



Research Article

The Role of Texture Analysis of MRI in Prediction of Local Recurrence and Distant Metastasis in Locally Advanced Rectal Cancer: A retrospective Cohort study

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Abstract

Purpose: Locally advanced rectal cancer (LARC) is treated by neoadjuvant chemoradiotherapy (NCRT) followed by surgery after restaging with magnetic resonance imaging (MRI). Texture analysis (TA) is a novel imaging biomarker that can assess heterogeneity in MRIs by measuring grey-level intensities distribution. This study hypothesizes that TA of MRI is an imaging biomarker that can predict local recurrence and distant metastasis.

Method: This is a retrospective analysis of all patients diagnosed with LARC who received NCRT and had MRI scans between 2003-2014 at Colchester University Hospital. Region of interest was drawn around the tumor or its location on T2 MRI images. Six texture parameters were systematically extracted from Textural histograms of post-treatment scans. These parameters were examined to determine their ability to predict local recurrence and distant metastases through Kaplan-Meier survival curves and log-rank tests.

Results: 113 patients with LARC were included. Two texture parameters were significantly able to predict local recurrence: Entropy ($p=0.033$) and mean of positive pixels (MPP) ($p=0.045$). Five parameters were able to predict distant metastases: SD($p=0.015$), entropy($p=0.017$), MPP($p=0.005$), skewness ($p=0.046$), and Kurtosis ($P=0.019$). Upon dichotomizing by the optimal cut-off values, Kaplan-Meier Log rank test showed that entropy and skewness significantly predicted distant metastases.

Conclusions: MRI textural features are potentially significant imaging biomarkers in predicting local recurrence and distant metastases in LARC.

Keywords: Texture analysis; MRI; locally advanced rectal cancer; local recurrence; distant metastasis

Introduction

The standard of care for patients diagnosed with locally advanced rectal cancer (LARC) includes neoadjuvant chemoradiotherapy (NCRT) followed by surgical resection, often with curative intent [1]. MRI is currently the gold standard modality for staging rectal cancer by detecting poor prognostic factors such as extra-mural venous invasion (EMVI) and the involvement of the circumferential resection margin (CRM)[2]. Its role in monitoring response to NCRT and predicting treatment outcomes such as distant spread and survival is evolving [3]. Several biomarkers, including genetic, blood markers, and imaging biomarkers, have been proposed to monitor and

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predict response to NCRT and identify either favorable or unfavorable parameters that might alter management plans. Texture analysis (TA) is a new imaging biomarker modality that assesses heterogeneity in medical images by measuring the distribution of grey-scale pixel intensities within a region of interest. A histogram of the distribution of the grey-level intensities can then be analyzed, and Radiomic texture features are then extracted [4]. Different Texture parameters can be derived from the histogram distribution. Their definitions and implications are summarized in table 1 below.

In a recent publication, Texture analysis of post-treatment MRI scans has been shown to be able to identify patients who had a complete response after their NCRT in LARC [5]. In that study, six texture features were extracted from post-treatment MRI scans. Its results showed that five of the six features, namely mean, Standard Deviation, entropy, skewness and mean of positive pixels, were able to identify a complete response. The area under the ROC curve ranged from 0.750 to 0.880. This study utilizes the same patient cohort with a longer follow up interval. This study aims to assess whether texture analysis of MRI images can directly predict local recurrence (LR) and distant metastasis (DM) among patients with LARC after receiving NCRT.

Material and Methods

This is a retrospective cohort study that included 114 patients diagnosed with LARC who received NCRT, followed by surgical resection of the rectum in a university hospital. Our standard protocol states that those patients undergo a pre-treatment MRI scan to stage the tumour locally.

Tumours greater than T3 or with involved or threatened circumferential resection margin (CRM) receive long course NCRT to downstage the cancer and clear the CRM. Six weeks after completion of the treatment, patients are restaged with a second MRI scan, and if downstaging has been achieved, proceed to surgical resection six weeks later (12 weeks after completion of the NCRT). Survival data, local recurrence and distant metastases rates have been updated retrospectively. Deceased patients were censored to their date of death, whilst alive patients and recurrence status were censored to 30/08/2020.

