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# TUMOUR GRADE REGRESSION (TRG) AND CORRELATION WITH MAGNETIC RESONANCE IMAGING (MRI) IN RECTAL CANCER

Oncology/Radiotherapy

**Ocanto A*** Department of Radiation Oncology. La Paz University Hospital, Madrid. Spain., Autonomous University of Madrid, Madrid. Spain. *Corresponding Author

**Dos Santos Y** Department of Radiology, Segovia General Hospital, Segovia. Spain.

**Cantero R** Autonomous University of Madrid, Madrid. Spain., Colorectal Unit, Department of Surgery, La Paz University Hospital, Madrid. Spain.

**Rodríguez I** Department of Radiation Oncology. La Paz University Hospital, Madrid. Spain.

**Morera R** Department of Radiation Oncology. La Paz University Hospital, Madrid. Spain., Autonomous University of Madrid, Madrid. Spain.

## ABSTRACT

**Purpose:** Colorectal cancer is the third most common cancer worldwide, neoadjuvant chemoradiotherapy (nCRT) is the standard treatment for locally advanced rectal cancer (LARC) and Magnetic Resonance Imaging (MRI) plays an important role in the management of this cases, determining the response to treatment but nowadays does not exist an unique criteria to unify tumour regression grade (TRG) and determinate possible patients for watch and wait and surgical option. **Method:** 137 patients: 71 (51,8%) men and 66 (48,2%) women with newly diagnosis of LARC underwent to nCRT and evaluate locally with MRI were analyzed to determinate the circumferential resection margin (CRM), extramural vascular invasion (EMVI), satellite tumour deposit (STD), the state of the sphincter complex (SC) and mrTRG evaluated by experienced abdominal radiologist. **Result:** Complete pathological response (cPR) was determinate in 30 patients, 57,5% presented partial pathological response (pPR), CRM were 26,4%, EMVI were 18,4%, STD were 14,6% and SCI 6,9% all of them with statistical significative ($p<0,05$) relationated with overall survival (OS), mrTRG 1-2 were 43,33% and mrTRG 3-5 40%. **Conclusion:** MRI is a feasible option to determinate TRG in patients with LARC underwent to nCRT and mrTRG criteria are the best option to classify these patients and with new biopsy could be the standard of care for offers watch and wait option to determinate patients, avoiding in many cases surgical option.

## KEYWORDS

Magnetic resonance imaging, rectal cancer, radiotherapy.

## INTRODUCTION

Colorectal cancer is the third most common cancer worldwide [1]. About 30% of these malignancies arise in the rectum and the incidence is increasing. Nowadays neoadjuvant chemoradiotherapy (nCRT) is the standard treatment for locally advanced rectal cancer (LARC), it has displayed that decreases the risk of local tumour recurrence after surgery and increase patient survival [2,3,4]. The nCRT typically takes 5−6 weeks (long-course therapy), and surgery is generally performed more than 8 weeks after the completion of nCRT. The current standard surgery is total mesorectal excision (TME) [5]. However less aggressive management (watch-and-wait approach) could be used as an alternative in selected cases when the patient has had complete response to nCRT [6]. Therefore, preoperative assessment of tumour has become essential for correct decision-making. Different imaging modalities have been used to assess locoregional tumour spread, like magnetic resonance imaging (MRI), endorectal ultrasound (ERUS), computed tomography (CT) and positron emission tomography (PET-TC) [7,8]. All these imaging modalities helps to determine the response to nCRT and the surgical procedures.

Of those imaging modalities the MRI is the best to demonstrate extramural spread assessment, that include circumferential resection margin (CRM), extramural vascular invasion (EMVI), satellite tumour deposit (STD) and the state of the sphincter complex (SC). This information should be taken to decide the adequately less aggressive surgical treatment [7] Imaging is becoming necessary for tumour response assessment (MRI) after finishing nCRT, but the gold standard is the histopathology within the final specimen [7], but the opportunity to alter the treatment is missing. For this reason, the TRIGGER trial EudraCT Number 2015-003009-40, is finding the detection of good and poor responders with imaging modalities (MRI) to adapt the following treatments [7].

In this article, we investigate the radiologist finding and the differences between pathological characteristics of Tumour Regression Grade (TRG) and its presentation in MRI for patient following nCRT with LARC.

## METHODS

### Patients

From 2016 to 2020, patients with newly diagnosed rectal adenocarcinoma, who was assessed by rectal MRI and were cT3-4 or cN+ status according to American Joint Committee on Cancer (AJCC 8th edition), were underwent long-course nCRT in our hospital. In accordance with the institutional protocol, the initial metastatic evaluation included CT. This study was approved by ethics committee of our institution (Nº PI-4819) June 10th, 2021.

