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DIAGNOSTIC IMAGING IN ONCOLOGY

Radiomics and machine learning analysis based on magnetic resonance imaging in the assessment of liver mucinous colorectal metastases

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Abstract

Purpose The purpose of this study is to evaluate the Radiomics and Machine Learning Analysis based on MRI in the assessment of Liver Mucinous Colorectal Metastases.Query

Methods The cohort of patients included a training set (121 cases) and an external validation set (30 cases) with colorectal liver metastases with pathological proof and MRI study enrolled in this approved study retrospectively. About 851 radiomics features were extracted as median values by means of the PyRadiomics tool on volume on interest segmented manually by two expert radiologists. Univariate analysis, linear regression modelling and pattern recognition methods were used as statistical and classification procedures.

Results The best results at univariate analysis were reached by the wavelet_LLH_glcm_JointEntropy extracted by T2W SPACE sequence with accuracy of 92%. Linear regression model increased the performance obtained respect to the univariate analysis. The best results were obtained by a linear regression model of 15 significant features extracted by the T2W SPACE sequence with accuracy of 94%, a sensitivity of 92% and a specificity of 95%. The best classifier among the tested pattern recognition approaches was k-nearest neighbours (KNN); however, KNN achieved lower precision than the best linear regression model.

Conclusions Radiomics metrics allow the mucinous subtype lesion characterization, in order to obtain a more personalized approach. We demonstrated that the best performance was obtained by T2-W extracted textural metrics.

Keywords Radiomics · Magnetic resonance imaging · Liver metastasis

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Introduction

Colorectal cancer (CRC) is the third most frequent worldwide cancer, accounting for 10% of new tumour cases in 2020[1]. Moreover, its prevalence is supposed to rise quickly to > 3 million cases per year by 2040 [2, 3]. Metastatic disease represents the main cause of death and the liver is the mainly metastasis site [4–8]. At the primary tumour diagnosis, liver metastases (CRCLM) are present in about 20% of patients, whereas almost 40–50% of patients will develop metastases during follow-up [8–16]. In addition, about 60% of patients will develop new liver lesions even after a R0 resection of the primary metastases. Several risk factors for liver recurrence have been recognised, as T3/T4 CRCs, node positive of the primary cancer, synchronous and more than 3 liver lesions [17, 18]. On the other hand, the adjuvant chemotherapy administration, with a complete or partial response of the CRCLM, has been associated a lower recurrence rate [19]. With regard to histological sub-types, there are few data on patient outcome. The most common sub-type is adenocarcinoma not otherwise specified (NOS), followed by mucinous one, which represents 5–15% of all CRCs. Mucinous adenocarcinoma is associated a greater burden of mutations in KRAS and BRAF genes, a higher rate of microsatellite instability and a higher rate of CpG island methylator phenotype high (CIMP-H) tumours [21, 22], so that mucinous sub-type causes an increased risk of metastases and worse overall survival (OS) so as a decreased response to conventional chemotherapy based on fluorouracil, oxaliplatin and irinotecan [20–22]. So, it is evident that a proper liver mucinous metastases characterization consents a better patient selection to avoid superfluous treatments [23–29].

Today, Radiomics analysis is a new tool in imaging setting, allowing to assess tissue at microscopic level, in order to obtain quantitative data that could be employed as biomarkers to increase diagnostic, prognostic and predictive accuracy in oncological setting [30–39]. The Radiomics key-targets are the rise of the tumour detection rate, a proper prognosis assessment and the detection of patients who are responsive to specific therapy [27, 40–47]. In this context, Radiomic is conceived to be applied in decision support of precision medicine, using standard of care images that are routinely acquired in clinical practice [38, 39, 48–54].

Although, several researches have assessed the role of Radiomics in CRCLM patients [55–57], at the best of our knowledge, no study have assessed the ability of Radiomics features, obtained by MRI, in mucinous liver metastases characterization. The purpose of this study is to evaluate the Radiomics and Machine Learning Analysis Based on MRI in the assessment of mucinous CRCLM.

Materials and methods

Local Ethical Committee board accepted this retrospective study renouncing to the patient informed consent.

