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Studying local tumour heterogeneity on MRI and FDG-PET/CT to predict response to neoadjuvant chemoradiotherapy in rectal cancer

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Abstract

Objective To investigate whether quantifying local tumour heterogeneity has added benefit compared to global tumour features to predict response to chemoradiotherapy using pre-treatment multiparametric PET and MRI data.

Methods Sixty-one locally advanced rectal cancer patients treated with chemoradiotherapy and staged at baseline with MRI and FDG-PET/CT were retrospectively analyzed. Whole-tumour volumes were segmented on the MRI and PET/CT scans from which global tumour features ($T2W_{\text{volume}}/T2W_{\text{entropy}}/ADC_{\text{mean}}/SUV_{\text{mean}}/TLG/CT_{\text{mean-HU}}$) and local texture features (histogram features derived from local entropy/mean/standard deviation maps) were calculated. These respective feature sets were combined with clinical baseline parameters (e.g. age/gender/TN-stage) to build multivariable prediction models to predict a good (Mandard TRG1-2) versus poor (Mandard TRG3-5) response to chemoradiotherapy. Leave-one-out cross-validation (LOOCV) with bootstrapping was performed to estimate performance in an ‘independent’ dataset.

Results When using only imaging features, local texture features showed an AUC = 0.81 versus AUC = 0.74 for global tumour features. After internal cross-validation (LOOCV), AUC to predict a good response was the highest for the combination of clinical baseline variables + global tumour features (AUC = 0.83), compared to AUC = 0.79 for baseline + local texture and AUC = 0.76 for all combined (baseline + global + local texture).

Conclusion In imaging-based prediction models, local texture analysis has potential added value compared to global tumour features to predict response. However, when combined with clinical baseline parameters such as cTN-stage, the added value of local texture analysis appears to be limited. The overall performance to predict response when combining baseline variables with quantitative imaging parameters is promising and warrants further research.

Key Points

- Quantification of local tumour texture on pre-therapy FDG-PET/CT and MRI has potential added value compared to global tumour features to predict response to chemoradiotherapy in rectal cancer.
- However, when combined with clinical baseline parameters such as cTN-stage, the added value of local texture over global tumour features is limited.
- Predictive performance of our optimal model—combining clinical baseline variables with global quantitative tumour features—was encouraging (AUC 0.83), warranting further research in this direction on a larger scale.

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Keywords Rectal neoplasms · Chemoradiotherapy · Positron-emission tomography computed tomography · Magnetic resonance imaging · Logistic models

Abbreviations

AIC	Akaike's information criterion
CRT	Chemoradiotherapy
FDG	2-[¹⁸ F]Fluoro-2-deoxy-D-glucose
Gy	Grey
LOOCV	Leave-one-out cross-validation
SUV	Standardised uptake value
TLG	Total lesion glycolysis
TRG	Tumour regression grade
VOI	Volume of interest
W&W	Watch-and-wait

Introduction

In the era of organ preservation, the assessment of response of rectal cancer to neoadjuvant chemoradiotherapy (CRT) has become an increasingly important issue. Early- and pre-treatment prediction of response is gaining interest as this could allow further optimisation of treatment based on the anticipated treatment response. The ultimate aim is to further increase response rates and avoid ineffective and potential harmful treatments in those who are unlikely to benefit.

Several studies have investigated the potential of imaging to predict response, with promising—albeit somewhat inconsistent—results for quantitative imaging biomarkers derived directly from either MRI (including functional sequences like diffusion and perfusion MRI) [1–5] or 2-[¹⁸F]fluoro-2-deoxy-D-glucose-PET (FDG-PET) [1, 4, 6]. So far, there are only few reports that have combined different imaging modalities to build multiparametric response prediction models. These studies have varying success rates (AUCs ranging from 0.51 to 0.94), which is likely related to the large methodological differences between studies and variations in outcome parameters used [7–11].