### Neoadjuvant chemoradiotherapy

Neoadjuvant treatment included whole pelvic radiotherapy (RT) and primary tumour boost using three-dimensional conformal radiotherapy (3D-C) with 6 MV photons from a linear accelerator (Elekta Synergy). A total dose of 50.4 Gy was delivered in 28 fractions on 5 days per week in 103 patients (75,2%) and 34 (24,8%) patients received 53.20 Gy whole pelvic radiotherapy (RT) and primary tumour boost using intensity-modulated radiotherapy (IMRT). Concurrent chemotherapy consisted of oral cabecitabine (825 mg/m2) twice daily during radiotherapy. TME was performed 8 to 10 weeks after the end of nCRT.

### MRI technique

Before and after nCRT, rectal MRI was performed using 1.5T scanners (MAGNETOM Avanto and Skyra; Siemens Medical Solutions, Erlangen, Germany). High resolution images (3mm slice thickness), T2 weighted, fast spin echo images in axial, coronal, sagittal and oblique planes.

### MRI analysis

Radiologist experienced in abdominal imaging MRI assessed response to nCRT using classic criteria and mrTRG (grades 1-5). According to the studies [9,10] grade 1, linear/crescentic, 1 – 2-mm scar in mucosa/submucosa or apparent normalization of the rectal wall; grade 2, dense fibrosis with no obvious residual tumour; grade 3, more than 50 per cent fibrosis or mucin with visible residual tumour signal; grade 4, small areas of fibrosis or mucin but mostly tumour; grade 5, same appearance as original tumour or tumour growth.

### Histopathological analysis

TME was the standard treatment after nCRT. Pathological evaluation was performed by pathologist experienced in colorectal tumour. Pathological tumour regression grade (pTRG) was categorized according to Dworak system: 0, no regression; 1, dominant tumour mass with obvious fibrosis and/or vasculopathy; 2, dominant fibrotic changes with few tumour cells or groups (easy to find); 3, very few

(difficult to find microscopically) tumour cells in fibrotic tissue with or without mucous substance; and 4, no tumour cells and only a fibrotic mass (total regression or response) [11].

### Statistical analysis

All statistical operations were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY). All statistical significance levels were with $p<0.05$. The Mann–Whitney test was used for continuous variables. Fisher exact test was used to assess differences in radiological response. Primary outcome was radiological response (cPR and pPR). The clinical response was determined by histologic confirmation after surgery and compare retrospectively with MRI response.

## RESULTS

### Patient characteristics

137 patients: 71 (51,8%) men and 66 (48,2%) women were evaluable for primary tumour response analysis with MRI. Baseline characteristics are summarized in table 1. Median age was 68,15 years (range 40-88). MRI was done a median of 48 days (range 44-66) after nCRT had ended. Surgical resection was performed a median of 63 days (range 54-72) days after completion of nCRT. All patients had TME. (Table 1).

**TABLE 1. Patient characteristics**

| Characteristic | Value |
|---|---|
| Age (years) | 68,15 ± 11,01 |
| Gender | |
| Male | 71 (51,8%) |
| Female | 66 (48,2%) |
| Tumour location | |
| Low | 40 (29,2%) |
| Medium | 77 (56,2%) |
| High | 20 (14,6%) |
| Surgery | |
| URA* | 47 (34,3%) |
| LAR** | 47 (34,3%) |
| AP*** | 43 (31,4%) |
| cPR**** | 30 (22,4%) |
| pPR***** | 101 (75,4%) |
| No response | 6 (2,2%) |

* URA: ultralow anterior resection. **LAR: low anterior resection. ***AP: abdominoperineal resection. cPR****: Complete pathological response. pPR*****: Partial pathological response.

### Pathological characteristics of tumour regression grade

MRI post nCRT were performed in 137 patients, and we found a median tumour size of 5,47cm with a reduction at the end of nCRT of 35,46% (3,53cm) ($p<0,05$).

From 137 patients, only 30 (21,9%) presented cPR in the histopathologic analysis. 79 patients (58%) presented pPR corresponding with Dworak grade 2 and 3 and 28 patients (20,1%) does not showed response in concordance with Dworak grade 0 and 1. Patients with cPR were evaluated with mrTRG criteria: 43,33% were mrTRG 1-2, 40% were mrTRG grade 3-4 and 16,7% were mrTRG 5 (Table 2 and figure 1).