Patients were selected by radiological database considering the period from January 2018 to June 2021, according to the following inclusion criteria: (1) Liver pathological proven metastases; (2) MRI study of high quality in presurgical setting and (3) A follow-up Computed Tomography (CT) study of at least six months after surgery. The exclusion criteria were: (1) Discordance among the imaging diagnosis and the pathological one, (2) No MRI study with hepatospecific contrast agent (EOB-MRI).

The patient cohort included a training set and an external validation set. The internal training set was formed by 51 patients (18 women and 33 men) with 61 years of median age (range 35–82 years) and 121 liver metastases. The validation cohort, from "Careggi Hospital", Florence, Italy, was formed by 30 patients with single lesion (10 women and 20 men) and 60 years of median age (range 40–78 years). The patient characteristics are summarized in Table 1.

MR imaging protocol

MR studies were performed with two 1.5 T MR scanners: Magnetom Symphony (Siemens, Erlangen, Germany) and Magnetom Aera (Siemens). The images were acquired before and after an intravenous (IV) contrast agent (CA) injection.

The MRI study protocol included conventional sequences, T1 weighted (W), without contrast medium administration, and T2-W, Diffusion Weighted Imaging (DWI) with seven b values in order to obtain functional parameters with mono-exponential model, and T1-W sequences after the

Table 1 Characteristics of the study population (81 patients)

Patient description	Numbers (%)/range
Gender	Men 53 (65.4%)
	Women 28 (34.6%)
Age	61 y; range: 35–82 y
Primary cancer site	
Colon	52 (64.2%)
Rectum	29 (35.8%)
Prior chemotherapy	81 (100%)
Hepatic metastases description	
Patients with single nodule	52 (64.2%)
Patients with multiple nodules	29 (35.8%)/range: 2–13 metastases
Nodule size (mm)	mean size 36.4 mm; range 7–58 mm
Mucinous carcinoma	25 (30.9%)
RAS mutation	42 (51.9%)

administration of contrast medium. In Table 2 we reported MR study protocol.

According to the different phase of patient management, our study protocol includes the possibility to administrate a liver-specific contrast (in pre-surgical setting) and a non-liver-specific contrast (in characterization and staging phase).

In this study, we assessed images obtained employing a liver-specific agent (0.1 mL/kg of Gd-EOB-BPTA-Primovist, Bayer Schering Pharma, Berlin, Germany). The VIBE T1-W sequence was acquired with two different flip angle (10 and 30 degrees). A power injector (Spectris Solaris® EP MR, MEDRAD Inc., Indianola, IA, USA) was used to administrate the CA at an infusion rate of 2 mL/s.

After contrast medium administration, VIBE T1-weighted FS (SPAIR) sequences were acquired in different phases: arterial (35 s delay), portal/venous (90 s), transitional phases (120 s), and hepatospecific phase (20 min).

MRI post-processing

For each volume of interest (VOI), 851 radiomics features were extracted as median values using open-source PyRadiomics python package [58] and as reported previously in [76]. The extracted features are in compliance with feature definitions as described by the Imaging Biomarker Standardization Initiative (IBSI) [59] and as reported in [https://readthedocs.org/projects/pyradiomics/downloads/ Accessed on 21 December 2021]. Median values of radiomics features were considered for each segmented VOI.

Reference standard

Histopathologic data, from routine report, were used as reference standard for determining metastasis histological subtype.

Statistical analysis

Statistical analysis includes both univariate and multivariate approaches performed considering a per-lesion analysis.

The assessment of observer variability was performed by calculating the intraclass correlation coefficient. A non-parametric Kruskal–Wallis test was performed to identify differences statistically significant of radiomics metrics of two groups (mucinous type versus non-mucinous type).

Receiver operating characteristic (ROC) analysis was performed using the Youden index to calculate the optimal cut-off for each metric and then the area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy.

Given the high number of textural features, a first selection of variables was made based on the results obtained from the univariate analysis: significant at nonparametric Kruskal–Wallis test and with an accuracy $\geq 80\%$. A linear regression modelling was used to assess the best linear combination of significant textural features.

Pattern recognition techniques including support vector machine (SVM), k-nearest neighbours (KNN), artificial neural network (NNET), and decision tree (DT)) were performed to calculate the diagnostic performance considering the significant features [60]. The best model was identified calculating the highest area under ROC curve and highest accuracy. Each classifier was trained with a 10-k fold cross validation. Moreover, an external validation cohort was used to validate the findings of the best classifier. McNemar test was used to evaluate that the results of the dichotomy tables were statistically significant. A p value < 0.05 was considered as significant. The statistical analyses were performed using the Statistics and Machine Toolbox of MATLAB R2021b (MathWorks, Natick, MA, USA).

