The Egyptian Journal of Hospital Medicine (January 2023) Vol. 89 (2), Page 99- 106

Downstaging of Rectal Cancer Following Neoadjuvant Chemoradiotherapy; How Far Could Functional MRI Support Organ Preservation Approach

Roaa M Farahat[1], Mohamed R Habba[2], Ahmed F Elserafy[2], Ahmed MM Gomaa[3], Radwa A Noureldin[2]

[1] Department of Radiodiagnosis, Ismailia Medical Complex

[2] Department of Radiodiagnosis and [3] Department of Surgery, Faculty of Medicine, Suez Canal University

Address for Correspondence: Ahmed Mohamed Gomaa, Tel: 01002416360, E-mail: gomaaahmed@hotmail.com

ABSTRACT

Background: Rectal cancer constitutes a distinct subset of colorectal carcinoma necessitating a dedicated multidisciplinary approach through the journey of diagnosis and treatment. Neoadjuvant chemoradiotherapy (CRT) has the advantage of tumor down staging, with a chance of pathologic complete response (pCR) with reflection on locoregional recurrence rates, and increased overall survival. In this study we aim to assess the response to neoadjuvant chemoradiotherapy offered to patients with locally advanced rectal cancer using functional MRI then to be validated through final pathological result following standard surgical management.

Patients and Methods: This study included 29 patients with rectal cancer eligible for neoadjuvant therapy. Patients had their MRI before and after neoadjuvant CRT, then they underwent surgical intervention in the form of anterior resection with total mesorectal excision (TME) or abdominoperineal resection (APR). Final pathological results were compared to post CRT functional MRI results. **Results:** We found that neoadjuvant CRT downstaged our patients to the extent that rendered around 15 percent of patients with complete pathological response could have made benefit from organ preservation approach with either 'watch-and-wait' or local excision, a chance could be offered in regards to good standardized functional multiparametric MRI assessment.

Conclusion: Response to neoadjuvant treatment in locally advanced rectal cancer could be assessed with multiparametric functional MRI giving the patient good chances regarding the best tailored surgical options that influence disease control and overall survival.

Keywords: Organ preservation, Watch and wait strategy, Functional MRI, Cancer rectum, Neoadjuvant chemoradiotherapy

INTRODUCTION

Rectal cancer constitutes a special subset of colorectal carcinoma and it comes second between all female malignancies and third in male cancers worldwide. This raises the need to a dedicated multidisciplinary approach through treatment journey [(1)].

Conventional MRI gained broad acceptance in pretreatment evaluation of rectal cancer and local staging via its prospect to assess and predict circumferential margins, extramural invasion and venous invasion with good accuracy by high resolution T2 TSE [(2)].

Nowadays, locally advanced rectal carcinoma is given neoadjuvant chemoradiation therapy (CRT) targeting reducing local recurrence and increasing disease free survival [(3)].

Although numerous diagnostic methods proposed to assess the degree of tumor response to neoadjuvant CRT, it is vital to emphasize that a definitive diagnosis of complete response can only be considered via examination of the primary tumor area histologically. Histological tumor response is estimated by applicating what is recognized as "tumor regression grades". Most of these schemes identify proportions of residual malignant cells as well as the surrounding fibrosis and inflammation, subsequently a final number is then assigned [(4)].

Response to neoadjuvant CRT is variable. A work carried out by Glynne-Jones in 2016 reported a cPR in nearly 25% of cases [(4)].

Many systems were developed for grading response to therapy, the first of which was the Mandard system [(5)], then came the Dworak method [(6)], which was widely employed in Europe. Following the idea of these authentic systems, the College of American Pathologists designed a regression grade (Figure 1) [(7)] focusing on recording residual tumor and found to correlate with better outcomes [(8)].

Grade 0	Complete response – no viable cancer cells
Grade 1	Moderate response – single or small groups of cancer cells
Grade 2	Minimal response – residual cancer outgrown by fibrosis
Grade 3	Poor response – minimal or no tumor kill, extensive residual cancer

Figure (1): AJCC and College of American Pathologists Regression Grade [(7)]

Received: 10/8/2022
Accepted: 10/10/2022

It is accepted nowadays that tumor regression grade, identified by final histopathology after neoadjuvant chemoradiotherapy (CRT), is considered a good prognostic parameter allowing physicians to risk-stratify patients according to its variable response, a way that helps to decide needs for adjuvant treatment and modality of follow up[9].