Eligibility criteria

Patients were excluded if they did not receive long course NCRT or did not have an MRI after treatment. Furthermore, patients who have undergone a local excision procedure such as endoscopic mucosal resection or transanal resections and other patients with missing full histopathological assessment or lymphatic status were also excluded. Mucinous tumors and adenocarcinomas with mucinous degradation were excluded from the analysis, as mucinous cancers represent a separate entity pathologically and radiologically. This cohort of patients and methodology have been published previously in Aker et al’s study to predict the complete responders of rectal LARC patients to NACT [5].

Neoadjuvant Protocol

In order to pre-operatively downstage the tumour and achieve a negative CRM, the local trust CRT treatment for LARC utilizes long-course chemo-radiotherapy. 45–50.4 Gy are administered in 25-28 portions over a 5-week period in

Table 1: Texture parameters derived from the histogram distribution of grey-level intensities, their definition, and implications.

Parameter	Definition	Implications
Mean (1 st order)	The average intensities of pixels within a ROI	Higher mean suggests a whiter image.
		Low or negative mean suggests a darker area.
SD (1 st order)	A measure of dispersion from the average	A low SD means that distribution of intensities is close to the mean, i.e more homogenous.
		A high SD means that intensities are spread out among a large range of values, i.e. more heterogeneous.
Skewness (1 st order)	A measure of the asymmetry of the histogram.	Positive skewness: indicates that the right tail of the histogram is longer than the left side.
		Negative skewness: indicates that the left tail of the histogram is longer than the right side.
		A zero value indicates that the values are evenly distribute on either side of the mean (normal distribution).
Kurtosis (1 st order)	A measure of the peakedness (or flatness) of the histogram	Positive kurtosis: distribution is more peaked than the normal distribution.
		Negative kurtosis: distribution is flatter than the normal distribution.
Entropy (2 nd order)	Measures disorder of the distribution of the intensities.	Higher values mean more chaos.
		Lower values mean more homogeneity.

long-course radiation. On days 1 to 28, oral Tegafur-uracil (240 mg/m²) is administered in conjunction with 90 mg/day of leucovorin [6].

MRI protocol

According to the trust MRI protocol, post-treatment restaging MRI scans are carried out six weeks following the end of the neoadjuvant therapy. Ordinarily, surgery is performed 12 weeks following the end of the therapy. Four weeks after receiving therapy, a small sample of patients got a second MRI scan. An initial localizing scan and a sagittal T2-weighted fast spin-echo (FSE) sequence scan were both part of the imaging technique. To determine the pelvic side wall and nodal illness, an axial T2-weighted FSE was performed to scan the whole pelvis from the iliac crest to the symphysis pubis. To facilitate precise tumour staging, an oblique axial T2-weighted FSE high-resolution sequence was carried out with slices positioned perpendicular to the long axis of the rectum. For the purpose of procedure validation,

two radiologists examined and evaluated MRI pictures. The histological staging and the patients' clinical outcomes were hidden from both radiologists.

Local recurrence

Local recurrence was defined as evidence of recurrent disease within the pelvis, at the site of anastomosis, or perineal wound after surgical resection; this can be evident on CT, MRI pelvis, or positron emission tomography (PET-CT).

Distant metastasis

Distant metastasis was defined as any spread of cancer to the lung or liver, as diagnosed by the Multi-Disciplinary Treatment (MDT) team. No histopathological confirmation was necessary to diagnose distant metastases.

Texture analysis

Texture analysis was performed by drawing the region of interest (ROI) on the axial MRI T2-weighted slice across the

Table 2: Means and Standard deviation of textural parameters extracted from post-treatment scans in predicting LR. Statistically significant results are in bold. SD: standard deviation. MPP: Mean of positive pixels.

