RESEARCH ARTICLE

RADIOMIC BIOMARKERS IN AMULTIVARIATE ANALYZE FOR PREDICTING OUTCOME IN LOCALLY ADVANCED RECTAL CANCER

Camil Ciprian MIRESTEAN[1,4]., Ovidiu PAGUTE[1]., Ramona ROMAN[1]., Alexandru Dumitru ZARA[1]., Calin BUZEA[1]., Roxana Irina IANCU*[2,3] and DragosTeodor IANCU[1,2]

[1]Regional Institute of Oncology Iasi
[2]"Gr. T. Popa" University of Medicine and Pharmacy Iasi
[3]"Sf. Spiridon" Universitary Hospital Iasi
[4]University of Medicine and Pharmacy Craiova

ARTICLE INFO	ABSTRACT
	Tumor regression grade (TRG) is a predictor factor response to multimodal neo-adjuvant treatment in rectal cancer (chemo-radiotherapy followed by curative resection). DWORAK TRG score is considered a good predictor of disease free survival (DFS). Despite a correctly applied multimodal treatment, only 20% of the patients will have complete tumor regression (complete pathological response) while 20-40% will experience no regression or progressive disease on the surgical sample. The purpose of these study is to identify in a multivariate analysis the clinical, pathological and imagistic predictors and to identify possible correlations between the radiomics markers (Haussdorf distance for tumor contours, grey level matrix analysis), the length and volume of the tumor and mesorectum, pathological biomarkers (lymphovascular an perineural invasion) and the response to the neoadjuvant therapy evaluated by DWORAK TRG score. One of the major challenge in the use of radiomics is the standardization of acquisitions. Although IRM imaging is considered superior in the evaluation of rectal tumors extention, the use for computerized image processing of data obtained from CT-planning simulation for radiotherapy was preferred for uniformity in the acquisition of CT data. Radiomic computerized imaging analysis can become a non-invasive method that will identify "bad responders" to neoadjuvant treatment and will select patients requiring an intensification of preoperative treatment.

INTRODUCTION

Neoadjuvant chemo-radiotherapy with 5-Fluorouracil or Capecitabine followed by surgical treatment by total mesorectal excision (TME) is recommended as standard multimodal therapy for patients with non metastaic, locally advanced rectal cancer (LARC). This therapeutical protocol provide improved locoregional control and higher anal sphincter function preservation rates. Neoadjuvant chemo-radiotherapy also offers an increased rate of complete pathological response (ypT0N0M0), consisting of absence of tumor cells in the resected specimen. Magnetic resonance imaging is essential in assessing the local extent of the disease and in the correct staging of rectal cancer. MRI imaging is also used in the delineation of target volumes for performing the radiotherapy treatment plan. MRI biomarkers like tumor volume, apparent diffusion coefficient (ADC) ,dynamic contrast enhanced magnetic resonance imagining (DCE-MRI) were evaluated in correlation with tumor response to neoadjuvant therapy without proving prognostic value. Radiomics is a relatively new method of analyzing quantitative imaging features or texture parameters from medical imaging and by correlating these results with pathological diagnostics, data sets for feature extraction can be created in order to be used as non-invasive imaging biomarkers. Tumor heterogeneity characterization in relation to multimodal treatment response by extracting textural features begins to be more and more frequently used. Correlation of response to treatment with parameters extracted from textural analysis create a huge potential for texture analysis to be a noninvasive, cheap and rapid method of assessing the intratumoral heterogeneity for various types of cancers [1].

✉Corresponding author: **Roxana Irina IANCU**
"Gr. T. Popa" University of Medicine and Pharmacy Iasi

Radiomics was a defined complex method that consisted in the development of processes for the extraction of quantitative features that resulted in the conversion of medical images into mineable data and the processing of these data in order to guide medical decisions[2].

Despite all these encouraging results of radiomics use in preclinical studies, there are a few things that need to be taken into account to allow a radiomics transition to clinical routine. Imaging Biomarker Standardization Initiative is a project that includes experts in various areas of medical imaging and its role is to solve the problem of radiomic imaging biomarker standardization, mainly focusing on CT and PET imaging. The standardization is relatively straightforward for CT and PET imaging, both techniques based on quantitative imaging parameters (Hounsfield Units and Standardized Uptake Values). MRI brings in more issues in image analysis. Radiomics texture analysis consisting of a large number of features derived from the analysis of pixel-to-pixel neighborhoods and the relationship of one (or several) pixels to another. Non-standardized pixel-values and variations of signal intensities, depending on some acquisition parameters, including type scanner, selected sequence, coil and field parameters. These reasons for standardized extraction of quantitative imaging features remain extremely challenging and robust of diagnostic radiomics for a translation to clinical routine remains questionable.

Quantitative MR technique might represent interesting alternatives for radiomics analyses, which should be further investigated. Besides this, radiomics remains an extremely interesting trend in radiology, moving towards a concert with other 'omics' fields such as genomics, proteomics, metabolomics etc. in a 'multi-omics' approach and finally leading the way towards precision medicine for better patient outcome. In order to have a valid and reproducible result in radiomics, it is essential to ensure the repeatability of features of extraction algorithms and some studies have shown that radiomics features reproducibly measured from CT images in CT imaging for non-small cell lung cancer[3].