The challenge, yet, is how to employ all these information to modulate the clinical path of the disease and if possible, offering different treatment options in the form of organ preserving strategies either local excision or watch-and-wait policy. [4]

Conventional MRI is based on classical morphological evaluation rendering sensitivity and specificity short in terms of evaluating the response to neoadjuvant CRT and postoperative assessment. Due to these limitations, the "multiparameteric MRI" was introduced involving addition of functional MRI sequences namely diffusion and perfusion to usual protocol [3].

This issue has been emphasized also by **MacGregor *et al.*** who insisted on the necessity for a worldwide agreeable standard (Figure 2) regarding MRI assessment of tumor regression [10].

mrTRG scale	mrTRG [Low no. – More regression]
1	Radiological complete response (rCR): no evidence of ever treated tumour
2	Good response (dense fibrosis; no obvious residual tumour, signifying minimal residual disease or no tumour)
3	Moderate response (50% fibrosis or mucin, and visible intermediate signal)
4	Slight response (little areas of fibrosis or mucin but mostly tumour)
5	No response (intermediate signal intensity, same appearances as original tumour)

Figure (2): MRI tumor regression grading [10]

Regarding that multiparametric MRI stands out as a promising tool, we tried to highlight the value of MRI with addition of functional technique by diffusion and perfusion analysis in assessment of response to neoadjuvant therapy and postoperative follow up for a more accurate method to predict response to neoadjuvant therapy in rectal cancer and so the outcome of the disease.

PATIENTS AND METHODS

A prospective cohort study on 29 patients was conducted during the period from January 2021 to January 2022 at two settings; Suez Canal University Hospital and the Ismailia Cancer Teaching Hospital.

The MRI evaluation, both conventional and multiparametric studies were performed using 1.5 Tesla single shot turbo spin echo, Siemens, Germany, equipped with additional multiparametric capabilities to measure the changes to neoadjuvant. All patients were designated as stage II or III rectal cancer and referred to neoadjuvant therapy after having their initial MRI baseline scan.

They received neoadjuvant therapy in the form of RT 50Gy fractionated over 25 sessions with 5-fluorouracil or capecitabine.

Patients had their MRI (post CRT) within 8 – 10 weeks, then they underwent surgical intervention in the form of low anterior resection with TME or APR.

MRI Protocol:

- **Conventional MRI:**
  Axial oblique, sagittal and coronal T2 weighted images were translated into TNM staging.

- **Diffusion weighted images and ADC analysis:**
  - Apparent diffusion coefficient ADC values were obtained at diffusion weighted MRI as reflection to tumor cellularity with **cutoff point of** ADC mean SNR of b value at 1000 sec/mm^2 is **21.4+/- 4.0**

- **Dynamic contrast analysis:**
  - T1 maps images were obtained for more accurate determination of contrast quantification with multiple flip angle (2 degree and 15 degree), TR 3.88 msec, TE 1.31 msec, FOV 26x26 cm, section thickness 4 mm.
  - Temporal resolution 10 sec, were taken approximately 5 minutes at minimum rate of contrast injection 2.5 ml/sec.

- **Perfusion qualitative and quantitative analysis:**
  - Tissue 4D perfusion parameters were obtained as following:

  #Volume Transfer contrast (K^{trans}): reflecting the contrast exchanges from plasma compartment to extra vascular extra cellular space.
  # Initial area under the curve (iAUC).
  Quantitative data interpretation:
  ^{Ktrans} was 0.732, with a 95% CI of 0.610 – 0.854, and the diagnostic cutoff value was 0.088 min-1 (sensitivity 60.5%, specificity 81.5%). [11]

Following surgical procedure, histopathological results were retrieved and designated according to the AJCC regression scale [7] and plotted against the MRI tumor regression grades obtained by the Multiparametric MRI.