	Local recurrence n=16/113 (14.2%)	Non-Local recurrence n=96/113 (85%)	P-Value	AUC	Youden's Optimum cut-off
Mean	-70.12 +/- 25.24	-63.15 +/- 26.35	0.069	--	--
SD	180.83 +/- 24.42	220.84 +/- 36.68	0.164	--	--
Entropy	5.93 +/- 0.66	6.08 +/- 0.68	0.033	0.716	6.105
MPP	141.91 +/- 10.48	213.48 +/- 13.69	0.045	0.682	154.75
Skewness	0.166 +/- 0.005	0.259 +/- 0.005	0.056	--	--
Kurtosis	0.650 +/- 0.12	0.44 +/- 0.12	0.139	--	--

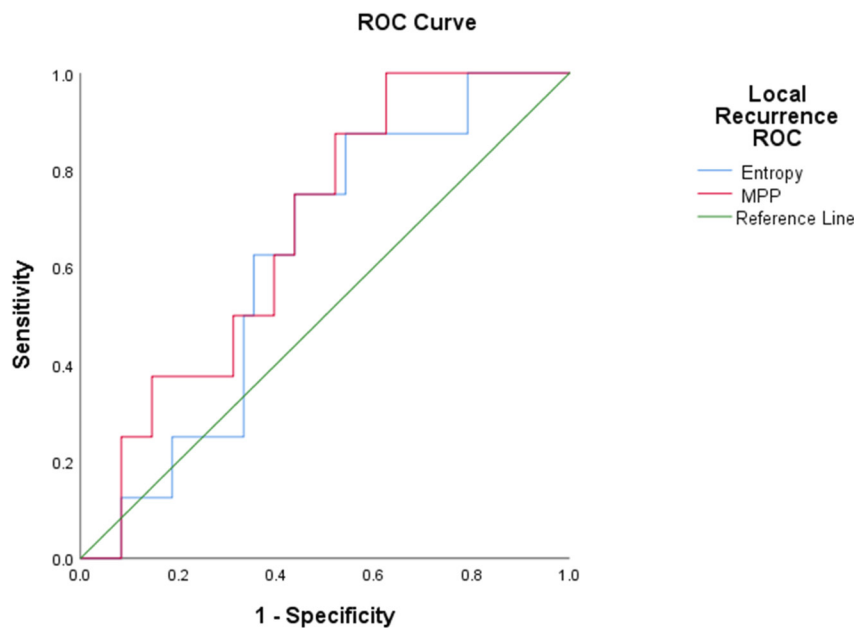


Figure 1: ROC Curve of Entropy and MPP in predicting Local Recurrence. ROC: Received operator characteristic. MPP: mean of positive pixels.

widest segment of the tumour, or in cases of good response, its previously localized area. Six texture features describing the distribution of grey-level pixel intensities within the ROI were extracted from the histogram of grey-level intensities. This was performed using proprietary commercially available TexRAD research software (version 3.3, TexRAD Ltd www.texrad.com - part of Feedback Plc, Cambridge, UK). The work in this study has been reported in line with the STROCSS criteria [7].

Statistical analysis

After extracting the texture parameters from post-treatment MRI scans (methodology has been published previously [5]), Mann-Whitney U test was first utilized to determine whether extracted texture parameters have the ability to identify patients who have developed either local recurrence (LR) or distant metastases (DM). Receiver operating characteristic (ROC) analysis of each statistically significant parameter was performed to identify the area under the ROC curve (AUC). Youden's index was then used to determine the optimal cut-

off value of each parameter with the highest discriminatory sensitivity and specificity, i.e. the value point closest to the left upper corner of the ROC curve. Those cut off values were then used to dichotomize the patients in order to determine whether that parameter has a prognostic role in predicting LR or DM using the Kaplan-Meier survival log-rank test.

Results

One hundred and thirteen patients were included in this study. Pathological complete response was encountered in 24 (21%) patients. Patients were followed up for a median of 120 months. Local recurrence occurred in 16 patients (14.2%). Distant metastases occurred in 27 patients (24%). Two of the six extracted texture parameters were, in fact, able to statistically predict local recurrence. While 5 of the six parameters were able to predict distant metastasis. Table 2 and 3 summarizes the findings, the significant texture parameters, their p-values, the area under the ROC curve (AUC), and the Youden index optimal cut-off value.