**Table 2: MRI characteristic**

| Characteristic | Value | p value |
|---|---|---|
| Tumor size | | |
| Pre nCRT* | 5,47cm | 0,05 |
| Post nCRT** | 3,53cm | |
| STD*** | | 0,001 |
| Pre nCRT | 14,6% | |
| Post nCRT | 15,4% | |
| EMVI+ | | 0,001 |
| Pre nCRT | 24,4% | |
| Post nCRT | 18,4% | |
| SCI++ | | 0,0035 |
| Pre nCRT | 12,7% | |
| Post nCRT | 6,9% | |
| CRM+++ | | 0,000 |
| Pre nCRT | 40% | |
| Post nCRT | 26,4% | |
| mrTRG$^{o}$ | | |
| mrTRG 1-2 | 43,3% | |
| mrTRG 3-4 | 40% | |
| mrTRG 5 | 16,7% | |

*Pre nCRT: Pre-neoadjuvant chemoradiotherapy. **Post nCRT: Post-neoadjuvant chemoradiotherapy. ***STD: satellite tumour deposit. +EMVI: extramural vascular invasion. ++SCI: sphincter complex invasion. +++CRM: circumferential resection margin. $^{o}$mrTRG: magnetic resonance tumour regression grade.

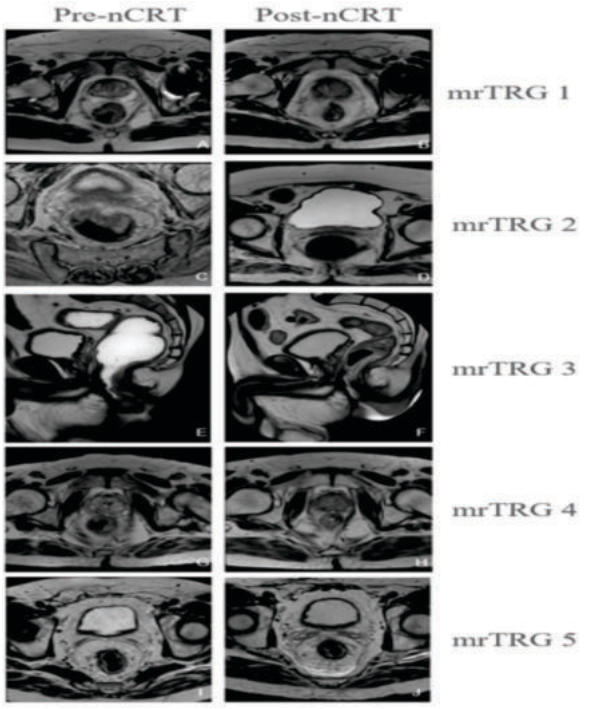


**Figure 1:** Correlation of pre-nCRT and post-nCRT with Tumour regression grade (TRG).

Previous nCRT: 24,4% of patients have EMVI and then 18,4% ($p<0,00$). STD were 14,6% at the diagnosis and later 15,4% ($p<0,001$). CRM were at the beginning 40% and finishing nCRT 26,4% ($p<0,000$) and finally SCI 12,7% previous nCRT y 6,9% at the end ($p<0,035$). All this risk factor were significant relationship with OS ($p<0,005$).

### Relationship between tumour regression grade and surgery

From 30 patients with cPR and in concordance with MRI to determinate mrTRG only 13 were available for watch and wait option (43,3%), the rest of them (56,7%) will be available with this technique for TME and not watch and wait option, (figure 1).

## DISCUSSION

Patients with mrTRG 3-5 are not candidates for less aggressive management after nCRT, been mrTRG 1-2 more favorable to conserving management, including watch and wait option and organ-preserving transanal excision (TAE) like an option suggested in some studies alternative to watch and wait in patients with mrTRG1 and 2 [5].

In a selection of patients, such as no apparent residual tumours at endoscopy and clinical examination the watch and wait could be a good option [12].

The TRIGGER Trial (Number 2015-003009-40) is an open, randomized, parallel assignment clinical trial who will help to determinate the importance of good classification by image (MRI) of patients during nCRT. The protocol establishes two arms. Patients in the control arm will receive current practice of surgery at 6-8 weeks after nCRT and then standard course of chemotherapy (CAPOX [capecitabine and oxaliplatin] or FOLFOX [5-fluorouracil, oxaliplatin, folinic acid], or single agent capecitabine or 5-fluorouracil)). The intervention arm will receive a treatment plan according to their response to nCRT, assessed using the mrTRG. Patients who have a good response to nCRT will defer surgery until the

cancer stops reducing in size or avoid surgery altogether if the cancer cannot be detected with repeat scans and assessments. Patients who have poor response to nCRT will have additional pre-operative chemotherapy. [7]

Therefore, mrTRG will guide the making decisions in these patients and will help to include patients in watch and wait options, avoiding or differing the surgical procedure.

In our results, 52% of patients achieve mrTRG1-2, therefore, these patients could be not candidates to surgical option, avoiding the surgical risk. However, nowadays we need more studies to determinate the rate of relapse in this patients OS and need of surgery in a second time with the consequences of an irradiated tissue for surgeon. Moreover, old patients with comorbidities and mrTRG favorable are the best candidates for conservative management with an adequate follow up.

