quantitative parameters were transfer constant (K_{trans}), extracellular extravascular space volume fraction (V_e), plasma volume fraction (V_p), and the rate constant of contrast agent escape from the extracellular extravascular space into the plasma compartment (K_{ep}).

Semiquantitative DCE analysis

Semiquantitative analysis was performed using the same VOIs described above with Olea Sphere 2.2 Software permeability module (Olea Medical, La Ciotat, France). The following parameters were calculated on a pixel-by-pixel basis: wash-in, wash-out rates, and peak enhancement (Fig. 2).

Statistical analyses

Descriptive statistics were used to provide baseline characteristics. Correlation between quantitative and semiquantitative parameters was assessed by the Spearman rank correlation coefficient, as not all variables were normally distributed. Analyses were performed in all patients and then correlation between quantitative and semiquantitative parameters was repeated for both the primary staging group and post-CRT group. Measurements were performed per slice. For analyses, a single value was obtained for the tumor volume by averaging the values across ROIs and calculating a weighted average based on the respective ROI surface area. IBM Statistical Package for the Social Sciences (SPSS, version 20.0, Inc., Chicago, IL) was used for statistical analyses. A p value of ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

In total, 19 patients were included with a mean age of 67 years (SD $\pm$ 11). Table 1 shows baseline patient characteristics. For nine patients, DCE-MRI was performed for primary staging; for nine patients DCE-MRI was performed for restaging after CRT. For one patient, both the primary staging and restaging MRI were used for analysis. So in total, 20 DCE-MRI examinations were analyzed in 19 patients. From the patients in the primary staging group, 6 received CRT because of locally advanced rectal cancer and DCE-MRI post-CRT was

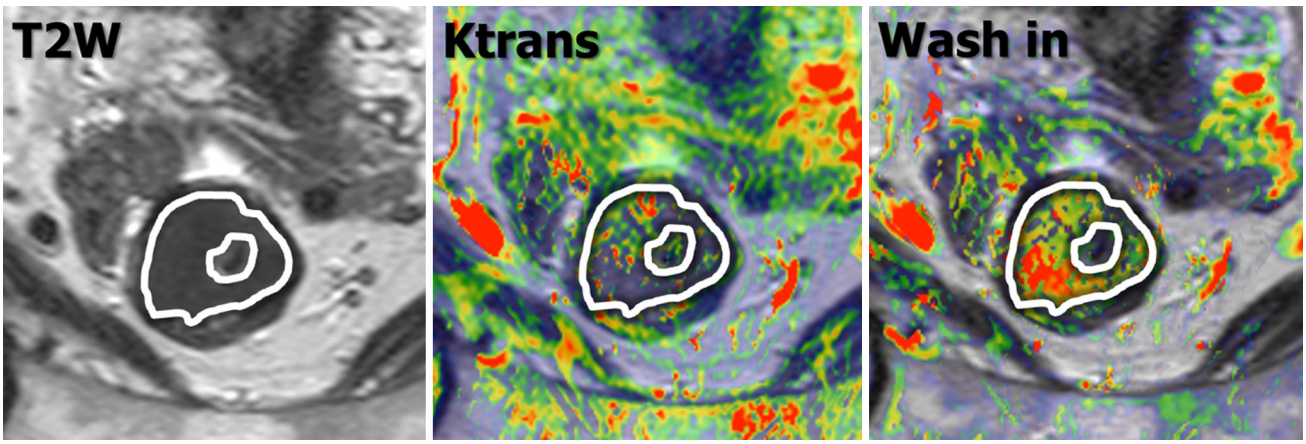

Fig. 1. A rectal tumor before treatment. **A** T2W image with a free hand drawn region of interest (ROI) of a primary tumor on a transversal scan. **B** Same primary tumor with free hand drawn ROI and corresponding parametric map of K_{trans}. **C** Same primary tumor with free hand drawn ROI and corresponding parametric map of wash-in. *Red areas* indicate a high value of the parameter and *green values* indicate a low value of the parameter.

