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Current status on response to treatment in locally advanced rectal cancer: what the radiologist should know

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Abstract. – The assessment of tumor response, after neoadjuvant radiochemotherapy (nCRT), allows stratifying the patient in order to consider the proper therapeutical management. Histopathology analysis of the surgical specimen is considered the gold standard to assess tumour response and the definition of a complete cancer response is related to the clinical and endoscopic features, by direct evaluation of the rectal wall. However, imaging studies, especially Magnetic Resonance Imaging (MRI) have provided additional parameters, as the evaluation of nodal or mesorectal status. MRI provides a radiological tumour regression grade (mrTRG) that is correlated with the pathologic tumor regression grade (pTRG). Functional MRI parameters have additional impending in early prediction of the efficacy of therapy and can be valuable in drug development processes. Some of functional methodologies are already part of clinical practice: diffusion-weighted MRI (DW-MRI) and perfusion imaging (dynamic contrast enhanced MRI [DCE-MRI]). Other technologies, such as radiomics with MRI are still in the experimental phase. An adequate radiological report describing the restaging of rectal cancer after nCRT should be a "structured report" to improve communication in a multidisciplinary team.

Key Words:
Rectal Cancer, Magnetic Resonance Imaging, DCE-MRI, DWI-MRI, Radiomics.

Introduction

An estimated 606,880 people died from cancer in 2019 in the USA, corresponding to almost 1,700 deaths per day. The greatest number of deaths are from cancers of the lung, prostate, and colorectum (CRC) in men (9%) and lung, breast, and colorectum (8%) in women[1]. CRC incidence patterns are generally similar in men (45.2 per 100,000 population) and women (34.3 per 100,000 population), although in the past 5 years, rates have continued to decline by approximately 3% per year in men but appear to have stabilized in women. Reductions in CRC incidence prior to 2000 are attributed equally to changes in risk factors. However, despite the introduction of the screening programs, several patients are diagnosed in a locally advanced stage[1]. The prognosis of rectal tumor is straight correlated to the mesorectum involvement and the capacity to surgically realize negative circumferential resection margins (CRMs). The mesorectal excision (TME) is the standard of care and the introduction of neoadjuvant chemoradiotherapy (n-CRT) has led to improvements in local disease control[2-6]. However, according to European Society for Medical Oncology (ESMO) Clinical Practice Guidelines[7], in the intermediate/more locally advanced rectal cancers (LARCs) [cT3a/b (very low, elevators clear, mesorectal fascia (MRF) clear or cT3a/b (in mid- or high rectum,

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cN1-2 (not extranodal), no extramural vascular invasion (EMVI)], the use of preoperative RT, either CRT or short-course preoperative radiotherapy (SCPRT) remains controversial. Conversely, for LARC (>cT3b, and EMVI), treatment decisions regarding neoadjuvant therapy should be based on preoperative MRI, in relation to the prediction of CRM involvement (≤ 1 mm), EMVI and more advanced T3 substages[7]. In addition, n-CRT may cause a significant response, determining a complete pathologic response in up to 42% of subjects[8]. Evaluation of tumor status after nCRT and before TME should recognize patients with complete clinical response that could be treated with strict follow-up [watch and wait (WW) strategy] in order to avoid post surgical complications with good oncological outcome[9-13]. Therefore, patients with significant tumor response with a decrease in tumor size, depth of tumor penetration, and even nodal sterilization, could be subject to organ-preserving treatment, as local excision of small and superficial residual lesions[14]. In these cases, knowing a potentially new "anatomy", post nCRT, ahead of time may allow the surgeon to optimize intraoperative surgical strategy and to know in advance what challenges could be anticipated during the procedure. Therefore, the assessment of tumor response allows stratifying the patient in order to consider the proper therapeutical management. The assessment post nCRT can be difficult due to doubts regarding the optimal timing and the most accurate radiological tools[14].

Timing of Re-Assessment

The rate of tumor regression is a time-dependent phenomenon. A 6-week time interval between nCRT conclusion and surgical treatment has been deemed the optimal time for many years[15]. However, several investigations have assessed that the grade of tumor regression might keep rising after nCRT for as long as 6 weeks from treatment conclusion. However, there is an open issue of whether this protracted interval from nCRT would cause excessive fibrosis that could lead to increased surgical complexity and postoperative morbidity[16-20]. Although the optimal timing is still undetermined, now it is known that responder lesions may necessitate an advantage from prolonged interval from nCRT, whereas not responder lesions may not. It is possible that responder lesions that are being considered for organ-preserving treatment should have their evaluation and eventually surgical strategy decision delayed to more than 12 weeks[20].