The rest of parameters describe in MRI (EMVI, STD, CRM and SCI) are well known biomarkers of good response to nCRT related with OS in different studies, and in the present study were coincident with describe, associating a relationship between absence of EMVI, STD and SCI as well as negative CRM and survival statistically significant (Figure 1).

Is important to emphasize that like in other localization of solid tumour, different histologies are different in imaging modalities (MRI) like is the case of mucinous rectal cancer who has special histopathological characteristics, with high signal intensity on T2 weighted image (WI) in MRI for example and his changes during nCRT could be difficult for radiological evaluation [13].

On the other hand, the addition of diffusion-weighted imaging (DWI) could be beneficial in determinate the real response to nCRT in patients with mrTRG 1-2 and optimize the treatment (TAE vs watch and wait). This modality could have been helpful too in the 48% patients with a mrTRG 3-5 and maybe we would have classified these patients in other category with better response. Other options that could help a better classification is the colonoscopy post-nCRT [5]. Some radiologists propose key points to standardize the report case [14, 15, 16].

The combination of mrTRG and ctDNA is an interesting proposal and with its combination could be complementary to assess local response and systemic disease status previous surgery and adapt therapy treatment [17].

A meta-analysis [18] reported higher rates of pCR when the time lag between nCRT and surgery was longer than 6-8 weeks. This concept is relevant in results of Stockholm III but with short course of radiotherapy [19]. Despite it, is necessary randomised trials to demonstrated it.

It's important to announce that different techniques less invasive like brachytherapy in T3 tumours with apparently comparable rates of pCR with EBRT [20] and other authors emphasize the importance of intensity modulated radiotherapy with simultaneous integrated boost [21] and others in the possibly of radiotherapy omission in selected patients with low risk [22]. On the other hand, Hearn et al [23] propose radiotherapy dose escalation above 54Gy for his association with high rates of pCR and less risk of acute grade 3 toxicity.

Jootun et al [24] propose a different selection of patients for nCRT focusing in margin-threatening tumours, with low local relapse rates, different propose at MERCURY trial which use nCRT in all LARC [9].

Analysis molecular have permitted identified levels of acid ceramidase (AC). AC is a lysosomal cysteine hydrolase, which catalyzes the conversion of ceramide into fatty acid and sphingosine, playing an important role in response to cellular stress. AC is overexpressed in different cancers and its relationship with radioresistance of colorectal cancer cell lines [25]. Clifford et al demonstrates that AC inhibition leads to significantly enhanced radiosensitivity through an elevation in apoptosis.

Birkman et al [26] studied the overexpression of cancerous inhibitor of protein phosphates El 2A (CIP2A) in several cancers and his relationship with response to nCRT. CIP2A is a tumour suppressor activity and promotes malignant cell transformation and tumour growth. Low CIP2A expressing tumours had more frequently moderate or excellent response to long course nCRT than patients with high CIP2A expressing tumours.

Epiregulin (EREG) are ligands of the EGFR that regulate cell proliferation, migration, and adhesion, overexpressed EREG are commonly observed in rectal cancer and his high levels are associated with wild-type KRAS, wild-type BRAF and micro satellite stable status. Therefore, EREG high expression is significantly associated with higher tumour regression [27].

The use of checkpoint inhibitors like PD-1/PDL-1 blockage is uncertain in rectal cancer. Boustani et al studied the impact of nCRT and fractionation on PDL-1 expression. The results showed no effect of RT fractionation on PDL-1 expression even CD8 TILs infiltration and TRG [28].

Secreted Protein Acidic Cysteine-Rich (SPARC) is an extracellular matrix component and high expression of this protein is related with worse prognosis in rectal cancer patients [29] Massaras et al [4] studied the possibly of anorectal sphincter dysfunction, but in concordance with literature review nowadays the limits of contouring exclude anal canal from radiation field or sphincter-sparing techniques for nCRT, however the literature showed that radiotherapy could cooperate in nerve damaging more than muscular fibers and participate in bowel dysfunction observed in these patients, but more well-designed studies are required.

A recently meta-analysis demonstrates a minimal increased risks for second primary rectal cancer in patients who received RT to pelvic region, RR 1,43 (CI 1,18-1,72) however, this modest rise risk does not change the management of this patients [30].

## CONCLUSION

This study has limitations for the small number of patients, the variability interobserver and short time of following, but we can conclude that MRI is a feasible technique to determinate TRG and obtain a better classification of patients with LARC who finishing nCRT. The combination of MRI with DWI and/or molecular markers (ctDNA, AC, CIP2A, EREG, SPARC) could be more feasible to offer less aggressive management in selected cases but more studies and clinical trials must be made. The actually approach probably could be modify with results of TRIGGER trial.

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