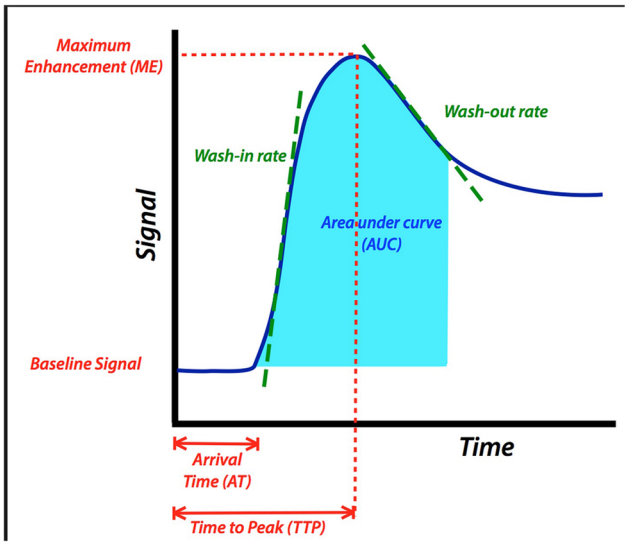

Fig. 2. Signal intensity time curve, used as the basis for the assessment of semiquantitative parameters. Wash-in rate: the time it takes for contrast to be taken up in the tissue resulting in contrast enhancement of that tissue. Wash-out rate: the time it takes for contrast to leave the tissue resulting in loss of contrast enhancement of that tissue. Maximum enhancement (ME): maximum contrast concentration in the tissue. Time to peak (TTP): time it takes for the maximum contrast concentration to be reached in the tissue. In the current study, the ROIs were drawn around the whole tumor, therefore these parameters depict whole tumor characteristics.

not available. One of these patients proceeded to wait-and-see policy due to complete response. One patient underwent transanal endorectal microsurgery (TEM). In the restaging group, one patient had a transanal endorectal microsurgery (TEM). Two patients were eligible for the wait-and-see policy and therefore did not undergo surgery. Additionally, two patients had a complete tumor response (ypT0). The one patient who had both primary staging and restaging DCE-MRI was not eligible for surgery and received palliative treatment instead.

Correlation between quantitative and semiquantitative DCE parameters

Table 2 summarizes all the correlations between the quantitative and semiquantitative parameters. Overall, the semiquantitative parameters mean and maximum peak enhancement showed the strongest correlations with the quantitative DCE parameters, with the strongest positive correlations between mean peak enhancement and mean K_{trans} with a correlation of 0.79 for all patients ($p < 0.0001$) and 0.83 ($p = 0.003$) for the subgroup of primary staging examinations. For the restaging subgroup, a good correlation was also found, albeit not statistically significant (0.81, $p = 0.054$). Mean peak enhancement also showed significant correlations with mean V_e in all patients (0.61, $p = 0.005$). Maximum peak enhancement significantly correlated with V_e max

Table 1. Patient characteristics [(y)cTNstage based on MRI]