Radiological Tool for Assessment

Imaging is now an indispensable tool for tumour assessment post nRCT. Although histopathology analysis of the surgical specimen is considered the gold standard for assessing tumour response and that the definition of a complete cancer response has related to the clinical and endoscopic features of rectal wall, imaging studies, principally MRI, provide other findings, as nodal or mesorectal status. In addition, significant developments in technical imaging have increased the accuracy for the evaluation of treatment not only within the mesorectum compartment, but also within the rectal wall. Therefore, the possibility that imaging might identify responder and not responder patients before surgical approach could guide a multidisciplinary team for a proper patient management: preoperative recognition of poor responders may lead to additional consolidation therapy in order to decrease the risk of local and distant recurrence. Current guidelines[21] recommend routinely performing MRI for assessing rectal cancer after CRT. In the restaging phase, MRI can help in regression grade assessment, tailoring surgical planning, detecting a complete response and monitoring patients undergoing the non-surgical approach. Finally, after local treatment, MRI is important during follow-up for the early detection of local recurrence[22]. Conversely, there are many disputes concerning the utility of positron emission tomography/computed tomography (PET/CT); however, there is no agreement about PET/CT in this scenario, so as there are no validated data about the useful of CT or endorectal ultrasound (ERUS). Nevertheless, a combination of different modalities required for recurrent disease[22].

MR Assessment of Tumor Response

MRI is an excellent tool for rectal cancer patients, thanks to high soft-tissue contrast, multiplanar imaging, and functional assessment[21]. MRI allows assessment of the primary tumor, of the relationship of the lesion to the surrounding structures, as well as assessment for associated features that may affect the approach to therapy. Primary tumor staging is predominantly performed by using high-spatial-resolution (HR) T2 weighted (W) sequences. The assessment of T1 and T2 tumors can be limited at MRI, although T1 lesion is confined to the hyperintense submucosa layer, and T2 lesion extends beyond the submucosa but not through the muscularis propria[21,22]. Considering the depth of the extramural invasion into the mesorectal fat, T3 tumor

can be classified as T3a (<1 mm), T3b (1-5 mm), T3c (5-15 mm), and T3d (>15 mm). Several other features are critical to assess for the treatment planning and prognosis: the location of the primary tumor extension, the smallest distance between tumor involvement and the mesorectal fascia, solitary tumor deposits, extra-mural vascular invasion, and suspicious lymph nodes[21]. These features should influence the type of the treatment and each should be re-assessed post treatment. Assessment of tumor response should be performed with the same protocol that was used in the initial staging assessment, in order to optimize the comparison between pre- and post treatment study, so as it would be preferable that the examination be performed with the same scanner and by the same radiologist[22].

Post Treatment Restaging

Tumor assessment and staging after nCRT are evaluated by using the TNM and AJCC criteria. The *y* prefix is used for cancers classified after neoadjuvant chemoradiation therapy[2]. MRI is useful in differentiating ypT0-T2 lesions from ypT3 lesions with high accuracy, conversely shows lower accuracy among lower-stage (ypT0 versus T2). Anyhow, the MR assessment post n-CRT should be based on morphological and functional parameters.

Morphological Magnetic Resonance Imaging

MR is usually performed for the evaluation of the treatment efficacy in rectal cancer after nRCT, though the accuracy of tumor staging at MRI in this phase is lower than that of primary staging. The major limit of morphological examination is the capacity to recognize fibrosis or residual disease, although the advances in technology have improved the diagnostic accuracy, placing as a critical tool to confirm clinical and endoscopic features[23]. MRI provides a precise radiological tumour regression grade (mrTRG) that is associated with the pathologic tumor regression grade (pTRG). The use of mrTRG may recognize good and poor responders with important impact on disease-free and overall survival[23]. In mr-TRG, scores are attributed to dimensional and structural tumour changes. Conventionally, a reduction in lesion volume has been used as a feature to evaluate the efficacy of treatment[24]. Tumor volume should be evaluated on axial T2-W MR images, obtained before and after nCRT (Figure 1) describing contours to estimate tumor cross-sectional areas on each slice, and then, summing the slices to assess the volume. More than a few limits are present for this analysis. First, it might be complicated discriminating between residual tumor from other post-treatment changes on