In addition to these reports, several groups have focused on more advanced parameters derived from image post-processing, in specific parameters related to image texture as a measure of tumour heterogeneity [7, 12–20]. This makes sense from a histopathological perspective, as tumours are typically not homogeneous but show spatial variations in cellular microarchitecture, necrosis, vascularisation and gene expression [21]. Increased intra-tumoural heterogeneity has often been suggested as a potential prognostic factor in oncology as it has been related to the emergence of resistant subpopulations of cells that drive resistance to treatment [12, 22, 23]. A similar relation has been reported for rectal cancer, as several pathology reports have shown an association between tumour heterogeneity and response to neoadjuvant treatment [24, 25].

Image texture analysis offers opportunities to non-invasively study tumour heterogeneity, although quantifying heterogeneity at a microstructural level using medical imaging is challenging due to the large difference in scale between MRI and histology. Hence, texture analysis in medical imaging is most often applied to the tumour as a whole, rendering only global measures of heterogeneity such as mean tumour entropy and uniformity. These measures do not specifically take into account the local variations within the tumour (local heterogeneity), as a result of which potentially important predictive information may be overlooked or averaged out [12].

The goal of this study is to investigate whether quantifying local tumour heterogeneity has added benefit compared to global tumour features to predict response to CRT using pre-treatment multiparametric PET and MRI data.

Materials and methods

This study was approved by the local institutional review board and informed consent was waived due to the retrospective nature of this study.

Patients and outcome definition

The study cohort consisted of 61 locally advanced ($\geq T3$ and/or $N+$) rectal cancer patients, derived from a previously published single institute study cohort [13]. All patients were treated with neoadjuvant chemoradiotherapy (50.4 Gy with concurrent capecitabine-based chemotherapy), underwent pre-treatment MRI+DWI and FDG-PET/CT, and sufficient information was available to establish the final treatment response (histopathology after surgery or > 2 years clinical follow-up to confirm a sustained clinical complete response in patients undergoing watch-and-wait (W&W)). Final response was documented according to the 5-point histopathological tumour regression grade (TRG) by Mandard [26]. Patients with TRG1–2 were categorised as ‘good responders’. Patients with TRG3–5 were categorised as ‘poor responders’. Watch-and-wait patients ($n=7$) with a sustained clinical complete response for > 2 years were considered TRG1 for the purpose of this study.

Imaging and image segmentation

MRI was acquired at 1.5 T (Intera Achieva $n = 43$ or Ingenia $n = 18$, Philips Healthcare). Imaging and image segmentation were performed according to previously published protocols [13] provided in detail in Table 1. In short, the protocol consisted of T2-weighted sequences with 3–5-mm slice thickness in 3

Table 1 MRI protocol

	T2-weighted	Diffusion-weighted
Echo time (ms)	130–150	65.74–84.88
Repetition time (ms)	3427–16738	2480–5545
Echo train length	25–28	53–87
Slice thickness (mm)	3–5a	5
Slice gap (mm)	3.3–7.03	4–6.02
In-plane resolution (mm)	0.78125	1.25–1.71875
Number of averages	2–6	3–10
<i>b</i> values (s/mm ²)	-	0, 1000b
Fat-suppression	-	STIR (<i>n</i> = 32), SPIR (<i>n</i> = 7), SPAIR (<i>n</i> = 22)

STIR, short-TI inversion recovery; SPIR, spectral presaturation with inversion recovery; SPAIR, spectral attenuated inversion recovery

^a *n* = 23 patients were scanned with 5 mm and *n* = 38 with 3-mm axial slice thickness

^b Protocols included 3–7 *b* values ranging from *b*0 to *b*2000 s/mm², but for the purpose of this study, only the *b* = 0 and *b* = 1000 s/mm² series were used for analyses and to calculate the ADC map