		All patients ($N = 19$)	Primary DCE ($N = 10$)	Restaging DCE ($N = 10$)
Age	Mean (±SD)	67 (±11)	71 (±4)	63 (±3)
Sex	Male	14 (74%)	9 (90%)	6 (60%)
Primary cT-stage	cT1-2	1 (5%)	1 (10%)	0
	cT2	5 (26%)	3 (30%)	2 (20%)
	cT2-3	2 (11%)	1 (10%)	1 (10%)
	cT3	6 (32%)	0	6 (60%)
	cT4	5 (26%)	5(50%)	0
Primary cN-stage	cN0	3 (16%)	2 (20%)	1 (10%)
	cN0-1	1 (5%)	0	1 (10%)
	cN1	8 (42%)	5 (50%)	3 (30%)
	cN2	7 (35%)	3 (30%)	4 (40%)
Restaging ycT-stage	ycT0	–	–	4 (40%)
	ycT2	–	–	3 (30%)
	ycT3	–	–	3 (30%)
Restaging ycN-stage	ycN0	–	–	8 (80%)
	ycN1	–	–	1 (10%)
	ycN2	–	–	1(10%)
Pathology T-stage	(y)pT0		1 (%)	2 (29%)
	(y)pT1		4 (%)	1 (14%)
	(y)pT2		2 (%)	1 (14%)
	(y)pT3		0	3 (43%)
Pathology N-stage	(y)pN0		4 (57.1%)	4 (57%)
	(y)pN1		1 (14.3%)	2 (29%)
	(y)pN2		1 (14.3%)	0
	Missing due to local excision		1(14.3%)	1(14%)

In one patient, both primary and restaging dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) were included for analysis
SD, standard deviation

Table 2. Correlation between quantitative and semiquantitative parameters of all patients, on both primary and restaging DCE-MRI

Groups	Semiquantitative parameters	Quantitative parameters							
		K_{trans}	p value	V_e	p value	V_p	p value	K_{ep}	p value
All patients	Mean								
	Peak	0.79	<0.0001	0.61	0.005	0.28	0.238	0.667	0.002
	Wash-in	0.43	0.066	−0.086	0.726	0.788	<0.0001	0.582	0.009
	Wash-out	0.55	0.015	0.41	0.079	0.398	0.091	0.416	0.077
	Max								
	Peak	0.68	0.001	−0.035	0.887	0.54	0.018	0.6	0.006
	Wash-in	0.53	0.019	0.24	0.318	0.64	0.003	0.44	0.058
	Wash-out	0.25	0.293	0.32	0.188	0.44	0.059	−0.116	0.115
Primary patients	Mean								
	Peak	0.83	0.003	0.62	0.054	0.07	0.855	0.67	0.033
	Wash-in	0.48	0.162	0.091	0.803	0.36	0.310	0.67	0.033
	Wash-out	0.42	0.229	0.32	0.365	0.54	0.108	0.41	0.244
	Max								
	Peak	0.46	0.187	0.66	0.038	0.49	0.150	0.36	0.310
	Wash-in	0.53	0.117	0.27	0.446	0.53	0.117	0.37	0.293
	Wash-out	0.15	0.676	0.75	0.013	0.69	0.029	-0.018	0.960
Restaging patients	Mean								
	Peak	0.81	0.054	0.66	0.038	0.09	0.803	0.81	0.054
	Wash-in	−0.18	0.627	−0.2	0.580	0.81	0.054	−0.13	0.726
	Wash-out	0.48	0.162	0.50	0.138	0.19	0.603	0.41	0.244
	Max								
	Peak	0.75	0.013	−0.25	0.489	0.36	0.310	0.60	0.067
	Wash-in	0.59	0.074	0.30	0.405	0.60	0.067	0.62	0.054
	Wash-out	0.46	0.187	0.14	0.701	0.30	0.405	−0.006	0.987

* p value >0.05 is considered not statistically significant

for the primary staging subgroup (0.66, $p = 0.038$). Maximum peak enhancement correlated significantly with mean V_e for the restaging subgroup (0.66, $p = 0.038$). In the primary staging group, mean peak enhancement was significantly correlated with mean K_{ep} (0.67, $p = 0.033$); for the restaging group, a high correlation was found (0.81, $p = 0.054$), although not statistically significant. Mean wash-in showed a significant correlation with mean V_p and K_{ep} (0.79 and 0.58, respectively, $p<0.0001$ and $p = 0.009$) in all patients. Mean wash-in showed a significant correlation with mean K_{ep} (0.67, $p = 0.033$) in the primary staging group. On the restaging MRI, mean wash-in only showed a correlation with mean V_p, albeit not statistically significant (0.81, $p = 0.054$). No consistent results were found regarding correlation between wash-out and quantitative parameters.