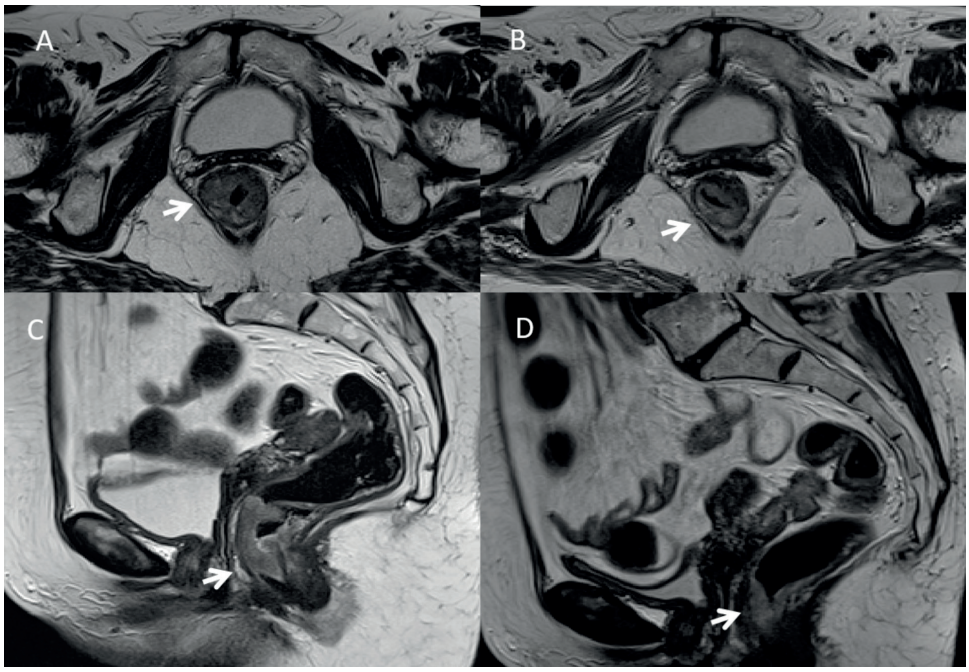

Figure 1. Woman 46 y with T3 rectal cancer as shows by morphological MRI (arrow) in A (T2-W in axial plane) and C (T2-W in sagittal plane). After nCRT the lesion shows a partial response (arrow) in B (T2-W in axial plane) and D (T2-W in sagittale plane).

T2-W sequences alone. Then, the formation of contours and estimating of volumes may need dedicated software which might be difficult in tumor with irregular and speculated borders[25]. In addition to evaluating volume, assessment of morphologic changes is essential for evaluating treatment response. Several morphologic changes at histopathology analysis have been reported, including fibrosis and mucin production, all of which correlated with particular findings at imaging[26]. Fibrosis is well evaluated on T2-W images as a combination of a decrease in tumor volume and in signal intensity (SI). Conversely, to fibrosis, residual tumor is typically more nodular and shows more intermediate SI[25]. Increased mucin production, after nCRT, is characterized to an interval increase in T2-W SI of tissue that previously had an intermediate SI. The development of mucinous or colloidal changes is dependable with a form of treatment response[25]. Lesion can manifest with one of three different mucin responses: (1) Mucin (or colloid degeneration) response can arise in non-mucinous lesion that become mucinous after CRT. It is correlated to a response and better prognosis. (2) Acellular mucin response is a pathologic response of a mucinous lesion with no impact on recurrence-free survival. (3) For a mucinous lesion without response, the tumor no shows changes after CRT, with an increased risk of local recurrence and poor outcome[27]. The mr-TRG shows significant prognostic implication, with the 5-year disease-free survival rate of 86% for patients with histopathology grade 4 tumors, 75% for the combined group of patients with histopathology grade 2 and grade 3 tumors, and 63% for the combined group of patients with histopathology grade 0 and grade 1 tumors[28]. However, morphological evaluation is not sensitive to early changes, and it makes difficult to differentiate between active lesion and post-CRT changes. So, that morphological parameters extracted by T2-W sequences hve been considered not to be conclusive in tumour response evaluation[29-34]. Although, according to Fusco et al[35], some morphologic parameters as lesion vascularization score, lymph node number and T2 SI shows a good predictive value for neoadjuvant treatment complete response and for local rectal recurrences[35].

Functional Magnetic Resonance Imaging

It is known that the visual inspection of morphological parameters provides only part of the data on how the tumour could responde to nCRT. Advances MR technology combine morphological with functional data on the biological microenvironment of the lesion[36]. Functional MR parameters provide quantifiable data on tumour characteristics. The combination of objective biomarkers with morphological data makes functional MRI a potentially powerful response tool that provides comprehensive data on tumour heterogeneity and changes in heterogeneity as a result of treatment. Functional MRI has additional potential in early phase to assess the efficacy of therapy and can be valuable in drug development processes. Some of the functional analysis are already part of clinical practice: diffusion-weighted MRI (DW-MRI) and perfusion imaging (DCE-MRI). Other technologies, such as metabolic imaging with MRI are still in the experimental phase[36]. In the assessment of treatment response, Fusco et al[37] showed that DCE-MRI following to PET/CT had a high diagnostic accuracy. Instead, morphological MRI alone showed a sensitivity of 76% and a specificity of 78% and DW-MRI a sensitivity of 76% and specificity of 79%.

