Challenges and Promises of Radiomics for Rectal Cancer

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Challenges and Promises of Radiomics for Rectal Cancer

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Abstract

Purpose of Review This literature review aims to gather the relevant works published on the topic of Radiomics in Rectal Cancer. Research on this topic has focused on finding predictors of rectal cancer staging and chemoradiation treatment response from medical images. The methods presented may, in principle, aid clinicians with the appropriate treatment planning options. Finding appropriate automatic tools to help in this task is very important, since rectal cancer has been considered one of the most challenging oncological pathologies in recent years.

Recent Findings Radiomics is a class of methods based on the extraction of mineable, high-dimensional data/features from the routine, standard-of-care medical imaging. This data is then fed to machine learning algorithms, with the goal of automatically obtaining predictions regarding disease stage and therapeutic response.

Summary The literature reviewed suggests that Radiomics will continue to be a part of the body of research in oncology in the upcoming years. However, and excluding very few studies, proper validation on the performance of the methods (mainly with external datasets) is still one of the main limitations of the field, which strongly limits their clinical applicability. Progress will only occur if the community opens itself to collaborate with different groups, as data availability and limited shareability continues to be the barrier for its development. Nowadays, Radiomics is used for nearly every type of cancer. In particular, for rectal cancer, the need for predicting treatment response will continue to demand and boost research in this field.

Keywords Rectal cancer · Radiomics · Staging · Treatment response

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Introduction

According to the latest global epidemiological assessment of *rectal cancer* (RC) performed by GLOBOCAN in 2018, there are more than 700,000 new cases of RC annually worldwide making it the 8th most common cancer. In 2018, the estimated number of deaths worldwide caused by RC was more than 310,000 (3.2% of the total number of cancer deaths, 10th most common cause of cancer-related deaths) [1•]. New studies project that "the global burden colorectal cancer is expected to increase by 60%, to more than 2.2 million new cases and 1.1 million deaths by 2030" [2]. These figures show that RC is one of the most challenging malignancies in modern oncology, as it also requires multidisciplinary approach of different specialties (gastroenterology, radiology, surgery, radiation oncology, histopathology, and medical oncology). In fact, medical imaging is fundamental to the staging and assessment of treatment response of RC tumors and guides clinicians to plan the optimal treatment regimen for their patients [3].

The standard of care for *locally advanced rectal cancer* (LARC) patients has been, in the last decade, *total mesorectal excision* (TME) after preoperative neoadjuvant chemoradiotherapy (CRT) [4–6]. The latter has been demonstrated to lead to tumor downstaging and downsizing and therefore improving surgical resectability, rate of sphincter-saving procedures, and long-term disease-free survival [7]. In particular, CRT has been shown to be associated with a 50–61% reduction in risk of loco-regional recurrence (for stage T3–4 and/or N1–2 LARC) compared to surgery alone [8, 9].

Unfortunately, CRT can lead to serious adverse effects, such as drug toxicity, fecal incontinence, and urinary and sexual dysfunctions [10–12]. It is therefore highly desirable to accurately stage rectal cancer, both to identify patients who will benefit from CRT and to avoid overtreating those who do not. But even if we avoid CRT, TME by itself is not free of functional complications and can also lead to patient morbidity. Additionally, many LARC patients may end up with a permanent stoma—abdomino-perineal amputation with terminal colostomy—due to low located lesions or tumor invasion into the sphincter complex.

In a growing number of specialized centers worldwide, an alternative approach known as the "watch-and-wait" policy has been implemented [13•], based on the fact that approximately 15–30% of LARC patients show a *pathologic complete response* (pCR) after CRT [7, 14••]. Consequently, it is of extreme importance to provide clinicians with accurate information that allows for the prediction of which cases are the most likely to present a complete response, rendering TME unnecessary [15].

Medical imaging (all different modalities) has had a relevant role in the staging of rectal cancer and has played an important part both in treatment planning and in selecting patients that may show response to CRT [15]. Particularly, T2-weighted (T2w) and diffusion-weighted (DW) magnetic resonance imaging (MRI) have shown to be important imaging biomarkers for the detection, characterization, and assessment of therapeutic response of cancers [7]. In fact, DW MRI is nowadays recommended in international clinical practice for rectal cancer imaging [15], specifically to assess response to CRT.

The most accurate modality for identification of complete response after CRT is digital rectal examination and rectoscopy, combined with MRI with DWI [16]. Unfortunately, clinical assessment is mainly dependent on the experience of the examiner; henceforth, the qualitative interpretation is subjective and often leads to suboptimal positive and negative predictive values. Consequently, there is a growing shift away from qualitative and subjective interpretations of medical images, towards the use of quantitative techniques that can help to reduce variability and, in principle, improve patient outcomes [17]. Quantitative imaging allows the high-throughput extraction of informative features that provide clinical insight into differences that the tissues exhibit [18–20]. Additionally, there is a current focus on, and demand for, increased personalization, on the basis of the characteristics of each specific disease and particular patient, an approach that is termed "Personalized or Precision Medicine" [21].