Ethical approval:

The Committee of Research Ethics at Faculty of Medicine, Suez Canal University approved this study protocol and an informed consent had to be taken before and from all patients. This work carried out according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistics:

Collected data were imported into the Statistical Package for the Social Sciences (SPSS IBM version 24.0- IBM Corp, Armonk, NY) software for analysis. Differences between frequencies and means were compared by Fisher exact and Mann-Whitney tests, respectively. Wilcoxon signed-rank test was used for dependent paired samples.

Specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were estimated according to final pathological result in comparison to mrTRG.

A p value of < 0.05 was considered significant.

RESULTS

The study included 29 patients with locally advanced rectal cancer designated as stage II and III according to AJCC staging system. The baseline data of the studied patients are shown in table (1).

Table 1: Baseline data of the studied patients

	(n = 29)
Age (years)	
Min. – Max.	30.0 – 79.0
Mean ± SD.	55.1±10.6
Sex	
Male	15(51.7%)
Female	14(48.3%)
Interval between preoperative CRT completion and restaging MRI (weeks) , **Mean**	8.5
Min. – Max.	8-10
Interval between preoperative CRT completion and surgery (weeks), **Mean**	10.5
Min. – Max.	8-12

After having their initial pre-treatment MRI, both conventional and functional, all patients received the long course radiotherapy with chemosensitizing agent then new MRI was obtained after 8 to 10 weeks assessing the ADC, K^{trans} values and AUC (Figure 3 and 4). These images were compared and the obtained values were assessed. These data are shown in table (2) and revealed a statistically significant change as a response to treatment.

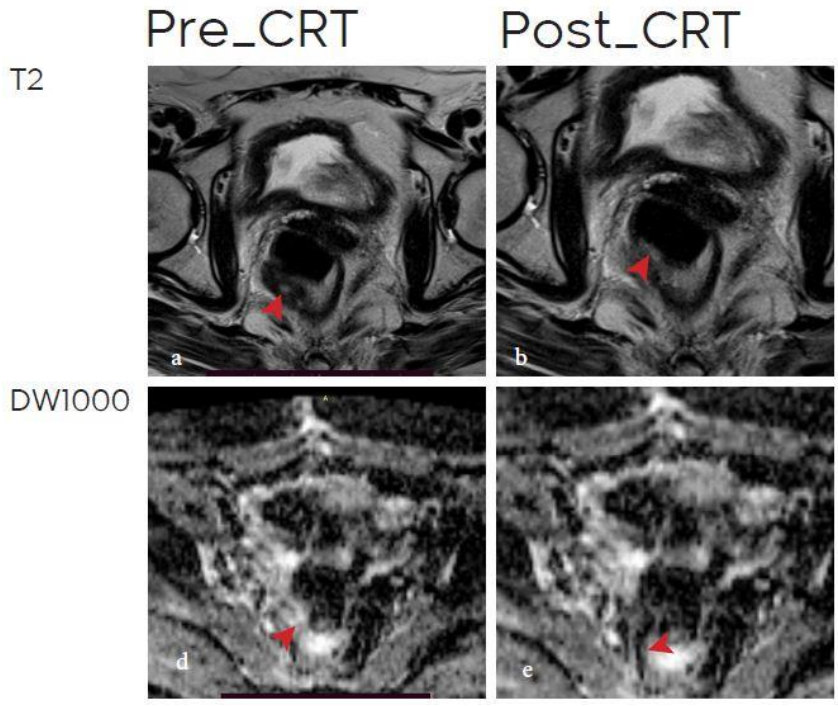

Figure (3).