Dynamic Contrast Enhanced-MRI

DCE-MRI provides functional parameters on tumour perfusion, vessel permeability and extracellular-extravascular space composition by assessing the changes in SI after the injection of a paramagnetic contrast medium[38]. DCE-MRI may estimate data of the tumour vascular microenvironment, such as hypoxia and microvascular density, and also vascular changes induced by nCRT. DCE-MRI can assess lesion downstaging, therefore identifying good from poor responders to therapy. The perfusion on DCE-MRI can be evaluated by qualitatively, semi quantitatively and quantitatively method[38]. Quantitative analysis involves the assessment of the pharmacokinetics of an administered contrast medium. The most commonly used feature is the volume transfer constant Ktrans, which represents the rate of contrast medium that moves from the blood to the extracellular space and relates to microvascular blood flow, vessel wall permeability, and vessel density. Ktrans has been shown to be correlated with tumor vascular endothelial growth factor and tumor aggressiveness[39-42]. Higher pre nCRT value of Ktrans has been revealed an important biomarker in predicting the treatment response. Furthermore, several researches[39-42] have shown the efficacy of DCE-MRI in the assessment of a partial or complete response to nCRT. However, being influenced by many variables and since many

different models are present in the literature, the quantitative approach still suffers from high output variability, poor clinical consistency and reproducibility[37]. Qualitative DCE-MRI (qMRI) analyzes the time–intensity curve (TIC), involving the visual inspection and classification of TIC in agreement with Daniel et al[43]. Quantitaive MRI study (qMRI) can extimate tumor viability based on the associations between tumor growth and angiogenesis. The main weakness of qMRI is the ROI positioning that makes this approach operator dependent (Figure 2). However, the selection of multiple ROI inside and outside the rectal wall makes the qMRI more robust[44]. According to Petrillo et al[44], the persistence of malignancy is strong-minded by the concomitant presence of a fast wash-in followed by a fast wash-out or a plateau, with a sensitivity of 81% and a specificity of 85%. In addition, functional qMRI showed an increase in negative predictive value, sensitivity, and specificity at TRG evaluation. Moreover, the performance of morphologic MRI and qMRI assessment in complete responders reached an accuracy of 74 and 89%, respectively, while qMRI had a lower diagnostic accuracy in pathological incomplete responder patients[44]. Semi-quantitative DCE-MRI is based on the analysis of Time Intesity curve (TIC) shape descriptors providing immediate data, correlated to the pathophysiology of the tumour. This approach could be more robust in clinical practice compared to quantitative o qualitative method, since many critical issues are reduced. However, semi-quantitative parameters do not show a direct analysis of physiological appearances[31]. Petrillo et al[44] assessed a quantitative parameter extracted by a semiquantitative analysis of DCE-MRI to discriminate responders by non-responders after nCRT in LARC. The authors showed that the combination of the percentage change in Maximum Signal Difference (ΔMSD) and Wash-out Slope (ΔWOS), defined as Standardized Index of Shape (SIS), was the best parameter in discriminating responders from non-responders after nCRT in LARC, with a cut off value of -3.0% (Figures 3)[45]. Linear fitting of the TIC in evaluating pixel-by-pixel perfusion adding the TIC normalization, by Petrillo et al[45], allow to eliminate the dependence on proton density, relativity and other equipment parameters, and to identify more suitable indexes in detecting CRT tumour response[45]. Petrillo et al[46] showed that SIS had a higher predictive value than PET/CT in LARC patients allowing to better discriminate significant responders after pCR.