Discussion

The aim of this study was to assess the correlation between quantitative and semiquantitative parameter analyses of DCE-MRI data in rectal cancer patients. The results show that several semiquantitative DCE parameters correlate well with their quantitative counterparts, particularly for the whole group combined and for the primary staging examinations. For the restaging examinations, the same trend was observed, although not statistically significant, probably related to the relatively small number of patients per subgroup. Our results thus suggest that the semiquantitative analysis method could be used as a surrogate method to interpret DCE-MRI data. The semiquantitative parameter 'peak enhancement' showed the strongest correlation with quantitative parameters, especially K_{trans}. The volume transfer constant K_{trans} is defined as the number of contrast agent particles that are delivered to the extracellular space per minute, tissue volume, and arterial plasma concentration [18]. Several studies have shown that K_{trans} is the most important quantitative DCE parameter with regard to response prediction and evaluation after chemoradiation for rectal cancer. Even though conflicting results have been reported, most studies show that a high K_{trans} before and a large decrease in K_{trans} during chemoradiation predict therapy response [19, 20]. A high K_{trans} before CRT indicates high permeability and vascularity of the tumor, which is believed to make the tumor more accessible to chemotherapy, and less hypoxic, making the tumor more sensitive for radiation [1]. Based on these findings, George et al. concluded that preselecting patients with higher tumor permeability based on primary DCE-MRI K_{trans} for chemoradiation would be appropriate [21]. A decrease in K_{trans} indicates replacement of tumor tissue with fibrosis and necrosis, also corresponding with response [19]. As a high K_{trans} reflects increased vascularity and tumor permeability in specific, it is not surprising that it correlates well with peak enhancement; when contrast leaks into the interstitium easily (high K_{trans}), peak enhancement will be higher as well. Therefore, applying 'peak enhancement' as a surrogate for K_{trans} could be considered both in a primary and restaging setting. In future studies, the predictive

value of peak enhancement for response after CRT should therefore be addressed.

In addition to the strong correlation between peak enhancement and K_{trans}, the mean wash-in and peak enhancement also strongly correlated with the constant flow rate K_{ep} in the whole patient group, as well as for the primary staging subgroup. K_{ep} has been shown to correlate well with micro vessel density (MVD), a marker of tumor angiogenesis [22], and with T-stage [15]. This could be explained by more extensive neoangiogenesis in more aggressive tumors, which causes greater accumulation of contrast in these tumors [15]. Therefore, K_{ep} has been proposed as an imaging biomarker for tumor aggressiveness [22].

In the current study, mean wash-in and peak enhancement strongly correlated with the constant flow rate K_{ep} in all patients and also on primary DCE-MRI. So, potentially peak enhancement and wash-in might be used as a surrogate for K_{ep} and thus assessment of tumor aggressiveness. In the current study, we used gadofosveset trisodium as a contrast agent, while in other studies conventional gadolinium-based agents are usually applied. Gadofosveset trisodium is a blood pool contrast agent that binds to albumin and is thus a relatively large-sized molecule in contrast to conventional gadolinium-based contrast media in DCE-MRI. The estimate of the ratio of K_{trans}/K_{ep} for gadofosveset trisodium is nearly identical to that of conventional gadolinium-based contrast media, supporting the hypothesis that the two contrast agents exhibit very similar pharmacokinetics [23]. Therefore, it is possible to use the conventional two compartment model to quantify K_{trans}, $K_{ep}K_{ep}$, V_e, and V_p. Although the pharmacokinetics of gadofosveset trisodium have been hypothesized to be similar to that of other contrast agents regarding the inflow parameters, it does not show a typical wash-out, due to its larger molecular size, leading to blood pooling rather than rapid wash-out. Therefore, the applicability of the extended Tofts model will likely be limited in gadofosveset trisodium-enhanced DCE-MRI with regard to wash-out-related parameters [3]. This probably also explains the lack of correlation between the wash-out as determined from the semiquantitative analysis and the wash-out-related quantitative parameters (K_{ep}).