Reprint of Table 1 [13]

planes, and an axial echo-planar imaging (EPI) DWI sequence with *b* values 0–1000 s/mm² and slice thickness 5 mm, angled in the same plane as the axial T2W-MRI. No bowel preparation or spasmolytics were given. Apparent diffusion coefficient (ADC) maps were derived from the DWI images by fitting the data to a mono-exponential decay function. 18F-FDG-PET/CTs (3-mm slice thickness) were acquired on a Siemens Biograph 40 TruePoint PET/CT scanner (SIEMENS Healthineers AG) 60 min after an intravenous bolus of 18F-FDG with an activity of either 2.5 MBq/kg (*n* = 52) or 4.0 MBq/kg (*n* = 9) after 6-h fasting and with a full bladder. Attenuation correction was performed using a non-enhanced CT scan with automatic dose modulation. Standardised uptake values (SUV) were calculated according to the recommendations of the Quantitative Imaging Biomarker Alliance [27]. For each patient, volumes of interest (VOI) covering the whole tumour volume were segmented by a board-certified expert radiologist on the T2W and b1000-DWI MRI. PET images were segmented using semi-automated segmentation (using a threshold of 42% of the maximum SUV) [13, 28–30]. These segmentations were then transferred to the corresponding ADC maps and unenhanced CT images.

Quantitative modelling of local texture

Local texture features were extracted from the segmented tumour VOIs of each imaging modality/sequence using the following steps:

1. Normalisation: because T2W-MRI and b1000-DWI images are expressed in arbitrary units that can differ between study visits, protocol settings and subjects, these images were normalised (mean pixel intensity = 300 and standard deviation = 100). ADC, SUV and CT were processed using their original units.

2. Local texture maps: For each imaging type, 3 local texture maps (entropy, mean and standard deviation) were derived from the VOIs using PyRadiomics [31] with a neighborhood of $5 \times 5 \times 5$ pixels. Bin widths of 20, 20, 0.05, 0.5 and 50 were used for T2W-MRI, b1000-DWI, ADC, SUV and CT respectively. A visualisation of the extracted local entropy is depicted in Fig. 1.
3. Histogram metrics: From each local texture map, histogram features (10th, 25th, 50th, 75th, 90th percentile, mean and standard deviation) were derived to describe the distribution of local texture features within the tumour.

This resulted in 21 features per image type/sequence, i.e. 63 MRI features (T2W-MRI, b1000-DWI and ADC) and 42 PET/CT features (SUV and CT). In addition, clinical baseline parameters (mrT-stage, mrN-stage, age, gender and interval between last radiotherapy fraction and final response evaluation) and global tumour measures (tumour volume, mean entropy, mean tumour ADC, mean SUV, total lesion glycolysis (TLG) and mean Hounsfield units) were collected that were available from a previously published study in the same patient cohort [13].

Statistical analysis

The analysis workflow comprised 4 main steps. First, when two or more features showed a strong correlation (Pearson's $\rho > 0.8$), only the feature with the lowest mean absolute correlation was retained for further analysis to reduce the effects of multicollinearity. Second, multivariable logistic regression models were trained with the remaining feature set using forward stepwise feature selection. The modelling process was repeated separately for (1) global imaging features only (including separate sub-analyses using only MRI or PET/CT data

Fig. 1 Example of local entropy heatmaps in a 66-year-old male patient with a large (clinically T4aN1) rectal tumour. Red areas correspond to a high local entropy whereas blue areas represent areas of low local entropy

respectively), (2) local texture features only (including MRI-only and PET/CT-only sub-analyses), (3) global imaging features + clinical baseline parameters, (4) local texture features + baseline parameters and (5) global + local texture features + clinical baseline parameters combined. Third, to prevent the effects of overfitting, the maximum number of selected features for each model was set to 3 (i.e. 1 per 10 patients in the smallest outcome group). Finally, the performance of the different models was compared using Akaike's information criterion (AIC), as a measure of the 'goodness-of-fit' of the model taking into account model complexity [32, 33], and by calculating the area under the receiver operator curve (AUC) to predict a good (TRG1-2) versus poor (TRG3-5) response. Confidence intervals for the training AUC were calculated using the DeLong method [34]. For the models combining clinical baseline parameters with imaging features, an estimate of the model's performance on unseen data was obtained by using bootstrapped leave-one-out cross-validation (LOOCV AUC; 5000 bootstrap samples to calculate LOOCV AUC confidence intervals), in line with methods previously reported [13].