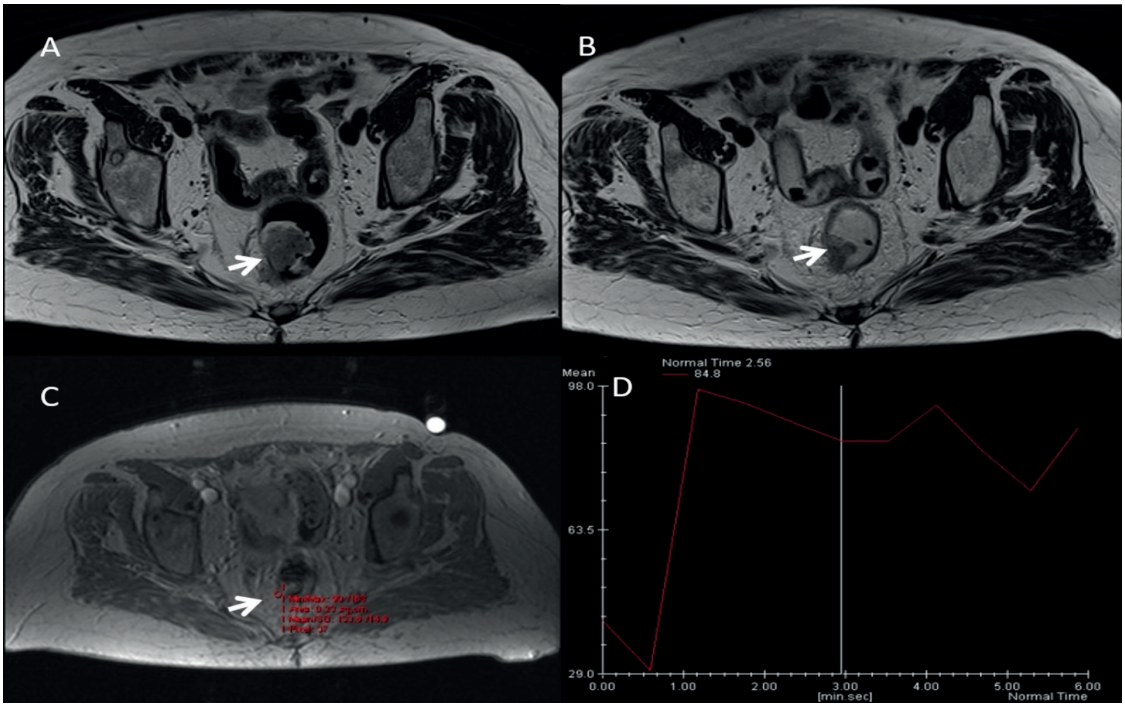

Figure 2. Man 64 y with rectal cancer (arrow) that envolves MCR (in A T2-W in axial plane). After nCRT the lesion shows a volumetric response (B: TSE T2-W in axial plane), with residual desease as it has shown by arrow in B and C (DCE-MRI). In D qDCE-MRI: TIP; early wash-in and wash-out.

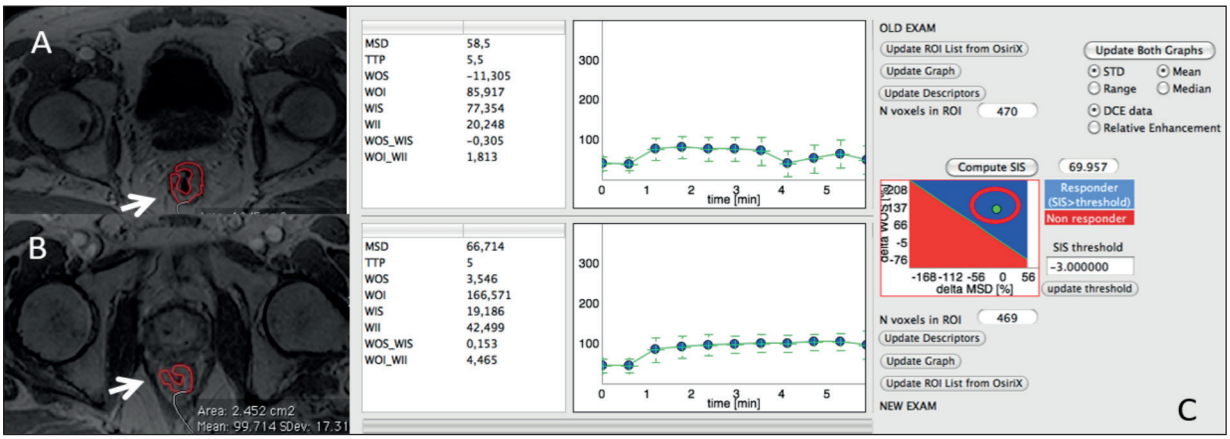

Figure 3. Man 72 y with Rectal Cancer before in A (DCE-MRI; Fl 3 d T1-W sequences) and after in B (DCE-MRI; Fl 3 d T1-W sequences). Responder patient: in C the evaluation of the Standardized Index of Shape that was equal to 69.96%.

Conventional Diffusion Imaging, Intravoxel Incoherent Motion (IVIM) and Diffusion Kurtosis Imaging

The opportunity to obtain functional parameters by DW-MRI has facilitated the spread of this technique into clinical practice, increasing clinical confidence and decreasing false positives for detection and characterization of lesion. The major field of application of DW-MRI is oncology[47-50]. The analysis of DW-MRI data can be done qualitatively and quantitatively, through the apparent diffusion coefficient (ADC) map. DW-MRI signal depends on the water mobility that is related to tissue characteristics[47-50]. The ADC map is the graphical demonstration of the ratio of DW-MRI signal intensities and its measurements helps to identify between benign and malignant tissue. The ADC values are associated to the sequence and suffer from a lack of reproducibility, especially in respiratory triggering techniques[47-50]. Le Bihan et al[51,52] introduced the intravoxel incoherent motion (IVIM) and evaluated a more sophisticated process to describe the correlation between signal attenuation and increasing *b* value that separately reproduce diffusivity and perfusion. IVIM parameters can be analyzed qualitatively and quantitatively[51-56]. Since necrosis and perfusion modifications can happen before changes in size during therapy, DW-MRI may aid as an early biomarker of treatment effectiveness. Several researches have investigated the role of DW-MRI to predict and assess response to nCRT, showing that ADC values could distinguish good responders from poor responders. The accuracy of pre-therapy ADC values for prediction of good responders is variable between small prospective studies, with sensitivities, specificities, positive-predictive values (PPVs) and negative-predictive values (NPVs) ranging from 62% to 100%, 86-91%, 67-79%, and 62-100%, respectively[53-55]. In a meta-analysis the accuracy of DWI was compared respect to morphological MRI. Standard morphological data have showed a lower accuracy compared to DWI for tumour re-staging[55]. However, it is not easy to exactly recognize pathological complete response (pCR) on DW-MRI sequences, and therefore, DW-MRI should be associated with other sequences. It is estimated that in patients with no residual lesion, diffusion will be freer without restriction. However, Jang et al[57] reported diffusion restriction in 42% of patients with pCR. In fact, radiation proctitis and fibrosis were significant independent predictors of diffusion restriction in patients achieving pCR after CRT. Petrillo et al[58] investigated preoperative CRT response in comparing SIS obtained from DCE-MRI and ADC and IVIM derived parameters, showing that DWI-derived parameters reached less accuracy compared with SIS and combining linearly DCE- and DWI-derived parameters no increase the diagnostic accuracy was reported. Traditionally, DW-MRI method is based on the hypothesis that water molecules diffuse within a voxel with Gaussian behavior without any restriction. However, according to the presence of microstructures, water molecules within biologic tissues exhibit a non-Gaussian phenomenon known as Diffusion Kurtosis Imaging (DKI)[59]. This method assesses the kurtosis coefficient (K), which expresses the deviance of diffusion from a Gaussian method, and the diffusion coefficient