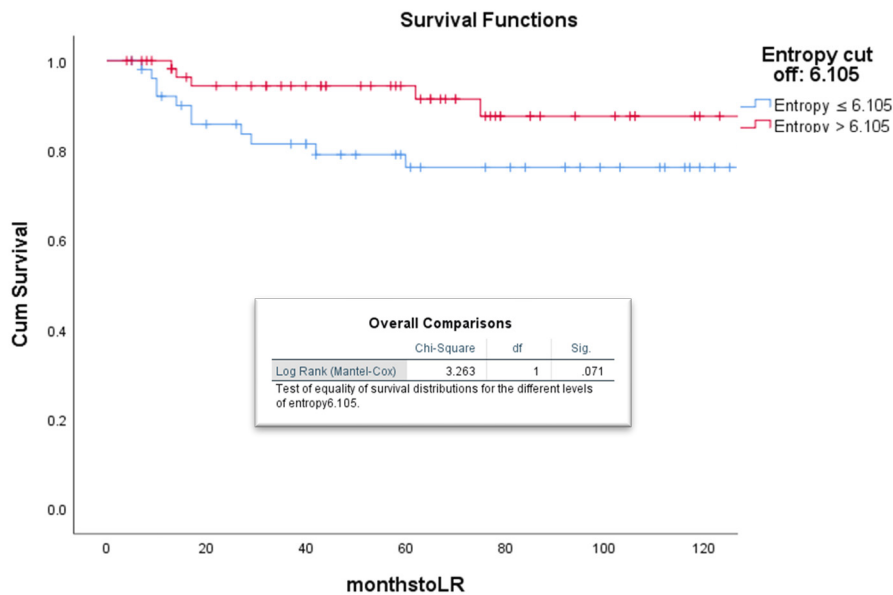


Figure 2: Kaplan-Meier Curve and log rank test after dichotomising Entropy in predicting Local Recurrence.

Table 3: Means and Standard deviations of texture parameters extracted from post-treatment scans in predicting distant metastases. Statistically significant results are in bold. SD: Standard Deviation. MPP: Mean of positive pixels.

	Distant metastasis n= 27/113 (23.9%)	No distant metastasis n= 86/113 (76.1%)	P-Value	AUC	Youden's Optimum cut-off
Mean	-81.28 +/- 29.95	-56.38 +/- 22.13	0.183		
SD	260.14 +/- 24.02	203.63 +/- 17.92	0.015	0.591	203.845
Entropy	6.17 +/- 0.73	6.02 +/- 0.67	0.017	0.588	5.84
MPP	226.48 +/- 18.14	180.78 +/- 16.54	0.005	0.624	155.265
Skewness	0.30 +/- 0.04	0.22 +/- 0.05	0.046	0.628	0.435
Kurtosis	0.24 +/- 0.01	0.53 +/- 0.01	0.019	0.623	--

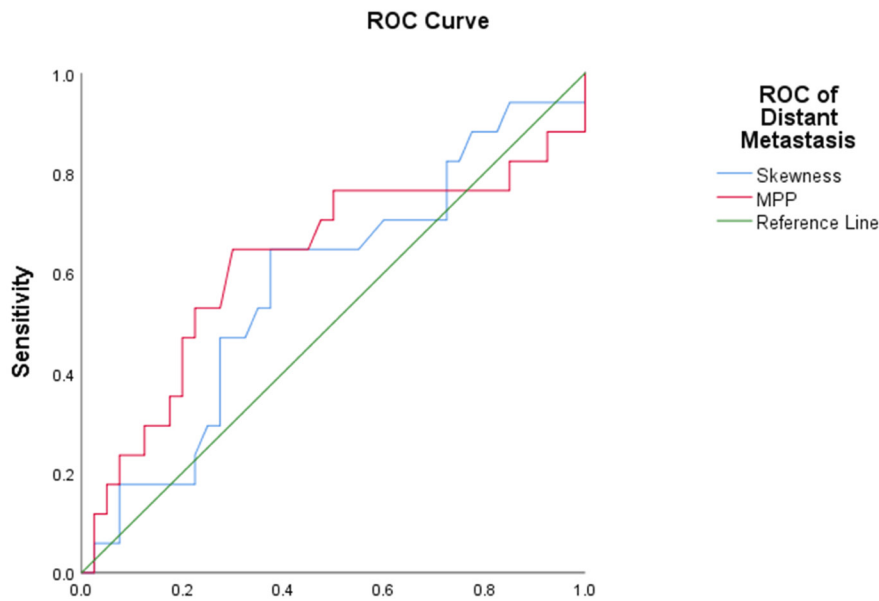


Figure 3: ROC Curve of skewness and MPP in predicting distant metastasis. ROC: Received operator characteristic. MPP: mean of positive pixels.