Results

Patient characteristics

Of the 61 study patients, 47 were male, and the median age was 69 years (range 46–88). In total, 13 patients were TRG1 (6 after surgery (10%) and 7 undergoing W&W (11%)), 18 TRG2 (30%), 19 TRG3 (31%), 11 TRG4 (18%) and 0 TRG5 (0%), resulting in a total of 31 good responders (TRG1-2) and 30 poor responders (TRG3-5).

Quantitative modelling of local texture

A correlation matrix for the total feature set and exclusion of features with Pearson's $\rho > 0.8$ is provided in Supplementary Table 1. Results of the multivariable regression models are summarised in Table 2. When looking at imaging features only, local texture features performed better than global tumour features based on the AIC (AIC = 68 vs. AIC = 82), resulting in a training AUC of 0.81 (95%CI 0.70–0.91) for the local texture features and AUC of 0.74 (95%CI 0.61–0.87) for the global tumour features. Similarly, in the MRI-only or PET/CT-only analyses, local texture features performed better (AUC 0.73 for MRI and 0.78 for PET/CT) than global features (AUC 0.70 and 0.50 respectively), though for MRI the difference was small. When imaging features were combined with baseline clinical parameters (e.g. T- and N-stage), performance for local versus global texture features was similar (AIC = 60 vs AIC = 58; AUC = 0.87 vs AUC = 0.88). Adding local texture features to the combination of baseline + global tumour features did not result in improved performance (AIC = 56 and AUC = 0.89). After leave-one-out cross-validation, the model incorporating clinical baseline + global tumour features achieved the highest AUC of 0.83 (95% CI 0.70–0.96) to predict a good response, though differences with the other models were small (Table 2).

Discussion

The aim of this study was to investigate whether there is added value in quantifying local tumour texture (heterogeneity) compared to global tumour features on baseline MRI and 18-F-FDG-PET/CT to predict response to neoadjuvant treatment in

Table 2 Multivariable logistic regression analysis

Imaging only—local texture versus global tumour models			
Model	AIC	AUC (training)	Selected features
Local texture	68	0.81 (0.70–0.91)	CT_mean_75perc, ADC_entropy_10perc, T2_standarddeviation_mean
Local texture MRI-only	76	0.73 (0.60–0.85)	ADC_entropy_10perc
Local texture PET/CT-only	74	0.78 (0.66–0.90)	CT_mean_75perc, CT_standarddeviation_10perc
Global tumour	82	0.74 (0.61–0.87)	T2_entropy, ADC_entropy, SUV_mean
Global tumour MRI-only	83	0.70 (0.57–0.84)	T2entropy, ADC_entropy
Global tumour PET/CT-only	87	0.50 (0.50–0.50)	-
Combined models including clinical baseline variables			
Model	AIC	AUC (training)	AUC (LOOCV)
Clinical baseline + local texture	60	0.87 (0.78–0.96)	0.79 (0.46–0.90)
Clinical baseline + global tumour	58	0.88 (0.80–0.97)	0.83 (0.70–0.96)
Clinical baseline + global tumour + local texture	56	0.89 (0.81–0.98)	0.76 (0.57–0.90)

AIC Akaike information criterion, a measure for ‘goodness of fit’ with lower values indicating a better fit; AUC, area under the receiver operator curve; LOOCV, leave-one-out cross-validation