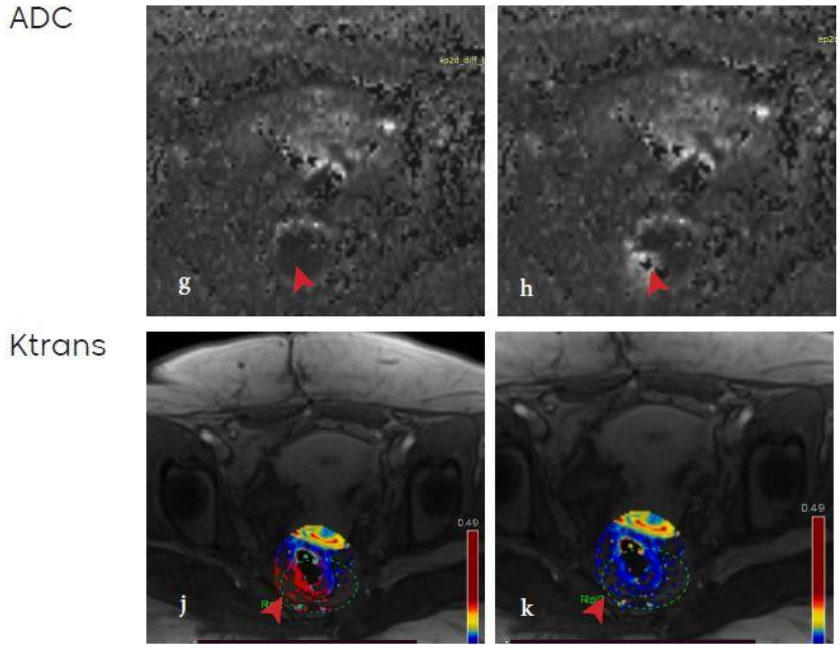

Figure (4).

Figure (3) and (4): MRI sequences, conventional and functional, that show difference between rectal lesion before and after RCT with complete radiological response (mrTRG1)

Table 2 compare between before and after neoadjuvant.

Table 2: Comparison of MRI findings at baseline (before) versus after CRT among the study patients (n=29)

	MRI finding		P-value
	Baseline	After CRT	
DWI			**<0.001*[1]**
Low	0(0%)	20(69%)	
High	29(100%)	9(31%)	
ADC			
Low	29(100%)	9(31%)	**<0.001*[1]**
High	0(0%)	20(69%)	
K^{trans}			
Low	0(0%)	19(65.5%)	**<0.001*[1]**
High	29(100%)	10(34.5%)	
AUC			**<0.022*[2]**
Min. – Max.	0.59–0.91	0.24–0.83	
Mean ± SD.	0.74±0.08	0.56±0.16	

*DWI; Diffusion-weighted imaging, ADC; Apparent diffusion coefficient, AUC; area under the curve, 1. Fisher exact test, 2. Wilcoxon signed-rank test, *;statistically significant*

Patients were operated upon either by low anterior resection with TME or abdominoperineal resection with permanent end colostomy, 22(75.8%) patients had low anterior resection (LAR) while 7(24.2%) had APR (Figure 5).

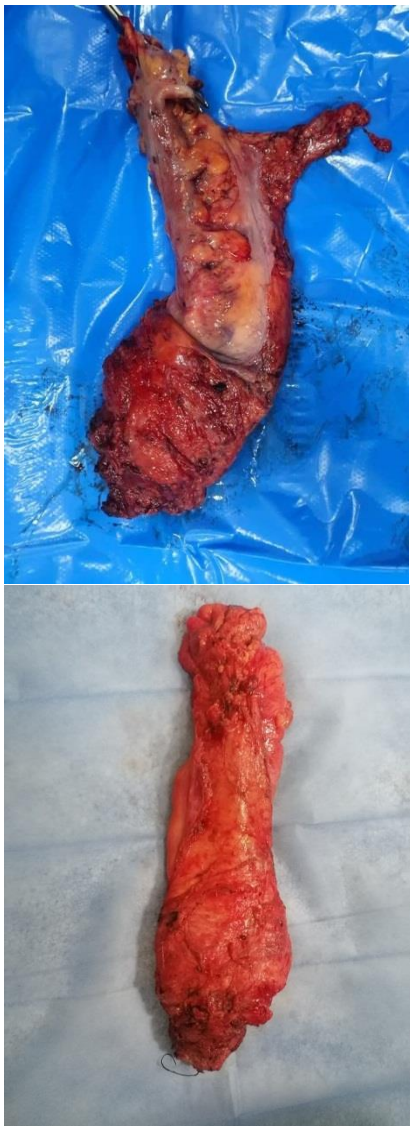

Figure (5): showed 2 different photos of 2 different specimens after APR showing TME

Final histopathological results were retrieved and patients were categorized into grades according to response to treatment following the AJCC grading scale as shown in table (3).