(D), which is the correction of non-Gaussian bias. After nCRT, the tissues are more heterogeneous and the spread of water molecules thus follows a non-Gaussian model, therefore the analysis of these is more accurate with DKI than ADC. Few researches[59-62] have assessed the role of DKI in the evaluation of nCRT in rectal cancer. Yu et al[60] have showed that the percentage change in Dapp showes higher diagnostic accuracy for assessing nCRT. Hu et al[61] assessed DKI in pCR in LARC compared to conventional DW-MRI. The authors showed that, although both DKI and conventional DW-MRI could predict the response, MK (mean kurtosis) post had a higher specificity compared to DWI data. Fusco et al[62] evaluated the preoperative short-course radiotherapy tumor response in LARC, comparing SIS by DCE-MRI, ADC, IVIM [tissue diffusion (Dt), pseudo-diffusion (Dp), and perfusion fraction (fp)], and DKI (MD and MK) parameters derived from DW-MRI. They showed that the mean pre-treatment Fp value was the more accurate parameter for prediction of a pCR. Promising results[62] were found using a decision tree tested with all ADC, IVIM, and DKI extracted features. DW-MRI is a useful tool to assess response after nCRT (Figure 4); however, it is essential that DW-MRI is a reproducible evaluation method. Therefore, standardization of the sequence is mandatory so as of kinetic model application and analysis methodology to calculate derivate quantitative features.

Future Direction: Radiomics

It is now possible to extract innumerable quantitative data from tomographic images (CT, MR or PET images). This translation of digital images into numeric data, a process called radiomic, is moved by the idea that radiological images comprise data that reflect underlying pathophysiology. Therefore, it is known that radiomic features provides data on tumor phenotype as well as cancer microenvironment. The primary challenge is the optimal collecting and combination of diverse multimodal data sources in a quantitative method that provides unequivocal clinical parameters that precisely and robustly allow outcome prediction as a function of the impending decisions[63,64]. The central hypothesis of radiomics is that the quantitative individual voxel-based variables are more sensitively associated with various clinical endpoints compared with more qualitative radiologic and clinical data that are also more commonly used today[65]. Several researchers assessed the role of radiomics as a tool of precision medicine that might move treatment approaches. Cui et al[66] assessed a radiomics model to predict a pCR in patients with LARC after nCRT, demonstrating that the pre-treatment radiomics nomogram can predict pCR and potentially guide selection of patients for a "wait-and-see" policy[66]. In addition, Liu et al[67] validated a radiomics model, with an excellent performance to assess pCR in patients with LARC, so as Shi et al[68] showed that Radiomics could give comprehensive quantitative data to predict pCR. Radiomics has recently shown potential in realizing personalized medicine for patients, however, the large number of radiomic features, small number of observations, and unbalanced datasets are major challenges when building radiomics-based prognostic models[68].

Nodal Assessment

Morphological criteria, such as the round shape, irregular border, and heterogeneous SI could support the detection of malignant nodes, although these criteria can be difficult to assess in small nodes. The accuracy of MRI for nodal restaging after CRT is improved than in the primary staging, with negative predictive values of up to 95% to identify ypN0 patients. Nodes that remain evidently visible after CRT are considered malignant. Although the optimal size cut-off remains a topic of debate, the recent European Society of Gastrointestinal Abdominal Radiology (ESGAR) guidelines have proposed a cut-off of 5 mm (short axis) to diagnose yN+ nodes after CRT[21,69]. The role of DW-MRI in evaluation nodal status after nCRT is uncertain, with one group of researches that have suggested that this tool does not offer additional data compared with morphologic data obtained on T2-W images. However, DW-MRI has shown a strong negative predictive value in this scenario: the absence of restriction at DW-MRI is indicative of node-negative status (Figure 5). Furthermore, the role of PET in evaluating of nodal status after nCRT is also uncertain; some researches have shown restricted sensitivity, possibly owing to the limited sensitivity of PET for small nodes[25].