NB: 95% confidence intervals (CI) are given in parentheses. CIs for the training AUC were determined using the DeLong method. The 95% CIs of the LOOCV AUC were determined using 5000 bootstrap samples

rectal cancer. Results indicate that, when including only imaging parameters, local texture features show a better performance compared to global tumour features to predict a good response with AUCs of up to 0.81 (versus 0.74 for global features) when tested within our own study dataset. While global tumour PET/CT features did not show any predictive performance (AUC 0.50, no significant features), local texture PET/CT features did perform substantially better with an AUC of 0.78. However, the selected local PET/CT features were all derived from CT imaging indicating a limited role for PET. When local texture features were combined with clinical baseline parameters (such as the cT- and cN-stage), the addition of local texture features did not improve the predictive performance of the model compared to the addition of global tumour features, neither on the training data nor after internal cross-validation, indicating that from a clinical point of view, local texture features may be of limited added benefit. Performance for the combination of clinical baseline parameters and global tumour features was encouraging, with an AUC of 0.83 to predict a good response after internal cross-validation.

In rectal cancer, there are multiple previous reports correlating image texture features with response to neoadjuvant treatment [7, 13–20, 35–47]. Some of these studies focused on relatively simple first- and second-order features derived from histogram analysis and grey-level co-occurrence matrices (GLCM) [7, 13, 40, 41, 45], while others assessed advanced features by applying more sophisticated radiomics modelling [14–20, 37–39, 42–44, 46–49]. Overall, studies incorporating higher order features into their analysis tended to achieve a higher performance to predict response (AUCs of 0.69–0.97) versus those using only simpler first- and second-order features (AUCs 0.51–0.89). Although this difference in

performance can be attributed to many factors, it might be a hint supporting the hypothesis of our current study that assessing spatial (local) variations within the tumour may be beneficial, as higher order features tend to take the local texture throughout the tumour into account (for example, often used radiomics features such as grey level size zone matrix features summarise the size and number of local homogeneous patches throughout the tumour). In our current image-based analysis, local texture features indeed showed a better predictive performance compared to global tumour measures (AUC 0.81 vs. 0.74).

Our analysis suggests that amongst the local texture features, those derived from the ADC-map, CT and T2W-MRI provide the best predictive value as these were amongst the selected features in the forward selection process. With respect to CT, there have only been a limited number of reports focusing on rectal tumour response prediction using CT texture analysis [42, 44, 47, 49], which is probably related to the fact that CT is not routinely used for the local staging of rectal cancer. Bibault et al derived 1683 texture features from planning CTs of which 28 features (first-order histogram and 2D and 3D second-order grey-level co-occurrence matrix features) were significantly correlated with pathological complete response and were combined with clinical T-stage to train a deep neural network. The performance of the resulting network (AUC 0.72) was compared to classical methods such as linear regression analysis (AUC 0.59) and support vector machines (AUC 0.62) [47]. However, since the selected features were not specified by the authors it is not possible to directly compare these findings to our current results. In a second study, Hamerla et al tried to reproduce the findings of Bibault, but with limited success (balanced accuracy score of 0.50) [42]. In another study by Chee et al, good responding

patients showed significantly lower entropy, higher uniformity and lower standard deviation on baseline CT images [49]. As a critical note, our results with respect to CT should perhaps be interpreted with some caution, because of the low-dose quality of our CT scans (that were merely acquired for PET attenuation correction), which are inherently more heterogeneous due to increased noise levels. Therefore, these findings should still be confirmed in future studies using diagnostic quality CTs. Based on our findings, the contributing role of PET appears to be limited. From a clinical point of view, the impact of this negative result is probably small, as PET is generally not routinely performed as part of the diagnostic workup for the local staging of rectal cancer.