MRTA in predicting Local recurrence:

In predicting local recurrence, entropy and mean of positive pixels were both significantly able to predict local recurrence (see Table 2)

Entropy had an AUC of 0.716 and an optimal cut off value of 6.105. While the mean of positive pixels (MPP) had an AUC of 0.682 and an optimal cut off value of 154.75. Using the Kaplan-Meier Long rank test, the results were not significant (log rank 0.071) (See figure 1 and figure 2).

MRTA in predicting Distant Metastases:

In predicting distant metastasis, 5 of the 6 extracted texture parameters were significantly able to predict patients who eventually developed metastatic cancer (see table 3).

The greatest AUC was for mean of positive pixels (MPP) and skewness, with and AUC of 0.624 and 0.628 respectively (figure 3).

Upon dichotomizing the patient cohorts by their optimal cut off values, entropy and skewness were both able to significantly predict distant metastases by the Kaplan-Meier Log rank test (see figure 4 and 5).

Discussion

This study aimed to establish the role of TA as an imaging biomarker in predicting whether patients with LARC who received NCRT will subsequently develop local recurrence or distant metastases. Patients were followed up for a median of 10 years. Texture features were systematically extracted from post-NCRT MRI scans. Our results showed that 5

of the 6 extracted texture features (SD, Entropy, mean of positive pixels, skewness, and kurtosis) were significantly able to predict patients who subsequently developed distant metastases. Two texture parameters (entropy and mean of positive pixels) were able to predict patients who eventually developed local recurrence. Furthermore, this study also identified the optimal cut off values for those parameters at which it is most discriminatory between those who will ultimately develop LR or DM. In a previous study utilizing the same patient cohort and process, Aker et al. [5] have shown that patients who have experienced complete response after NCRT have different texture features than patients whose cancers did not respond completely to the NCRT. Their results showed that 5 of the extracted texture parameters: mean ($p = 0.033$), SD ($p = 0.048$), entropy ($p = 0.007$), mean of positive pixels ($p = 0.032$), and skewness ($p = 0.000$) were all able to identify patients with complete response with an Area under the ROC curve as high as 0.88.

TA's role as a potential imaging biomarker in assessing tumour response to treatment or predicting outcomes, such as survival has recently been reported in some studies [8,9]. Ganeshan B et al. [10] investigated the role of texture analysis of non-enhanced CT scans of seemingly normal livers of patients with colorectal cancer in predicting those who will eventually develop liver metastasis. They extracted texture features from 15 control patients with no eventual malignancy, 9 patients with extra-hepatic metastasis but no liver involvement, and 8 patients who eventually developed liver metastases from colorectal cancers. They showed that 2 of the features, namely entropy and uniformity, were

statistically able to predict patients who eventually developed hepatic metastases compared to patients with no tumour (entropy, $p=0.0257$) and patients with the extra-hepatic disease (uniformity, $p=0.0143$). Our study did not include any TA of liver imaging; however, our results showed that entropy ($p=0.017$), extracted from post-treatment rectal MRI scans could independently predict distant metastasis (DM) with a cut off and AUC values of 5.84 and 0.588 respectively. In another study Jalil O et al. [11] aimed to examine whether MR textural features from the baseline and post-treatment rectal MRI could predict long-term survival. They recruited 56 LARC patients, extracted the Textural features from pre-and post-treatment MRIs and used the Cox analysis to reveal which features predicted overall survival

(OS), disease-free survival (DFS) and Relapse-free survival (RFS). They concluded that OS was significantly predicted by pre-treatment MPP ($p=0.008$) and post-treatment skewness ($p=0.034$). Furthermore, of the texture features extracted from post-treatment scans, entropy ($p=0.002$) and kurtosis ($P=0.009$) were able to predict DFS and RFS. Similarly, in our study, post-treatment MPP and entropy were significant among the features that predicted both local recurrence and distant metastasis, with AUC value ranging from 0.588 to 0.716. These results augment TA's role as a potential predictive marker of significant clinical events such as disease recurrence and distant spread. Other studies also analyzed the correlation between TA and clinical outcomes in different kinds of malignancies, such as, predicting survival