Table 2 MR acquisition protocol

Sequence	Orientation	TR/TE/FA (ms/ms/deg.)	AT (min)	Acquisition Matrix	ST/Gap (mm)	FS
Trufisp T2-W	Coronal	4.30/2.15/80	0.46	512×512	4 / 0	Without
HASTE T2-W	Axial	1500/90/170	0.36	320×320	5 / 0	Without and with (SPAIR)
HASTE T2w	Coronal	1500/92/170	0.38	320×320	5 / 0	Without
SPACE T2W FS	Axial	4471/259/120	4.20	384×450	3/0	With (Spair)
In–Out phase T1-W	Axial	160/2.35/70	0.33	256×192	5 / 0	without
DWI	Axial	7500/91/90	7	192×192	3 / 0	Without
Vibe T1-W	Axial	4.80/1.76/30	0.18	320×260	3 / 0	With (SPAIR)

TR Repetition time, *TE* Echo time, *FA* Flip angle, *AT* Acquisition time, *ST* Slice thickness, *FS* Fat suppression, *SPAIR* Spectral adiabatic inversion recovery

Results

On univariate analysis, a variable number of metrics were statistically significant, which were distinctive when extracted from the diverse MR sequences: 15 significant predictors extracted from T2W SPACE; 13 significant predictors extracted from the arterial phase; 12 significant predictors extracted from the portal phase; 12 significant predictors extracted from the EOB-phase.

The best results at univariate analysis were reached by the wavelet_LLH_glcm_JointEntropy extracted by T2W SPACE sequence with accuracy of 92%, a sensitivity of 83%, a specificity of 94%, a PPV and a NPV of 78 and 95%, respectively, with a cut-off value of 4.61 (Table 3).

Linear regression model increased the performance obtained respect to the univariate analysis (see Table 4). The best results were obtained by a linear regression model of 15 significant features extracted by the T2W SPACE sequence with accuracy of 94%, a sensitivity of 92%, a specificity of 95%, a PPV and a NPV of 83 and 98%, respectively.

These results were statistically different from the results of univariate analysis and compared to the results of metrics extracted by other MR sequences (p value < 0.01 at McNemar test).

Table 5 reported the coefficients of metrics and intercept of the best linear regression model. The ROC of this linear regression model was reported in Fig. 1.

The best classifier among the tested pattern recognition approaches was KNN; however, KNN achieved lower precision than the best linear regression model (Table 5).

All results of the dichotomy tables were statistically significant (p value < 0.01 at McNemar test).

Table 3 Univariate analysis results to predict mucinous type

	T2W SPACE	Arterial phase	Portal phase	EOB-phase
	wavelet_LLH_glcm_JointEntropy	wavelet_HLH_glszm_LargeAreaHighGrayLevelEmphasis	wavelet_LLL_glcm_ClusterTendency	Wavelet_HHL_glszm_ZoneVariance
AUC	0.85	0.59	0.70	0.63
Sensitivity	0.83	0.35	0.38	0.46
Specificity	0.94	0.99	1.00	0.96
PPV	0.78	0.90	1.00	0.75
NPV	0.95	0.85	0.86	0.87
Accuracy	0.92	0.85	0.87	0.85
Cut-off	4.61	−0.02	408.22	1,289,505

Table 4 Linear regression and Pattern recognition analysis with significant features

Linear regression of significant features extracted by	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	Cut-off
T2W SPACE	0.96	0.92	0.95	0.83	0.98	0.94	0.26
Arterial phase	0.93	0.77	0.99	0.95	0.94	0.94	0.37
Portal phase	0.88	0.77	0.96	0.83	0.94	0.92	0.36
EOB-phase	0.26	1.00	0.04	0.64	1.00	0.64	−0.17