Aim and Scopes

The aim of the study is to present the possibilities of using radiomics in the pre-therapeutic evaluation of non-metastatic advanced local rectal cancer in order to identify the risk of therapeutic failure. The use of extracted radiomic features associated with clinical and biological parameters can be used in multivariate analysis to identify a complex predictive model regarding the DWORAK tumor regression in the pathologic pathway.

MATHERIALS AND METHODS

Multimodal treatment of locally advanced rectal cancer includes radiotherapy in a total dose of 45Gy in 25 fractions on the target volume of the mesorectum and internal, externa, common iliac and presacral lymph nodes and with a boost of 5,4Gy in 3 fractins on the target volume of rectum and mesorectum, concomitant with oral chemotherapy with Capecitabine (825 mg / m2 orally twice daily) followed by surgery (total mesorectal excision) at 10-12 weeks after chemo-radiotherapy. Radiotherapy planning includes for all patients CT simulation for delineating the planning target volumes (PTVs) and radiosensitive organs at risk (OARs). CT simulation was performed using a Siemens Somatom AS CT scaner. A radio-opaque marker was placed on the anal verge and the patients were placed supine with both hands on the chest, taking a bladder filling protocol with 500ml of water 30 minutes before the procedure. CT scan was performed from the level of the third lumbar vertebra until the middle of the femur with incremental protocol thickness of 3 mm. Subsequently, the simulation images were fused with pelvic MRI with contrast agent images and a rigid co-registration algoritm was performed for a acurate delineation of the tumor extension. CT simulation is a standardized procedure and in the majority of cases is performed at the center where radiotherapy planning will be calculate and the treatment will be deliver to the patient[4].

The selection of radiotherapy planning CT simulation images for radiomics textural features extraction provides an increased level of standardization compared to MRI imaging. An image originated on a transversal slice selected from the half-length of the mesorectum, choosing the limits of the ROI (region of interest) a rectangle including the whole mesorectum was saved in bitmap image format and was selected for radiomic analysis. The acquired images were analyzed with a free application named MaZda of a computer program for calculating texture parameters in digitized images under development since 1998[5].

MaZda allows computation of a variety of statistical parameters that are derived from image histogram, absolute gradient, run-length matrix co-occurrence matrix and autoregressive model. One of the latest additions to MaZda are texture parameters derived from wavelet analysis. The run-length matrix-based parameters are computed 4 times for each ROI (for vertical, horizontal, 45-degree and 135-degree directions). The co-occurrence matrix-based parameters are computed up to 20 times, for (d,0), (0,d), (d,d), (d,-d) where the distance d can take values of 1, 2, 3, 4, and 5[6],[7].

For 5 cases of local rectal cancer, the mesorectum was delimited (figure1) and image analysis was performed by segmenting with Mazda software and other ROIs (rectum contour). The textural features were analyzed for both the entire image and the ROI of the rectum (figure 2, figure 3).
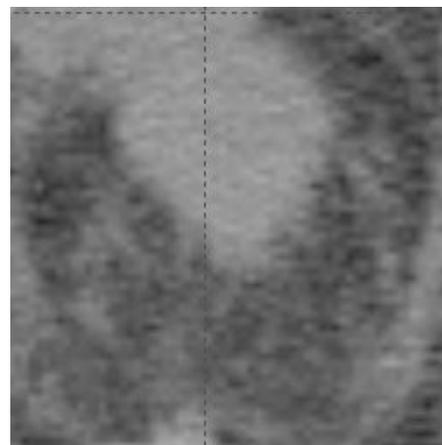

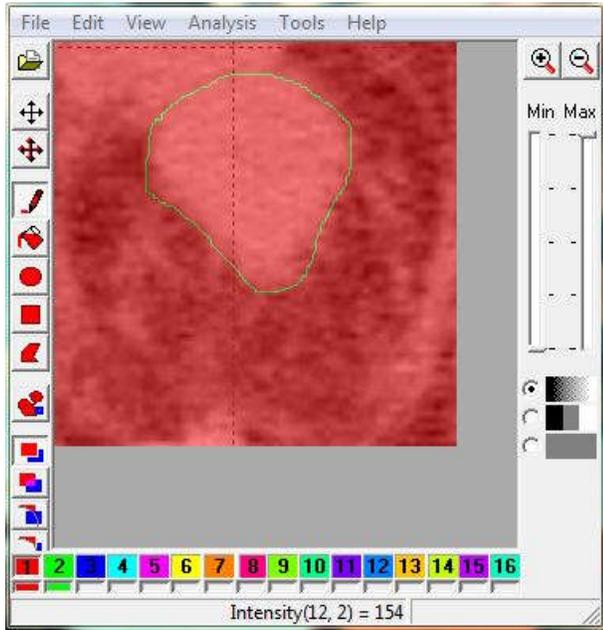**Figure no 1** ROI selected from one CT simulation image

