

# MAGNETIC RESONANCE IMAGING TO EVALUATE NEOADJUVANT THERAPY EFFECTS ON RECTAL CARCINOMA

Amela Sofić<sup>1</sup>, Zora Vukobrat-Bijedić<sup>2</sup>, Azra Husić-Selimović<sup>2</sup>, Nedžad Šehović<sup>3</sup>, Deniz Bulja<sup>1</sup>, Dženana Eminagić<sup>4</sup>, Maja Banjin<sup>4</sup> and Aleksandra Đuran<sup>5</sup>

<sup>1</sup>Clinical Department of Radiology, <sup>2</sup>Clinical Department of Gastroenterohepatology, <sup>3</sup>Clinical Department of Oncologic Surgery, <sup>4</sup>Clinical Department of Oncology and Radiotherapy, <sup>5</sup>Department of Clinical Pathology, Sarajevo University Clinical Center, Sarajevo, Bosnia and Herzegovina

**SUMMARY** – Although total mesorectal excision reduces the local recurrence rate in comparison to other surgical approaches, the occurrence of local relapse is still common, especially in cases when there is malignant infiltration of the circumferential resection margin. Mesorectal fascia is an important prognostic and diagnostic factor and it may be argued that mesorectal fascia represents the circumferential resection margin if total mesorectal excision is used as a surgical approach. Tumor infiltration of mesorectal fascia warrants preoperative neoadjuvant therapy in order to reduce the risk of tumor relapse. The aim of this study was to show the importance of high-resolution phased-array magnetic resonance imaging (MRI) as a modality of choice in preoperative evaluation of the effects of neoadjuvant therapy on locally advanced rectal carcinoma. This prospective comparative study included 51 patients with locally advanced rectal carcinoma that infiltrated mesorectal fascia. All study patients underwent MRI scanning twice, i.e. before and after neoadjuvant chemoradiotherapy. MRI results before and after neoadjuvant chemoradiotherapy were compared to evaluate regression of tumor length and regression of tumor infiltration of mesorectal fascia. Gender distribution of 51 patients with rectal carcinoma subjected to neoadjuvant therapy was equal, and their average age was 51 (32-81) years. MRI results showed tumor regression from mesorectal fascia following chemoradiotherapy in 36 (70.5%) cases, and Wilcoxon test showed significant differences between pretherapeutic and post-treatment MRI findings ( $Z=-3.162$ ,  $p=0.002$ ) in the sense of regression of tumor infiltration of mesorectal fascia. In 41 (80.3%) cases there was a reduction of tumor length, where Wilcoxon test showed differences between pretherapeutic and post-treatment MRI findings ( $Z=-2.754$ ,  $p=0.006$ ) in the sense of tumor length reduction. The mean pretherapeutic tumor length was 5.4 (2.3-15) cm. The mean reduction of tumor length following chemoradiotherapy was 3.56 (0.3-4.1) cm. In all 36 patients that had tumor-free mesorectal fascia following surgical treatment, the post-treatment MRI results were confirmed by histopathology. In conclusion, MRI is important for evaluation of tumor infiltration of mesorectal fascia, and is useful on patient selection for appropriate treatment for rectal carcinoma. MRI reliably evaluates the effects of neoadjuvant therapy, which contributes to better outcome of treatment for this disease.

**Key words:** *Rectal carcinoma – therapy; Magnetic resonance imaging; Neoadjuvant therapy*

Correspondence to: *Assist. Prof. Amela Sofić, MD PhD*, Clinical Department of Radiology, Sarajevo University Clinical Center, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina  
E-mail: amelasofic@yahoo.com

Received April 20, 2015, accepted June 29, 2015

## Introduction

Rectal carcinoma is one of the most common carcinomas in Europe and the USA, with poor prognosis due to the high risk of local relapse and metastases<sup>1</sup>.

Although total mesorectal excision reduces the local recurrence rate to less than 10% when compared to other surgical approaches, the occurrence of local relapse is still common, especially if circumferential resection margin from the tumor is involved<sup>2</sup>. Involvement of the lateral or circumferential resection margin was the most important risk factor for local recurrence after rectal cancer surgery<sup>3</sup>, and is considerably more relevant than distal or proximal resection margins. Therefore, mesorectal fascia is an important prognostic factor and it may be argued that mesorectal fascia represents the circumferential resection margin if total mesorectal excision is used as surgical approach.

The aim of this study was to show the importance of high-resolution phased-array magnetic resonance imaging (MRI) as a modality of choice to preoperatively evaluate the effects of neoadjuvant therapy on locally advanced rectal carcinoma.

## Patients and Methods

This prospective comparative study included 51 patients with locally advanced rectal carcinoma which infiltrated mesorectal fascia. All of the patients underwent MRI scanning twice, i.e. before and after neoadjuvant chemoradiotherapy. The scanning was performed on a 1.5T scanner (Avanto Siemens, Erlangen, Germany), 3-mm slice thickness, field of view 160-200 mm, with the use of a pelvic phased-array surface RF coil. Lumen of the rectum was cleansed, free from intestinal content, and filled with ultrasound gel as intraluminal contrast agent. Intravenous application of contrast agent or antiperistaltic agent was not performed. MRI results before and after neoadjuvant chemoradiotherapy were compared in order to evaluate regression of rectal tumor. Evaluation parameters were regression of tumor length (because of proximal and distal resection margin) and regression of tumor infiltration of mesorectal fascia (because of lateral resection margin). Minimum tumor distance to mesorectal fascia -5 mm was taken as an indication of no involvement of mesorectal fascia. Post-treatment MRI results were compared with histopathologic finding.