Similar to our current findings, promising results have been previously reported for DWI texture features, in particular those derived from ADC maps, to predict response to CRT in rectal cancer. Reported AUCs when using these features in addition to other MRI features range between 0.69 and 0.97 [15, 17, 19, 35]. Most of these studies combined features derived from DWI/ADC with other modalities such as T1-weighted, T2-weighted and/or DCE-MRI and showed better performance when incorporating these features in a multiparametric model compared to models using features derived from only a single modality [17, 19, 35]. In contrast, there are also some reports in which ADC texture features were not included amongst the selected predictors when entered into a multivariate model together with other imaging features [7, 13, 18, 20]. For T2-weighted features (either alone or in combination with clinical variables), AUCs ranging between 0.71 and 0.93 have previously been reported to predict response, though methods of image analysis, image post-processing and statistical analysis differ substantially between reports [14, 16, 38, 45, 46, 48]. In addition to rectal cancer, there have been numerous reports focusing on image-based prediction models of tumour response and outcome in other target organs such as head and neck [50], breast [51], liver [52], lungs [53] and bladder and prostate [54]. The reported model performance and image modalities used vary widely between reports and there are major methodological differences between the various studies, making it difficult to draw any general conclusions yet on the value of such models in oncologic settings.

There are some limitations to our study design. Due to the retrospective design and small study cohort, only a limited number of features (max 3) were used in the multivariable analysis to prevent overfitting, which limited our analyses to simpler models. We assessed local texture for each modality individually (using histogram metrics), which does not take into account the local spatial correlation between different imaging modalities. Such analysis would require that cross-modality images are accurately registered on a voxel-basis, which is a challenge on its own as image registration can also introduce new uncertainties [55]. Finally, although all images were

resampled to a common pixel spacing, T2W images were in part acquired with 5 mm instead of the standard 3 mm slice thickness, which may have had an influence on the extracted feature values. Since the majority of features included in our final prediction models were derived from other modalities than T2W MRI, we believe this potential effect will likely be small.

In our current study, we correlated local texture patterns on imaging to one ‘global’ measure of the final tumour response (TRG). For future research, it would be interesting to gain more in-depth insights into how local therapeutic effects as assessed on imaging correlate to underlying response effects on corresponding histopathology. In addition, recent technical advances such as the introduction of integrated MR-linear accelerator systems into the clinical setting create new opportunities for day to day monitoring of global and local tumour changes during treatment [56]. Such developments can significantly increase our understanding of how local texture features can be related to local treatment outcome which might provide a basis for further personalised treatment (e.g. targeted boosting strategies) in the future.

In conclusion, this study has shown that it is possible to quantify local tumour heterogeneity using local texture maps derived from baseline MRI and FDG-PET/CT imaging. When entered in multivariate prediction models using only imaging data, quantification of local texture features offered a better performance to predict response compared to ‘simple’ global tumour measures, with features derived from MRI and CT being the main predictors and no clear role for PET. When combined with clinical baseline parameters (such as T- and N-stage), the added value of local texture versus global tumour analysis was limited, indicating that from a clinical perspective, the added benefit of such more advanced image analysis will likely be small. The predictive performance of our optimal model—combining clinical baseline variables with global imaging features—was encouraging, warranting further research in this direction on a larger scale.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr Doenja MJ Lambregts.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors, Mr Sander Roberti, has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Boards (retrospective analysis of prospectively obtained observational data).

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in:

Schurink (2020) *Eur Radiol*
 Curvo-Semedo (2011) *Radiol*
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 Janssen (2012) *Int J Rad Oncol Biol Phys*
 Van Stiphout (2011) *Radiother Oncol*
 Janssen (2010) *Int J Rad Oncol Biol Phys*
 Janssen (2010) *Radiother Oncol*
 Lambregts (2011) *Ann Surg Oncol*
 Lambregts (2015) *Ann Surg*
 Martens (2015) *Int J Radiat Oncol Biol Phys*
 Lambregts (2018) *Dis Colon Rectum*

Methodology

- retrospective
- diagnostic/prognostic
- performed at one institution

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