The best classifier (KNN) results with significant features extracted by	Dataset	AUC	Accuracy	Sensitivity	Specificity	Training time [sec]	Model Type and parameters
T2W SPACE	Training set	0.92	0.89	0.96	0.65	3.2	Weighted KNN; number of neighbours:10; distance metric: Euclidean; distance weight: squared inverse
	Validation set	0.83	0.89	0.93	0.71		
Arterial phase	Training set	0.87	0.88	0.97	0.56	8.55	
	Test set	0.91	0.91	0.96	0.73		
Portal phase	Training set	0.89	0.93	0.8	1	11.8	
	Test set	0.92	0.91	0.99	0.62		
EOB-phase	Training set	0.93	0.91	0.96	0.73	7.51	
	Validation set	0.89	0.88	0.89	0.8		

Table 5 Linear regression model to predict mucinous type

Features	*Coefficients*	*P value*
Intercept	− 2.42	0
original_gldm_SmallDependenceEmphasis	3.77	0.77
original_firstorder_RobustMeanAbsoluteDeviation	0	0.54
original_firstorder_90Percentile	0	0.89
original_glszm_ZonePercentage	− 1.79	0.85
wavelet_HLL_gldm_DependenceNonUniformityNormalized	18.81	0
wavelet_LLH_gldm_SmallDependenceEmphasis	5.18	0.74
wavelet_LLH_gldm_DependenceNonUniformityNormalized	6.79	0.28
wavelet_LLH_glcm_JointEntropy	− 1.35	0.04
wavelet_LLH_glcm_DifferenceEntropy	1.17	0.25
wavelet_LLH_glcm_SumEntropy	1.24	0.09
wavelet_LLH_glcm_DifferenceAverage	1.17	0.06
wavelet_LLH_firstorder_90Percentile	0.01	0.14
wavelet_LLH_glszm_ZonePercentage	− 12.59	0.28
wavelet_LLL_firstorder_90Percentile	0	0.99
wavelet_LLL_glszm_ZonePercentage	− 3.36	0.02

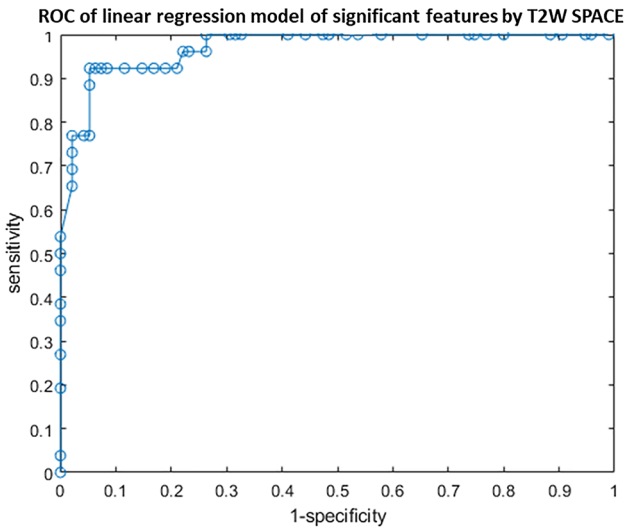

Fig. 1 ROC of linear regression model of significant features by T2W SPACE

Discussion

To date, the prognosis of mucinous CRC remains highly debated, mainly because of the treatment strategy deviation for metastatic disease [20–22]. Although this sub-type lesion has a greater propensity for peritoneal dissemination, the liver is still the most common metastatic site and accounts for up to 50% of all metastases [2]. Management mucinous CRCLM has long been controversial. One important reason is that liver metastases are frequently accompanied by metastases of other sites, thus, a large proportion of these metastases are considered unfit for surgical resection. However, the relatively poor response to chemotherapy, indicates that surgery may occupy a more important role in the treatment of these patients, although the probability of recurrence remains high. In this context, it is evident that a proper lesions identification during presurgical imaging setting is the crucial element that should allow an appropriate treatment approach. Also, considering the idea that the mucinous subtype lesion has an adverse prognostic impact compared to non-mucinous subtype, since, mucinous subtype is correlated to the idea that it has a higher risk of metastases, worse overall survival (OS) and an impaired response to conventional chemotherapy [20–22], it is clear that radiologists should correctly recognize mucinous metastases. However, the presence of mucin substantially characterizes the lesions' pattern on imaging studies that could suggest a diagnosis of benign lesions as hepatic cysts or haemangiomas, so that the correct diagnosis remains a challenging. At the best of our knowledge few studies have assessed the radiological features of mucinous colorectal metastases [55–57], and no one has evaluated the Radiomics and Machine Learning Analysis Based on MRI in the assessment of liver mucinous colorectal metastases.