Table 3: Distribution of patients according to pathological response to CRT (n=29)

	Responders	Non responders
Pathological TRG		
Complete response (0)	8(27.6%)	_
Moderate response (1)	8(27.6%)	_
Minimal response (2)	_	6(20.7%)
No response (3)	_	7(24.1%)
Total	16	13

The results were statistically significant on comparing mrTRG after CRT among the studied patients according to frequency (percentage) of responses (Table 4).

Table 4: Comparison of mrTRG after CRT among the study patients according to response distribution (n=29)

	pTRG					P-value
	complete response (n=8)	moderate response (n=8)	minimal response (n=6)	no response (n=7)	Total	
mrTRG						
Complete response (n=5)	**4 (50%)**	**1 (12.5%)**	**0 (0%)**	**0 (0%)**	**5**	**<0.001 *[1]**
Good response (n=10)	**4 (50%)**	**6 (75%)**	**0 (0%)**	**0 (0%)**	**10**	
Moderate response (n=1)	**0 (0%)**	**1 (12.5%)**	**0 (0%)**	**0 (0%)**	**1**	
Slight response (n=5)	**0 (0%)**	**0 (0%)**	**5 (83.3%)**	**0 (0%)**	**5**	
No response (n=8)	**0 (0%)**	**0 (0%)**	**1 (16.7%)**	**7 (100%)**	**8**	
Total	**8**	**8**	**6**	**7**	**29**	

1; Fisher exact test, *; statistically significant, pTRG: pathological tumor regression grade.
mr TRG: MRI tumor regression grade

In view of the specific potential of functional MRI showed in the changes in the values of ADC, K^{trans} and AUC when comparing between responders and non-responders patients; table (5) shows that the patients with complete pathological response and moderate response, responder group, had significant changes in these values before and after neoadjuvant CRT when compared to non-responders.

Table 5: Comparison of MRI findings (parameters) after CRT among the study patients according to response distribution (n=29)

	Response		P-value
	responders (Moderate and Complete) (n=16)	non responders (Minimal and no response) (n=13)	
DWI			
Low	16(100%)	4(30.8%)	**<0.001*[1]**
High	0(0%)	9(69.2%)	
ADC			
Low	0(0%)	9(69.2%)	
High	16(100%)	4(30.8%)	**<0.001*[1]**
K^{trans}			
Low	16(100%)	3(15.8%)	
High	0(0%)	10(84.2%)	**<0.001*[1]**
AUC			
Mean ± SD.	0.540±0.144	0.598±0.197	**0.505[2]**

1. Fisher exact test, 2. Mann Whitney U test. *statistically significant as p<0.05.

When projecting data of mrTRG to final pathological result, we found that multiparametric MRI had 95.2% specificity, 80% positive predictive value (PPV), and 83.3% negative predictive value (NPV) with overall accuracy of 82.8%.

DISCUSSION

Currently, radical resection is the main approach of treating rectal cancer. For precise TME with nerve-sparing method, advanced surgical training is necessary. Radical resection of the rectum is also a significant procedure that carries a high risk of morbidity and mortality, especially for elderly patients [(12)]. Additionally, radical resection renders patients vulnerable to a significant loss of sexual, anorectal, and urination function, that ultimately results in an impaired quality of life [(13,14)]. A concern on preventing postoperative severe morbidity and impaired quality of life after radical rectal surgery is further supported by the interest shown in organ preservation strategies, essentially for low seated rectal cancer, by many physicians and academics. [(14)]

The ability of neoadjuvant CRT to reduce the size or stage of a tumor is widely established. However, it can also cause a pCR, which is the full absence of malignant cells in the removed part. Up to 10%-32% of patients are found to have pCR [(15,16)]. Complete clinical response (cCR) is the term used when a tumor is no longer identifiable on multiple diagnostic methods, such as per rectal digital examination, endoscopy, endo-luminal ultrasound, or MRI, and non-operative management including stringent follow-up is provided [(17)].

Complete clinical response rates ranging from 11% to 16% were found in varying retrospective investigations [(18-21)]. While according to **Habr-Gama *et al.*** [(22)], the highest cCR rate following the recommended course of neoadjuvant CRT was 49.2%.