In a previous study, Martens et al. investigated the value of semiquantitative DCE-MRI analysis with gadofosveset trisodium to predict response to chemoradiation in rectal cancer and found that mainly the late slope of the enhancement curve at primary staging was a significant predictor of response. For inflow parameters, Martens et al. reported a trend that the decrease of initial slope and peak enhancement was higher in responders than non-responders, but this difference was not statistically significant ($p = 0.06$ and 0.08) [24]. This higher decrease in initial slope and peak enhancement seems to correspond with the decrease in K_{trans} in good responders reported in other studies that performed quantitative DCE analysis using conventional gadolinium agents. Furthermore, Petrillo et al. found wash-out slope and maximum signal difference (equivalent to peak enhancement) to be predictive of response in DCE-MRI with Gd-DOTA, similar to the results by Martens et al [25]. Although further studies are obviously required to investigate the effects of using different types of contrast agents, the above findings suggest that the semiquantitative parameters that predict response to neoadjuvant treatment may be similar when using both small as well as large molecular weight contrast agents.

No previous studies investigating the correlation between quantitative and semiquantitative DCE parameters in rectal cancer patients exist, but some studies have looked at this correlation in other types of cancer patients. For example, Woolf et al. conducted a study in 58 breast cancer patients and reported that SITC shapes in breast cancer significantly correlated with K_{trans}, and showed that changes in SITC during therapy correspond to changes in K_{trans} [8]. Rosenkrantz et al. found similar diagnostic performance for both semiquantitative and quantitative methods when identifying peripheral zone tumors in prostate cancer patients [14]. They concluded that both techniques can be used in clinical practice. In cervical cancer, Zahra et al. reported that both semiquantitative and quantitative parameters at primary staging are associated with tumor regression [16]. The findings of studies in other cancer types support the hypothesis that both quantitative and semiquantitative parameters can be used for (re)staging cancer. However, because DCE-MRI parameters can vary substantially between MR protocols, cancer types, patients, and even within patients at different time points, semiquantitative parameters should be validated for each type of cancer in a large sample size by multiple studies, before using them in clinical practice.

Our study has several limitations. First, our study is a small and single-center study. Results are therefore difficult to generalize across different institutions, especially since without standardization differences in protocols/sequences used (e.g., injection rates, temporal resolution) will influence measurements. Still, this is the first study to evaluate correlations between quantitative and semiquantitative parameters in DCE-MRI for rectal cancer and should therefore be considered as a hypothesis-generating study. Second, the atypical contrast agent gadofosveset trisodium was used, which is a larger molecule than generally used for DCE-MRI, as discussed in detail above. There is no wide experience with gadofosveset trisodium use for body perfusion applications, but it is relevant in rectal cancer where it has a value for nodal staging [17]. Unfortunately at the time of writing, gadofosveset trisodium is no longer manufactured. Although extrapolation to other small molecule gadolinium formulations may be impacted, the general concept will

likely remain valid. Third, in a restaging setting, it can be difficult to delineate the suspected residual tumor area, particularly in patients who have undergone a very good or even complete tumor response. The same goes for very small (partly mucinous) tumors that in addition may show different angiogenic properties. Fourth, a potential pitfall is motion (patient motion, bladder filling, and rectal peristalsis) which will lead to misregistration given the 6-min DCE acquisition time. Last, no attempt was made to correlate results with clinical outcome such as tumor aggressiveness and response as this was beyond the scope of the study aims. However, this should be evaluated in future studies.

Future perspectives

Larger and more studies are needed to confirm these findings and to evaluate the relationship of semiquantitative parameters with outcome (tumor aggressiveness, response, and long-term outcome), in order to validate the use of semiquantitative parameters further.