Quantitative imaging is becoming increasingly relevant in clinical practice, as it provides valuable information for clinicians. Further investigation has drawn attention to automated data characterization algorithms that convert imaging data into high-dimensional features, in a field currently referred to as *radiomics* [22•, 23]. Radiomic features provide a complete, multivariate, and detailed representation of a tumor's phenotype, which is clearly not possible for a human observer, even an experienced and trained one. However, the extracted radiomic features depend on the image acquisition, reconstruction, and processing choices and settings, which naturally vary across institutions and operators, creating a challenge for the robustness and reproducibility of this type of techniques [22].

This work proposes to review the existing literature on the application of radiomic analysis to rectal cancer. We will review the main results and divide them into how these studies try to predict rectal cancer's staging, disease progression, or response to treatment. Additionally, we will reference the work on texture analysis, which is a precursor of radiomics and contributed for the understanding of how this pathology evolves. In fact, texture analysis has been used to characterize tumor heterogeneity, and many of the features extracted are included in radiomics analysis.

T- and N-staging

T- and N-stages, as defined on staging MRI, are features to be taken into consideration in rectal cancer treatment decision-making. Sun et al. (2018) proposed to investigate how T2-weighted imaging-derived radiomic features could identify pathological characteristics of pretreatment rectal cancers. They concluded that both methods used (unsupervised clustering and least absolute shrinkage and selection operator—LASSO—combined with regression analysis) were able to distinguish between T1–2 and T3–4 stages. In this study, 97 rectal cancer patients that underwent surgery (the staging ground-truth was confirmed via the histopathological results) had pretreatment MRI scans available for radiomic analysis, where 256 features were extracted. All the features were used in non-negative matrix factorization (NMF)–based clustering, but LASSO was applied to select the most significant features for regression. Histogram variability and fractal dimension (useful tool for quantifying the irregularity of an object) allowed for the best staging prediction [24••].

Previously, Liu et al. (2016) had used texture analysis to tackle the same problem. In their case, skewness and entropy (part of the radiomics analysis) were found as the best independent predictors of extramural invasion of rectal cancer. However, their study was

based on apparent diffusion coefficients (ADCs) derived from preoperative DW imaging of 68 patients. Additionally, this study also concluded that entropy and maximum ADC could be used as independent predictors of positive nodal status (distinguishing N0 from N1–2) [25]. Cui et al. (2011) also focused on differentiating reactive from malignant lymph nodes in rectal cancer patients. They used enhanced computerized tomography (CT) and found that fractal dimension showed to be a good discriminator between these two conditions [26].

Treatment Response

Throughout the years, a strong body of research has been devoted to building models to predict response to treatment of rectal cancers, mainly because of the recent organ-preservation paradigm, which is being increasingly adopted by clinicians—the so-called watch-and-wait approach.

Bibault et al. (2018) selected 28 radiomic features from the treatment planning CT scans of 95 patients. These features were used to train a *deep neural network* (DNN) (a computational method which has been found particularly effective in solving demanding image analysis tasks, such as object recognition and image segmentation) to predict pCR. Classical machine learning methods were used as baseline, namely, linear regression using the TNM staging and a *support vector machine* (SVM). The DNN predicted complete response with 80% accuracy, outperforming linear regression (69.5%) and the SVM (71.58%) [27••]. One year earlier, texture features had already been used by Chee et al. (2017) to predict treatment response using pretreatment CT scans. Treatment responders (32 out of 95 patients) demonstrated that lower entropy, higher uniformity, and lower standard deviation were indicators of good response. They even argued that tumor homogeneity was associated with better CRT response. Chee et al. (2017) also proposed that the same texture features were independent predictors of disease-free survival (DFS) [28].

The first study that used multiparametric MRI data to create predictive models of the response to CRT in rectal cancer was performed by Nie et al. (2016). In this study, anatomical (T1- and T2-weighted), perfusion (DCE), and diffusion (DW) MRI were used both in a volume-average, and voxel-based manner. The authors used two neural networks to perform: (i) feature selection, and (ii) feature classification (the response prediction). The study concluded that voxelized heterogeneity analysis of combined features from different imaging modalities improves prediction, when compared to the volume-average approach [14••].

In another study, Liu et al. (2017) contributed to this field by performing radiomic analysis on pre- and post-treatment T2 and DWI. From 2252 radiomic features and after univariate statistical tests between pCR and non-pCR groups, and LASSO logistic regression, a total of 30 features were used to build the predictor. The radiomics signature achieved a classification accuracy of 94.29% and a PPV of 90.00% in an independent validation cohort. This study presents strong evidence suggesting that a combination of T2 and DWI radiomic analysis can successfully screen out pCR patients, making them eligible for the "watch-and-wait" protocol [29••].