The precise evaluation of tumor response and timing of the evaluation are the two most important components of the organ preservation strategy [(17)]. The primary foundation of the evaluation methodology is the detection of a clinically vanished tumor mass on the digital examination and direct view of mucosa of the rectum by endoscopy showing only scarring [(23)]. The majority of the studies that employed watch-and-wait strategy recorded cCR depending on assessment by digital rectal examination and endoscopic examination with or without biopsy [(24)].

As science develops different imaging modalities, which include trans-rectal US, CT scan, MRI, 18-FDG PET-scan used moreover to increment the detection rate of cCR. The evolution of imaging techniques has led to the emergence of high-resolution MRI that can distinguish between residual disease and fibrosis [(25-28)].

Predicated on the extent of tumor regression as quantified via MRI, pCR can be determined up to ten instances more than clinically assessed by endoscopy or digital rectal examination [(29)]. However, the weight of MRI in restaging following neoadjuvant CRT remains controversial and some authors raise the need to address the heterogeneity in the analysis of different sequences of magnetic resonance imaging in post-neoadjuvant rectal cancer staging [(30)].

During our study, we examined the importance of K^{trans} and ADC added to the conventional MRI in regard to the assessment of chemoradiotherapeutic effect on patients sustained rectal carcinoma. The results of this study elucidated the power of both K^{trans} and ADC, and their potential to be used as respectable tools in foreseeing the efficacy of chemoradiotherapy in patients suffering from rectal cancer.

Volume transfer constant (K^{trans}) is measured through analysis of the temporarily gained DCE-MRI data, which is an indirect measure of physiological parameters involving vascular attenuation and angiogenic activity and reflecting vascular permeability.[(31)] A particular key result of our study was the observation of a negative relationship between K^{trans} values and the leverage of neoadjuvant chemoradiotherapy given to rectal cancer patients. In non-responders, K^{trans} values were higher after neoadjuvant treatment when compared to responders who showed lowered values and this refer to an increased angiogenic activity in non-responders.

The major finding of this work revealed that after chemoradiotherapy treatment, ADC values in responder

and non-responder groups have increased with a positive correlation found between the ADC values and the reduction rate in tumor size. So, it highlights the power of ADC in evaluating the clinical response to neoadjuvant chemoradiotherapy in patients sustained rectal cancer effectively. Going with literature, throughout our study, a respectable change in tumor ADC values was detected following neoadjuvant treatment, which is considered as favorable response to therapy.

This study included 29 patients diagnosed with rectal cancer designated as stages II and III. Half of the patients (51.7%) were males. and (48.3%) were females with a mean age of 55.1 ±10.6 years (range 30-79) and this distribution was similar to the study of **Gamal Eddin *et al*.** [31] . Mean interval between completion of neoadjuvant chemoradiotherapy and restaging functional MRI was 8.5 weeks (8-10 weeks), and mean interval between completion of neoadjuvant treatment and surgical intervention was 10.5 weeks (8-12 weeks).

Regarding the type of surgical intervention for our patients, almost three quarters of them (22- 75.8%) had low anterior resection with total mesorectal excision, and 7 (24.2%) had abdominoperineal resection, all our data were comparable to the results of **Jimenez-Rodriguez *et al*.** [32]

MRI showed considerable downstaging following neoadjuvant chemoradiotherapy. Before CRT, 12 patient (41.4%) were designated as T3 and 17 patients (58.6%) were T4, while after CRT, 5 patients (17.2%) showed no residual tumor, 6 patients (20.7%) were T1 and 4 patients (13.8%) showed T2, 7 (24.1%) patients were T3, and 7 patients were T4. Also, in regards to N stage and involvement of mesorectal fascia, both showed improvement by MRI criteria after CRT. This downstaging was comparable to the final pathological staging.

Also, DW, ADC, K^{trans}, and AUC values had statistically significant differences before and after chemotherapy. All the results were found comparable to previous study [33] stating the effect of the therapy on the outcome of tumor status.