Optimally, these studies would perform both quantitative and semiquantitative parameters in order to substantiate and compare the predictive values of both quantitative and semiquantitative parameters for tumor aggressiveness and response after CRT. Additionally, future studies should also focus on reproducibility of the findings, as DCE-MRI is known to be variable on an inter-patient and intra-patient level. Given the relatively recent introduction of DCE-MRI with novel contrast agents such as gadofosveset trisodium, future studies should also aim at the development of new quantitative models specifically adapted to the pharmacokinetics of these novel contrast agents. When eventually semiquantitative parameters will be proven adequate surrogates for quantitative parameters, DCE-MRI can be more easily implemented in clinical practice.

Conclusion

This study shows that semiquantitative parameters correlate well with quantitative parameters in DCE-MRI for rectal cancer. Specifically, peak enhancement correlates strongly with K_{trans}, a factor that has been repeatedly shown to predict response to CRT. Peak enhancement and wash-in correlate strongly with K_{ep} that was correlated with tumor aggressiveness in some studies. Therefore, peak enhancement and wash-in could be considered surrogate measures for K_{trans} and K_{ep}.

Compliance with ethical standards

Funding No funding was received for this study.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Tong T, Sun Y, Gollub MJ, et al. (2015) Dynamic contrast-enhanced MRI: use in predicting pathological complete response to neoadjuvant chemoradiation in locally advanced rectal cancer. J Magn Reson Imaging 42(3):673–680. doi:10.1002/jmri.24835
2. Padhani AR, Khan AA (2010) Diffusion-weighted (DW) and dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) for monitoring anticancer therapy. Target Oncol 5(1):39–52. doi:10.1007/s11523-010-0135-8
3. Tofts PS (1997) Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. J Magn Reson Imaging 7(1):91–101
4. Tofts PS, Kermode AG (1991) Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. Magn Reson Med 17(2):357–367
5. Lollert A, Junginger T, Schimanski CC, et al. (2014) Rectal cancer: dynamic contrast-enhanced MRI correlates with lymph node status and epidermal growth factor receptor expression. J Magn Reson Imaging 39(6):1436–1442. doi:10.1002/jmri.24301
6. Hong HS, Kim SH, Park HJ, et al. (2013) Correlations of dynamic contrast-enhanced magnetic resonance imaging with morphologic, angiogenic, and molecular prognostic factors in rectal cancer. Yonsei Med J 54(1):123–130. doi:10.3349/ymj.2013.54.1.123
7. Zhang XM, Yu D, Zhang HL, et al. (2008) 3D dynamic contrast-enhanced MRI of rectal carcinoma at 3T: correlation with microvascular density and vascular endothelial growth factor markers of tumor angiogenesis. J Magn Reson Imaging 27(6):1309–1316. doi:10.1002/jmri.21378
8. Woolf DK, Padhani AR, Taylor NJ, et al. (2014) Assessing response in breast cancer with dynamic contrast-enhanced magnetic resonance imaging: are signal intensity-time curves adequate? Breast Cancer Res Treat 147(2):335–343. doi:10.1007/s10549-014-3072-x
9. Padhani AR, Leach MO (2005) Antivascular cancer treatments: functional assessments by dynamic contrast-enhanced magnetic resonance imaging. Abdom Imaging 30(3):324–341. doi:10.1007/s00261-004-0265-5
10. Kuhl CK, Mielcareck P, Klaschik S, et al. (1999) Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? Radiology 211(1):101–110. doi:10.1148/radiology.211.1.r99ap38101
11. Orel SG (1999) Differentiating benign from malignant enhancing lesions identified at MR imaging of the breast: are time-signal intensity curves an accurate predictor? Radiology 211(1):5–7. doi:10.1148/radiology.211.1.r99ap395
12. Renz DM, Diekmann F, Schmitzberger FF, et al. (2013) Pharmacokinetic approach for dynamic breast MRI to indicate signal intensity time curves of benign and malignant lesions by using the tumor flow residence time. Investig Radiol 48(2):69–78. doi:10.1097/RLI.0b013e31827d29cf
13. Hauth EA, Jaeger H, Maderwald S, et al. (2006) Evaluation of quantitative parametric analysis for characterization of breast lesions in contrast-enhanced MR mammography. Eur Radiol 16(12):2834–2841. doi:10.1007/s00330-006-0348-5
14. Rosenkrantz AB, Sabach A, Babb JS, et al. (2013) Prostate cancer: comparison of dynamic contrast-enhanced MRI techniques for localization of peripheral zone tumor. AJR Am J Roentgenol 201(3):W471–W478. doi:10.2214/AJR.12.9737
15. Huang B, Wong CS, Whitcher B, et al. (2013) Dynamic contrast-enhanced magnetic resonance imaging for characterising nasopharyngeal carcinoma: comparison of semiquantitative and quantitative parameters and correlation with tumour stage. Eur Radiol 23(6):1495–1502. doi:10.1007/s00330-012-2740-7
16. Zahra MA, Tan LT, Priest AN, et al. (2009) Semiquantitative and quantitative dynamic contrast-enhanced magnetic resonance