Also, in 2017, Cusumano et al. (2017) added fractal features to the statistical and morphological features of pretreatment T2-weighted gross volume tumor analysis. After feature selection, a logistic regression model was applied, and the fractal parameters (namely fractal dimension) were the ones that better predicted pCR. These authors reported an area under the curve (AUC) of 0.79 on an independent validation set [30••].

Horvat et al. (2018) proposed yet another analysis of how a combination of T2 and DWI radiomic analysis can improve the prognosis performance compared to the qualitative assessment of the two modalities taken separately. The authors achieved this by training a *random forest* classifier with 14 selected radiomic features. The radiomics-based classifier reached an AUC of 0.93, PPV of 74%, and NPV of 100% [31••]. Texture analysis was proposed by Meng et al. (2018) to predict pCR in rectal cancer. Uniformity and energy of tumors before treatment (on T2-weighted imaging) were significantly higher in patients that presented pCR, with the entropy exhibiting the reverse behavior [32].

Discussion

A common challenge in large part of the data science applications is the availability of large curated datasets. In fact, in most of the above-referred studies, one of the limitations pointed out was the rather small size of the datasets used. Additionally, the analysis performed in the largest cross-section of the tumor may lead to biased results; however, it has been shown that this analysis is sufficiently represented and provides comparable results to the whole-tumor analysis [32]. The vast majority of the published studies lack validation with external independent datasets, this being of the utmost importance to verify the ability of generalization of the models (generalize to different scanners, institutions, or even images based on different reconstruction algorithms or radiation doses).

The addition of data related to the biomolecular properties of the tumors (from biopsies) may be helpful, as the tumor biology can be tightly correlated to its response to treatment. All these techniques depend on the segmentation of tumors by experts. This task is tedious, expensive, and time-consuming [33], which obviously introduces inter-observer variability; consequently, it is not adequate for large-scale studies. Particularly for rectal cancer, segmentation can be cumbersome due to bowel movement artifacts, luminal content contamination, and variability in rectum morphology, size, and position. There has been a strong focus on research with the goal of developing accurate automatic segmentation

algorithms, in order to create reproducible and scalable approaches, adequate to being used in large cohort studies involving radiomic methods [15, 34, 35].

Finally, one of the challenges pointed out in the studies that try to predict treatment response is the imbalanced distribution of patients between the two classes observed (15–30% of patients exhibit pCR [7, 14••]). This can lead to an under-represented group of patients, producing biased results towards the more represented class. With the increase of a common understanding of the need for high-quality data, it is likely that data availability and access will become increasingly facilitated. However, some other challenges of data shareability might be hard to overcome. Recently, the concept of "federated learning" has been introduced, in which models are trained in multiple sites independently, without the need for sensitive data to leave the clinical centers. The trained models are put together in a master agent and delivered back to the separate centers where, hopefully, they will perform better as they received input from different sources. The latter was used in rectal cancer by Gatta et al. (2018) [36•]. As Summers (2016) pointed out in his review on "Texture analysis in radiology: Does the emperor have no clothes?," "… proper studies of validation, reproducibility, and observer variability must be performed" [37••]. This is, in fact, still true not only for texture analysis, but for radiomic analysis as well; although much research has been presented, many studies still lack proper validation. It is worrisome that papers that are being accepted for publication claim clinical "state-of-art," whereas in fact those methods cannot be generally applied.

Nowadays, when writing a review on machine learning methods, it is nearly impossible not to refer to the importance of deep learning in the upcoming years. Deep learning methods are being used to solve the segmentation problem, but also to predict and classify clinical outcomes. It is easy to understand that deep learning methods will continue to be a big part of the body of research in oncology. However (and this has been discussed in almost all related articles), deep learning methods have a problem of model interpretability. The fact that deep learning models are typically very complex and are not based on intuitive/understandable features may push these methods back in terms of clinical application. Features based on texture analysis or radiomics, on the other hand, can be intuitively explained and are thus easier to be applied to clinical settings. It will be interesting to observe how machine learning researchers will tackle this issue, either by looking into what is happening in the architecture of deep neural networks as it learns, or by creating some kind of attention maps that can explain which pixels/voxels in the medical image were important for decision-making.

Conclusion

In conclusion, this review shows the more relevant work applying both Radiomics and texture analysis to build rectal cancer predictive models on staging and treatment response. Due to the relatively new paradigm of treatment ("watch-and-wait" protocol), the need for an accurate predictor of treatment response has been the main focus of research in the last years. One of the major drawbacks for the use of these models in clinical practice is the so far not resolved lack of generalization to different centers. As readers, it is important to critically assign value to the publications, if proper validation was not performed. It is also of great importance that clinical centers come together to allow transference of both anonymized data and knowledge, in order to build more robust models.

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Compliance with Ethical Standards

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

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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