Regarding the MR grading (TRG) post neoadjuvant chemoradiotherapy, 5 patients (17.2%) showed complete response, 10 patients (34.5%) good response, 1 patient (3.4%) moderate response, 5 patients (17.2%) slight response and 8 patients (27.6%) showed no response. The earlier mentioned findings are comparable to the results of **Pham *et al.*** [34] and **Lambregts *et al*.** [35]

In view of final histopathological results, 8 patients (27.6%) showed **c**omplete pathological response (cPR), 8 patients showed moderate response, 6 patients (20.7%) had minimal response and 7(24.1%) of patients had no response.

In summary, the observations and findings of our study showed significant evidence suggesting that both K^{trans} and ADC in addition to the conventional MRI are effective predictor tools regarding assessment of clinical response to neoadjuvant RCT in patients with rectal cancer having 95.5% specificity and overall accuracy of 82.8% and this make functional MRI a promising modality that can support the tendency to organ preserving strategies in the form of local excision or watch-and-wait approach.

CONCLUSION

Functional multiparametric MRI is a promising tool to assess the response to neoadjuvant chemoradiotherapy when given to patients suffering locally advanced rectal cancer aiding in supporting the tendency to organ preserving strategies and giving the chance of tailoring treatment to responder patients in the form of local excision or watch-and-wait approach.

Conflict of Interest: None
Funding source: None
Acknowledgment: None.

REFERENCES

1. **Clinton S, Giovannucci E, Hursting S (2020):** The World Cancer Research Fund/American Institute for Cancer Research third expert report on diet, nutrition, physical activity, and cancer: impact and future directions. https://www.ncbi.nlm.nih.gov/pubmed/31758189
2. **Araghi M, Soerjomataram I, Jenkins M *et al.* (2019):** Global trends in colorectal cancer mortality: projections to the year 2035. International Journal of Cancer, 144(12): 2992-3000.
3. **Yu H, Hemminki A, Sundquist K *et al.* (2019):** Familial associations of colon and rectal cancers with other cancers. Diseases of the Colon and Rectum, 62(2):189-195.
4. **Glynne-Jones R, Hughes R (2016):** Complete response after chemoradiotherapy in rectal cancer (Watch-and-Wait): Have we cracked the code? Clinical Oncology, 28(2): 152-160.
5. **Mandard AM, Dalibard F, Mandard JC *et al.* (1994):** Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer, 73(11): 2680-2686.
6. **Dworak O, Keilholz L, Hoffmann A (1997):** Pathological features of rectal cancer after preoperative radiochemotherapy. International Journal of Colorectal Disease, 12(1): 19-23.
7. **Mace A, Pai R, Stocchi L *et al.* (2015):** American Joint Committee on Cancer and College of American Pathologists regression grade: a new prognostic factor in rectal cancer. Diseases of the Colon and Rectum, 58(1): 32-44.
8. **Jäger T, Neureiter D, Urbas R *et al.* (2017):** Applicability of American Joint Committee on Cancer and College of American Pathologists Regression Grading System in Rectal Cancer. Diseases of the Colon and Rectum, 60(8): 815-826.
9. **Fokas E, Liersch T, Fietkau R *et al.* (2014):** Tumor regression grading after preoperative chemoradiotherapy for

locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. Journal of Clinical Oncology, 32(15): 1554-1562.