How Report Re-assessment After CRT

There is increasing interest in "structured reporting" in radiology to increase the communication of imaging findings and generating consistent reports, for clarity and content, in order to improve the communication amoung multidisciplinary team[70]. This applies to rectal MRI reporting with recent consensus statements

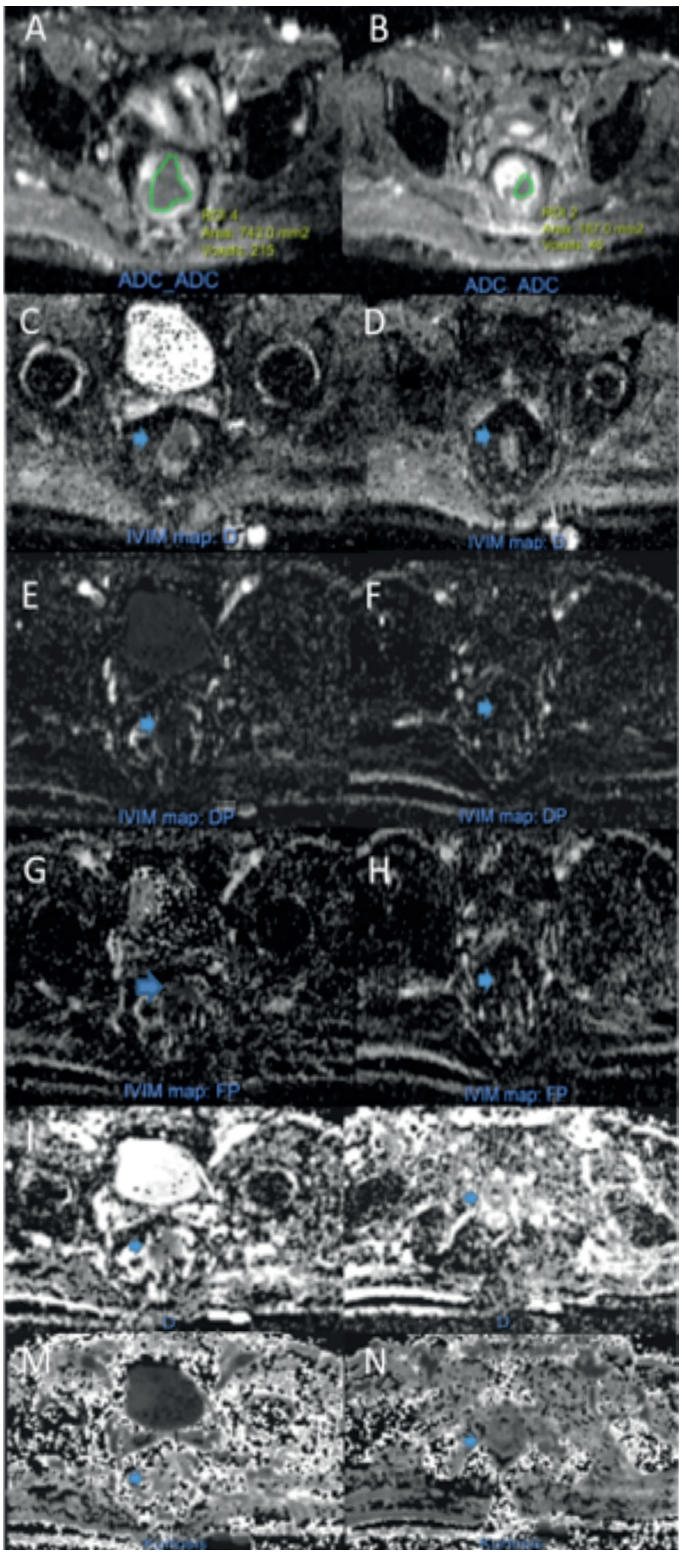

Figure 4. Man 58 y with rectal cancer. DWI assessment: ADC-, IVIM- and DKI derived parameters maps pre (A, C, E, G, I, M) and post treatment (B, D, F, H, L, N) for a responder patient (TRG 2).

published by European Society of Gastrointestinal and Abdominal Radiology and Society of Abdominal Radiology both recommending report templates for primary staging and restaging[25,71]. Tumour descriptions which should be included in a radiological report for primary staging and restaging are vertical location of tumours, tumour length, radial location of wall involvement by the