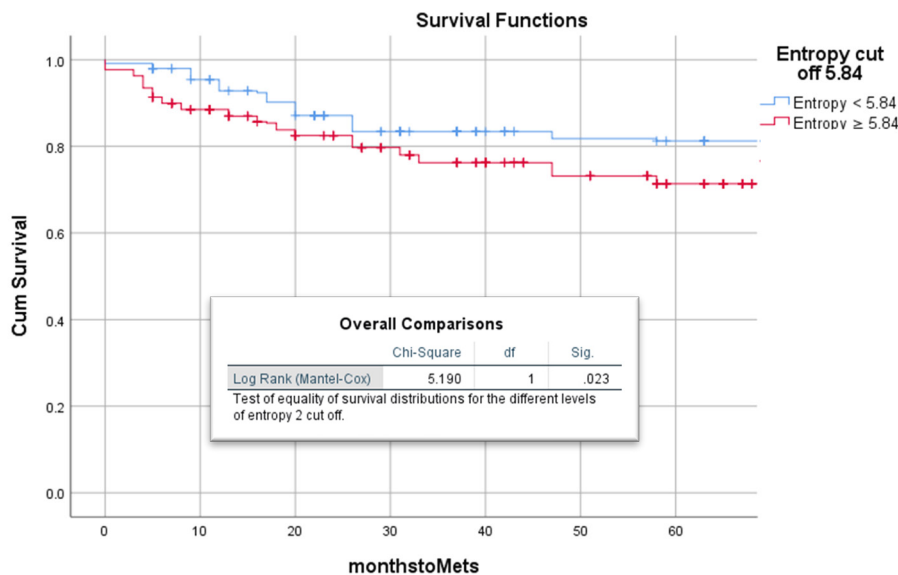


Figure 4: Kaplan-Meier curve of entropy in predicting distant metastasis.

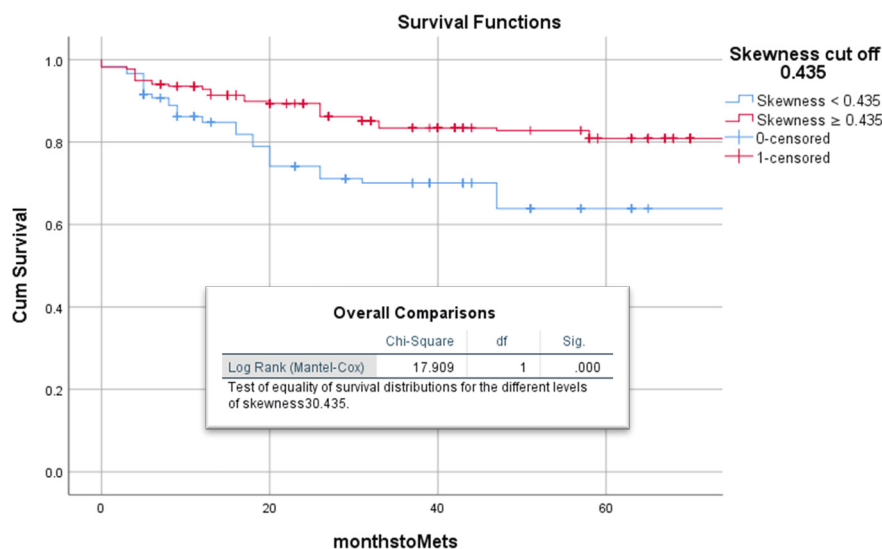


Figure 5: Kaplan-Meier curve of skewness in predicting distant metastasis.