Figure no 2 MaZda free software interface - image pepared for analysis and ROIs delineations
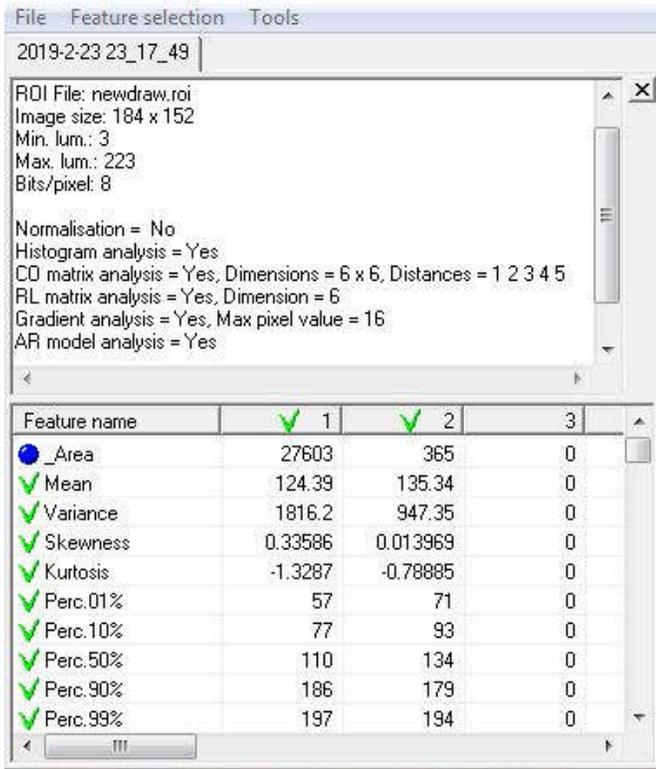

Figure no 3 MaZda free software analysis report - texture radiomics features

DISCUSSIONS

The concept of using extracted imaging parameters is not new, radiomics are currently being investigated by several research groups in terms of predictive value in medicine, the interest being increased in the context of increased digitization in the hospital, the introduction of medical records and the implementation of databases containing large amounts of information and images associated with increasing the processing power of these data. In this age of Big Data, in the field of medical research, a new field of medical research is being developed, which allows the integration of several sources and types of data to personalize the treatment, radiomics being a cornerstone in these steps for integrating images information in this context. One of the most difficult missions of radiomic research is the standardization of acquisition parameters to eliminate sources of errors due to false positives or false negatives, standardization being a mandatory step before the implementation of radiomics in the clinical practice [8].

Radiomics opens new opportunities in diagnosis and prediction of response to therapy by promoting the concept of precision medicine and by individualizing cancer management Radiomics opens new perspectives of a research direction, and the radiomics will underpin clinical trials combining image characteristics with molecular data genomics and proteomics with clinical information and biological informations. All these approaches are based on the concept of a non-invasive assessment with the final object - the improvement of patients therapy and prognosis. Radiomics could not be developed without the improvement of image processing performance[9].

The exact determination of tumor regression (TRG), primary tumor ypT, and pelvic lymph nodes ypN, and surgical-pathological staging after neoadjuvant chemo-radiotherapy, reflects the therapeutic response, being in many studies correlated with prognosis and the risk of unfavorable evolution. TNMs are relatively objective and reproducible, but for the neoadjuvant therapy response different classification systems have been proposed for TRG, which has led to variability of the in classification of tumor regression reported in studies. The most commonly used systems are proposed by Ryan *et al*., Mandard *et al*. Dworak *et al*. MARD and Dworak regression systems after neoadjuvant in rectal cancer are classified in 5 degrees due to residual tumor and fibrosis[10][11][12].

RESULTS

The choosing of the CT images obtained from virtual simulation for radiotherapy planning offers a standardization of acquisition of superior data through the uniformity of acquisition parameters (table 1).

Table no 1 Radiomics features values for 5 cases extracted from CT simulation images

Feature	Case 1		Case 2		Case 3		Case 4		Case 5	
	S 1	S2	S 1	S 2	S1	S2	S1	S2	S1	S2
Mean	112.3	122.38	144.25	141.43	145.13	153.56	112.1	129.62	124.39	135.34
Variance	638.79	318.99	615.25	323.77	1542.7	570.78	1797.8	509.7	1816.2	947.35
Skewness	0.30624	-4391	-0.6958	-0.1297	-0.5038	-0.6276	0.0009226	-0.2139	0.33586	0.01397
Kurtosis	-0.9762	-0.756	0.06754	-0.1234	-0.666	0.24802	-1.1252	-0.641	-1.3287	-0.7889
Perc 01%	67	85	78	101	51	83	27	80	57	81
Perc 10%	82	99	109	118	90	121	59	99	77	93
Perc 50%	107	121	148	142	151	157	106	130	110	134
Perc 90%	151	146	172	166	191	181	169	159	186	179
Perc 99%	160	155	183	180	202	197	180	175	197	194

CONCLUSIONS

The use of textural characteristics correlated with the clinical and biological parameters of the patient can be used to create a predictive model of response to neoadjuvant therapy, helping to personalize advanced local cancer therapy beyond the guidelines used in the clinic.

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