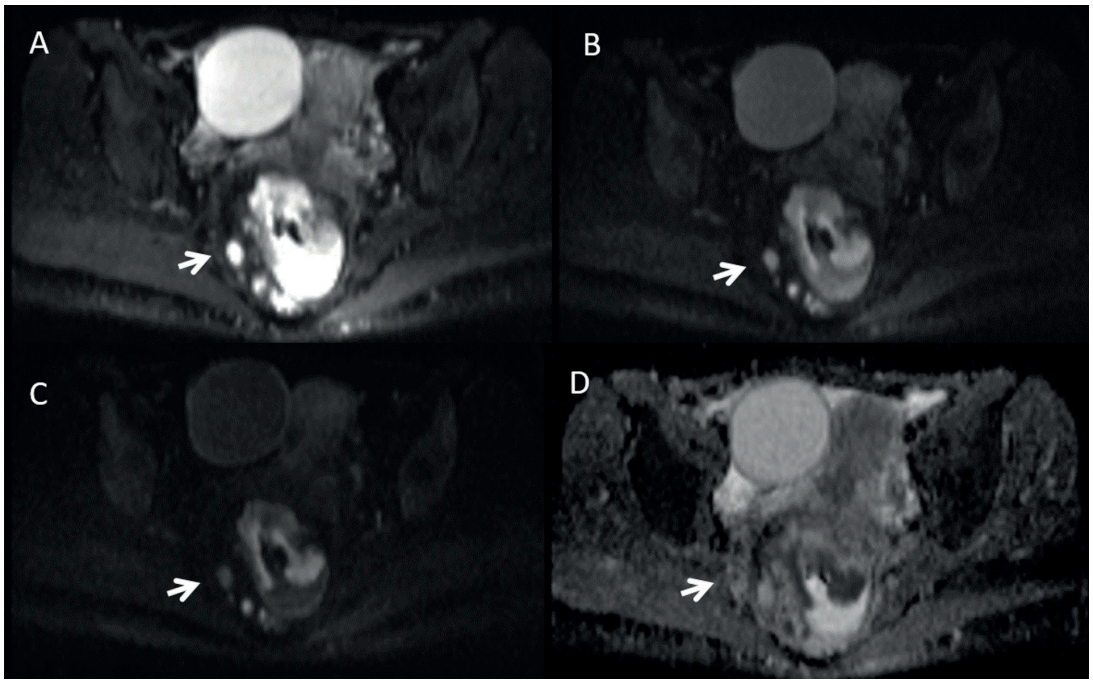

Figure 5. Woman 37 y with rectal cancer. After nCRT not responder patient. Nodal assessment (arrow): restricted diffusion (in A b 50 s/mm^2; in b 500 s/mm^2; in C b 800 s/mm^2; in D ADC map).

tumour, tumour distance from the anal verge, tumour size, tumour staging, including distance through the muscularis propria (for tumours > T3), tumour relationship to the peritoneal reflection and CRM status. Also should be included extra-mural venous invasion status, nodal staging, location of involved lymph, and in particular location of the most superior malignant mesorectal lymph node (relative to the sacral level) and distant metastatic status[25,71,72]. These features to be included are important prognostic factors and can guide the multidisciplinary team towards the more appropriate choice for the patients.

Therefore, an adequate report describing the restaging of rectal cancer after nCRT should include[72]:

- Presence/absence of remaining tumor
- Presence/absence of fibrosis
- Presence/absence of mucinous degeneration
- O'clock position of remaining tumor
- Remaining tumor length
- Distance from tumor to Anal Verge and Anal Rectal Junction
- yT stage
- yT3 depth
- Presence/absence of remaining tumor deposits in the mesorectum
- Smallest distance from primary tumor to CRM and or persisting involvement of the CRM
- yN stage
- Number of remaining suspicious nodes
- Presence/absence of suspicious extra-mesorectal/lateral nodes
- Presence of EMVI
- Presence of any remaining lymph nodes and/or EMVI within 2 mm of CRM.

Conclusions

The assessment of tumor response, after neoadjuvant radiochemotherapy allows to stratify the patient in order to consider the proper therapeutical management. The assessment post nCRT can be difficult due to doubts regarding the optimal timing and the most accurate radiological tools. Although the optimal timing is still undetermined, now it is known that responder lesions may necessitate and advantage from prolonged interval (6-12 weeks) from nCRT, whereas not responder lesions may not. MR is the more accurate diagnostic tool performed for the evaluation of the treatment efficacy in rectal cancer after nRCT, though the accuracy of tumor staging at MRI in this phase is lower than that of primary staging.

The major limit of morphological examination is the capacity to recognize fibrosis or residual disease, although the advances in technology has improved the diagnostic accuracy. Functional MRI parameters have additional impending in early prediction of the efficacy of therapy and can be valuable in drug development processes. Some of functional methodologies are already part of clinical practice: diffusion-weighted MRI (DW-MRI) and perfusion imaging [dynamic contrast enhanced MRI (DCE-MRI)]. Other technologies, such as radiomics with MRI are still in the experimental phase. An adequate radiological report describing the restaging of rectal cancer after nCRT should be a "structured reporting" to improve communication in a multidisciplinary team.

Conflict of Interest

The authors have no conflict of interest to be disclosed. The authors confirm that the article is not under consideration for publication elsewhere. Each author has participated sufficiently to take public responsibility for the manuscript content.

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