imaging measurements predict radiation response in cervix cancer. Int J Radiat Oncol Biol Phys 74(3):766–773. doi:10.1016/j.ijrobp.2008.08.023
17. Lambregts DM, Beets GL, Maas M, et al. (2011) Accuracy of gadofosveset-enhanced MRI for nodal staging and restaging in rectal cancer. Ann Surg 253(3):539–545. doi:10.1097/SLA.0b013e31820b01f1
18. Sourbron SP, Buckley DL (2013) Classic models for dynamic contrast-enhanced MRI. NMR Biomed 26(8):1004–1027. doi:10.1002/nbm.2940
19. Kim SH, Lee JM, Gupta SN, Han JK, Choi BI (2014) Dynamic contrast-enhanced MRI to evaluate the therapeutic response to neoadjuvant chemoradiation therapy in locally advanced rectal cancer. J Magn Reson Imaging 40(3):730–737. doi:10.1002/jmri.24387
20. Intven M, Reerink O, Philippens ME (2015) Dynamic contrast enhanced MR imaging for rectal cancer response assessment after neo-adjuvant chemoradiation. J Magn Reson Imaging 41(6):1646–1653. doi:10.1002/jmri.24718
21. George ML, Dzik-Jurasz AS, Padhani AR, et al. (2001) Non-invasive methods of assessing angiogenesis and their value in predicting response to treatment in colorectal cancer. Br J Surg 88(12):1628–1636
22. Yeo DM, Oh SN, Jung CK, et al. (2015) Correlation of dynamic contrast-enhanced MRI perfusion parameters with angiogenesis and biologic aggressiveness of rectal cancer: preliminary results. J Magn Reson Imaging 41(2):474–480. doi:10.1002/jmri.24541
23. Chwang WB, Jain R, Bagher-Ebadian H, et al. (2014) Measurement of rat brain tumor kinetics using an intravascular MR contrast agent and DCE-MRI nested model selection. J Magn Reson Imaging 40(5):1223–1229. doi:10.1002/jmri.24469
24. Martens MH, Subhani S, Heijnen LA, et al. (2015) Can perfusion MRI predict response to preoperative treatment in rectal cancer? Radiother Oncol 114(2):218–223. doi:10.1016/j.radonc.2014.11.044
25. Petrillo A, Fusco R, Petrillo M, et al. (2015) Standardized Index of Shape (SIS): a quantitative DCE-MRI parameter to discriminate responders by non-responders after neoadjuvant therapy in LARC. Eur Radiol 25(7):1935–1945. doi:10.1007/s00330-014-3581-3