In this study, we found that several metrics were statistically significant to characterize mucinous sub-type: 15 extracted from T2W SPACE; 13 from the arterial phase; 12 from the portal phase and 12 from the EOB-phase. The best results at univariate analysis were reached by the wavelet_LLH_glcm_JointEntropy extracted by T2W SPACE sequence with accuracy of 92%, a sensitivity of 83%, a specificity of 94%, a PPV and a NPV of 78 and 95%, respectively, with a cut-off value of 4.61. Also, linear regression model increased the performance obtained with a linear

regression model of 15 significant features extracted by the T2W SPACE sequence with accuracy of 94%, a sensitivity of 92%, a specificity of 95%, a PPV and a NPV of 83 and 98%, respectively.

To date, several researches have evaluated the Radiomics in liver metastases, focussing attention on mutational status, prognosis and recurrence [32, 33, 47, 61–77]. The study by Andersen et al. demonstrated a correlation between homogeneity features and worse overall survival (OS) [62]. Lubner et al. showed that the skewness degree was inversely correlated to KRAS status while the entropy with OS [64]. The possibility of stratifying patients for recurrence in liver remnants has been shown BY Ravanelli et al. [69]. In our previous studies, we showed that radiomics features obtained by EOB-MRI phase, arterial and portal phase so as by T2-W sequences, allow to predict clinical outcomes following liver resection in Colorectal Liver Metastases [19, 76–83].

Radiomics is an evolving research field that enables quantitative metrics to be obtained within medical images in order to acquire lesion characteristics such as heterogeneity and shape and which can, alone or in combination with other relevant data, be used for the resolution of clinical questions.

Ours results confirmed the capacity of radiomics and machine learning analysis to identify as biomarkers, several features that could guide the treatment choice in patients with liver metastases, in order to obtain a more personalized approach. In fact, the possibility to correlate radiomics parameters to mucinous sub-type offers notable advantages over qualitative assessment, allowing one to tailor cancer therapy to the patient, to predict response to treatment, to distinguish favourable subsets of patients from those with poor prognosis, to select patients that may benefit of surgical treatment.

Although many studies have shown that radiomics is very promising, there has been little standardization and generalization of radiomics analysis, which limits the use of this approach in the clinical setting. Clear limitations regarding data quality control, repeatability, reproducibility, generalizability of results and issues related to model overfitting [61–70, 84–86]. In fact, it is known that different aspects of data heterogeneity are due to variations in acquisition parameters (e.g. numbers of iterations and subsets, reconstruction type and algorithm, and temporal and spatial resolution) and image processing methods (segmentation method and gray-level discretization). Consequently, to allow the repeatability, reproducibility, generalizability of results, protocol studies should be optimized to obtain the standardization of protocols. In addition, depending on the software package for extracting features and the number of filters applied, the number of features extracted varies from a few to unlimited; reducing the number of features to build statistical and machine learning models is of crucial importance for generating valid and generalizable results [84].

This study has several limitations: (1) The small sample size, although the analysis was done on a homogeneous group and on all single lesion; (2) The retrospective nature, (3) A manual segmentation. Furthermore, we not evaluated: (4) The impact of chemotherapy on our data, while we assessed all single study protocol phase demonstrating that the best performance was obtained by T2-W extracted metrics. These data open the opportunity to radiomics analysis also on abbreviated study protocol, when the patient is unfit for contrast administration [47, 72].

Conclusion

In the present study, radiomics metrics, obtained by EOB-MRI study, allow to characterize mucinous subtype lesion, in order to obtain a more personalized approach. However, we did not assess the impact of chemotherapy, while we evaluated all single study protocol phase demonstrating that the best performance was obtained by T2-W extracted metrics. These data open the opportunity to radiomics analysis also on abbreviated study protocol, when the patient is unfit for contrast administration.

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Data availability The data presented in this study are available at link https://zenodo.org/record/6589924#.YpI6vGhBy3A.

Declarations

Conflicts of interest The authors have not disclosed any conflict of interest.

Ethical standard Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Institutional review board statement This study aligned with National appropriate guidelines and procedures. The Local Ethical Committee board approved this retrospective study.

Informed consent statement This study aligned with National appropriate guidelines and procedures. Renouncing the need for informed patient consent given the study nature.

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