10. **MacGregor T, Maughan T, Sharma R (2012):** Pathological grading of regression following neoadjuvant chemoradiation therapy: the clinical need is now. Journal of Clinical Pathology, 65(10): 867-871.
11. **Kalisz K, Enzerra M, Paspulati R (2019):** MRI evaluation of the response of rectal cancer to neoadjuvant chemoradiation therapy. Radiographics, 39(2):538-556.
12. **Rutten H, den Dulk M, Lemmens V *et al.* (2008):** Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol.,9:494-501.
13. **Downing A, Glaser A, Finan P *et al.* (2019):** Functional outcomes and health-related quality of life following curative treatment for rectal cancer: a population-level study in England. Int J Rad Oncol Biol Phys., 103:1132-42.
14. **Sun V, Grant M, Wendel C *et al.* (2016):** Sexual function and health-related quality of life in long-term rectal cancer survivors. J Sex Med., 13:1071-9.
15. **Cotte E, Passot G, Decullier E *et al.* (2016):** Pathologic response, when increased by longer interval, is a marker but not the cause of good prognosis in rectal cancer: 17-year follow-up of the Lyon R90-01 randomized trial. Int J Rad Oncol Biol Phys., 94:544-53.
16. **Hartley A, Ho K F, McConkey C *et al.* (2005):** Pathological complete response following pre-operative chemoradiotherapy in rectal cancer: analysis of phase II/III trials. British J Radiol., 78:934-8.
17. **Sao Juliao G, Habr-Gama A, Vailati B *et al.* (2017):** New strategies in rectal cancer. Surgical Clin North Am., 97:587-604.
18. **Perez R, Habr-Gama A, Sao Juliao G *et al.* (2014):** Predicting complete response to neoadjuvant CRT for distal rectal cancer using sequential PET/CT imaging. Techn Coloproctol., 18:699-708.
19. **Lai C, Lai M, Wu C *et al.* (2016):** Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait". Int J Colorectal Dis., 31:413-9.
20. **Renehan A, Malcomson L, Emsley R *et al.* (2016):** Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol., 17:174-83.
21. **Vaccaro C, Yazyi F, Ojra Quintana G *et al.* (2016):** Locally advanced rectal cancer: preliminary results of rectal preservation after neoadjuvant chemoradiotherapy. Cir Esp., 94:274-9.
22. **Habr-Gama A, Gama-Rodrigues J, Sao Juliao G *et al.* (2014):** Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Rad Oncol Biol Phys., 88:822-8.
23. **Habr-Gama A, Perez R, Nadalin W *et al.* (2004):** Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg., 240:711-7.
24. **Dattani M, Heald R, Goussous G *et al.* (2018):** Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and pooled analysis. Ann Surg., 268:955-67.
25. **Maas M, Beets-Tan R, Lambregts D *et al.* (2011):** Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol., 29:4633-40.
26. **Al-Sukhni E, Milot L, Fruitman M *et al.* (2012):** Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol., 19:2212-23.
27. **Patel U, Brown G, Rutten H *et al.* (2019):** Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. Annals Surg Oncol., 19:2842-52.
28. **Patel U, Blomqvist L, Taylor F *et al.* (2012):** MRI after treatment of locally advanced rectal cancer: how to report tumor response--the MERCURY experience. AJR Am J Roentgenol., 199:W486-95.
29. **Bhoday J, Smith F, Siddiqui M *et al.* (2016):** Magnetic resonance tumor regression grade and residual mucosal abnormality as predictors for pathological complete response in rectal cancer postneoadjuvant chemoradiotherapy. Dis Colon Rectum, 59:925-33.
30. **van der Paardt M, Zagers M, Beets-Tan R *et al.* (2013):** Patients who undergo preoperative chemoradiotherapy for locally advanced rectal cancer restaged by using diagnostic MR imaging: a systematic review and meta-analysis. Radiology, 269:101-12.
31. **Gamal Eddin B, Hemat E, Hamed M *et al.* (2022):** Added value of diffusion-weighted magnetic resonance imaging in characterization and staging of rectal cancer. The Egyptian Journal of Hospital Medicine, 86 (1): 845-851.
32. **Jimenez-Rodriguez R, Quezada-Diaz F, Hameed I *et al.* (2021):** Organ preservation in patients with rectal cancer treated with total neoadjuvant therapy. Dis Colon Rectum, 64(12):1463-1470.
33. **Birlik B, Obuz F, Elibol F *et al.* (2015):** Diffusion-weighted MRI and MR- volumetry--in the evaluation of tumor response after preoperative chemoradiotherapy in patients with locally advanced rectal cancer. Magnetic Resonance Imaging, 33(2): 201-212.
34. **Pham T, Liney G, Wong K *et al.* (2017):** Functional MRI for quantitative treatment response prediction in locally advanced rectal cancer. https://pubmed.ncbi.nlm.nih.gov/28055248
35. **Lambregts D, van Heeswijk M, Delli Pizzi A *et al.* (2017):** Diffusion-weighted MRI to assess response to chemoradiotherapy in rectal cancer: main interpretation pitfalls and their use for teaching. European Radiology, 27(10): 4445-4454.