in patients with non-small cell lung cancer [12], esophageal cancer [13] and head and neck cancer [14]. TA also used as an early marker of treatment response in metastatic renal cancer [15] and recurrence in advanced cervical cancer [16]. The studies mentioned above suggest that textural analysis is a promising non-invasive biomarker for predicting several clinical outcomes of tumors. Our study has a novel hypothesis to predict LR and DM from rectal MRI and would be significant in standardization of a prediction model in future trials. However, our study has some limitations. Firstly, this study's results showed an AUC of 0.628 and 0.716, which are not as accurate as other currently utilized modalities. This is partially due to this novel technique, which will require further studies, and perhaps dedicated imaging, in order to improve outcomes. Secondly, reproducibility is one of the main limitations in utilizing TA in clinical decision making. The absolute value of extracted texture features is dependent on MRI parameters and is user dependent. If used for decision making, each unit should calculate its own optimal cut off values, which is not feasible. Additionally, absence of a TA's unified protocol obstructs generalization and repeatability [8]. This study and many recent studies selected the ROI as the widest cross-sectional diameter for analysis [2,8,11] in order to limit sampling bias; in contrast, other studies suggest that implementing the whole tumor textural analysis would be more representative of tumor heterogeneity than using the single largest cross-sectional area analysis [16]. However, Aker et al. showed a high inter-rater and intra-rater reproducibility in selecting and in drawing the ROI. Another tool for enhancing repeatability of MRI by adding more reliable parameters, such as Apparent Diffusion Coefficient (ADC) and perfusion parameter (Ktrans). Some studies [17] suggested that Multiparametric MRI is a repeatable technique for the prediction of neoadjuvant treatment response in rectal cancer. Furthermore, choosing which timepoint of scanning (Pre- or mid- or posttreatment MRI) to analyze is another point of debate. Our TA was performed on post-treatment scans. In contrast, MRTA of pre-treatment scans (CT or MRI) showed significant outcomes in other cancer studies, such as colon [18], breast [19], lung [20] and rectum [21] as well, in predicting treatment response, recurrence and staging [18]. Pretreatment scan analysis allows evaluating inherent tumor heterogeneity [22] to predict the tumors which are intrinsically, genetically, or morphologically more aggressive, which are more prone to invasion or distant spread. This would remarkably alter the conventional management of cancers that depends only on visual and clinical staging of tumors. In our study, we only studied the intra-tumoral features without analysis of any textural features from outside the selected ROI, such as lymph nodes features. Studying the correlation between lymph node imaging features and tumor recurrence would improve the prediction of outcomes in further research.

Nevertheless, including TA in rectal cancer management routine investigations is still very challenging because of the above limitations. Therefore, a prospective multicentric trials and large collaborative work including clinicians, radiologist and software programmers might develop a more rewarding noninvasive unified textural model. Additionally, Further correlation studies between tumor heterogeneity and other parameters, such as genomic instability are critical to reflect the actual tumor microenvironment which augments the predictive ability of textural parameters. Radiogenomics is an emerging radiomic branch that links the imaging phenotypes to the tumour genetic profile to analyze the full tumour burden, without a need for invasive tissue biopsy. This would avoid the issue of invasiveness and sampling errors [23]. Texture features, therefore, could be a future non-invasive biomarker of tumour heterogeneity and genomic instability that would help to personalize the treatment without the complexity of further invasive procedures or sampling bias.

Conclusion

Our results indicate that textural parameters could predict local recurrence and liver metastasis in LARC patients. This could be a significant step in formulating a algorithmic model to personalize the treatment of cancer patients by using a non-invasive predictive imaging biomarker. However, more clinical, histological and genomic correlations is still required in the future research.

Provenance and peer review Not commissioned, externally peer-reviewed.

Main Points

- 1) Textural analysis (TA) assess the heterogenicity of lesions in radiological imaging. It has shown a prediction ability for detecting clinical outcomes in different types of cancers, such as treatment response, survival and recurrence.
- 2) Textural parameters extracted from rectal cancer MRI could assess the heterogenicity of the tumor and determine the potentially metastatic and recurrent lesions.
- 3) Our study hypothesize that TA could be utilized as an imaging biomarker in predicting whether patients with LARC who received NCRT will subsequently develop local recurrence or distant metastases.
- 4) This technique would personalize the treatment for each patient according to potential risk of metastasis in his imaging features. Either for "wait and watch" arm or further oncological/surgical treatment.
- 5) This technique could be applied in the prediction the outcomes in other types of cancer as well, such as lung, renal and liver.

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