Statistical program SPSS 15.0 (SPSS, Inc., Chicago, IL, USA) and MedCalc® Statistical Software version were used on data processing.

## Results

Statistical data showed that all 51 patients with carcinoma of the rectum that underwent neoadjuvant therapy were equally divided by gender and average age 51 (32-81) years. Histopathologic verification showed that all 51 (100%) patients had adenocarcinoma; G2 stage was present in 39 (76.4%), G3 stage in 12 (23.6%) and mucinous type in five (9.8%) patients. MRI results showed tumor regression from mesorectal fascia following chemoradiotherapy in 36 (70.5%) cases, and Wilcoxon test showed significant differences between pre- and post-treatment MRI findings ( $Z=-3.162$ ,  $p=0.002$ ) in the sense of regression of tumor infiltration of mesorectal fascia. In 41 (80.3%) cases, there was a reduction of tumor length, and Wilcoxon test showed differences between pre- and post-treatment MRI findings ( $Z=-2.754$ ,  $p=0.006$ ) in the sense of tumor length reduction. The mean pretherapeutic length of the tumor was 5.4 (2.3-15) cm. The mean reduction of tumor length following chemoradiotherapy was 3.56 (0.3-4.1) cm. In all 36 patients that had tumor-free mesorectal fascia following neoadjuvant therapy and who became operable the post-treatment results were compared with histopathologic findings. In all these patients, histopathologic findings confirmed the post-treatment MRI findings.

## Discussion

As an aperistaltic organ, the rectum is suitable for application of radiotherapy. After surgical treatment for rectal carcinoma, patients are subjected to adjuvant chemoradiotherapy. Patients with locally advanced tumor also need preoperative neoadjuvant chemoradiotherapy prior to surgery in order to reduce the size and stage of the tumor. Mesorectal fascia is an important prognostic and diagnostic marker, and tumor infiltration of mesorectal fascia warrants neoadjuvant therapy in order to prevent the occurrence of tumor relapse<sup>4-6</sup>. High-resolution MRI with use of phased coil is able to visualize the layers of the rectal wall, the mesorectal fascia, and to predict the depth of tumor invasion<sup>7,8</sup>. Mesorectal fascia is depicted as a thin, low-signal-intensity structure that envelops the mesorectum and surrounds the perirectal fat. If the distance of the tumor from mesorectal fascia is  $\geq 5$  mm, radiologist may consider the fascia uninvolved; if the distance

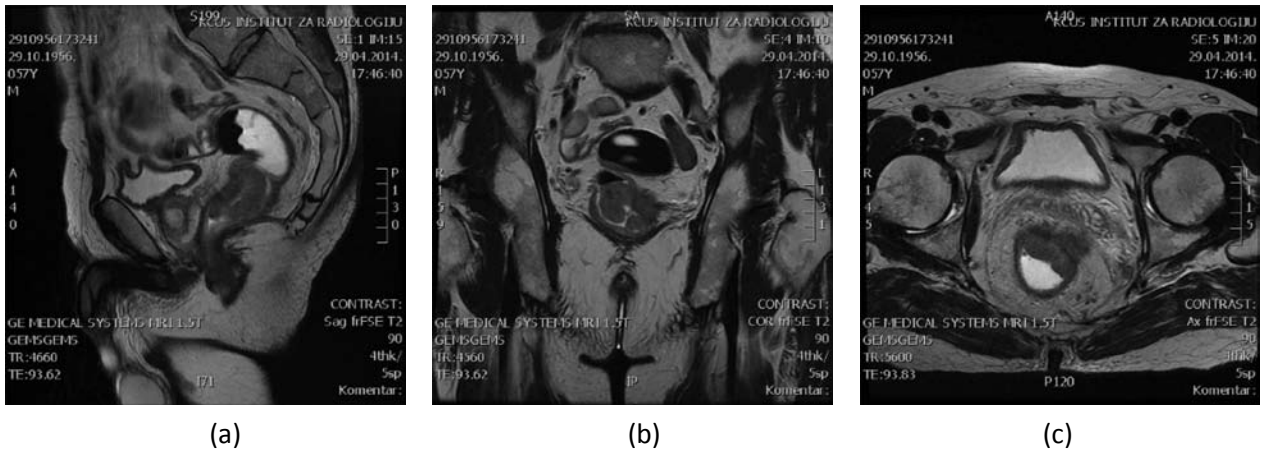


Fig. 1. Mesorectal fascia infiltration in rectal carcinoma: (a) sagittal, (b) coronal, and (c) axial T2w scans prior to initiation of neoadjuvant therapy.

is 2-5 mm, the involvement is considered borderline; if it is  $\leq 1$  mm, mesorectal fascia is involved. Radiologist is assured that the mesorectal fascia is free from tumor only when an intact rectal wall is detected<sup>9</sup>. Many randomized clinical studies indicate the importance of preoperative (neoadjuvant) and postoperative (adjuvant) chemoradiotherapy in decreasing the risk of local recurrence<sup>10-12</sup>. Neoadjuvant therapy is standard in the treatment of rectal carcinoma for locally advanced rectal carcinoma and cannot be compensated for by adjuvant therapy following inadequate non-radiation surgery with positive circumferential resection margin<sup>13,14</sup>. Study reports show that neoadjuvant therapy is less toxic and much more effective than adjuvant therapy<sup>15-17</sup>. Kapiteijn *et al.* report that preoperative

radiotherapy in combination with standardized total mesorectal excision reduces the local recurrence rate from 8.2% to 2.4% at 2 years<sup>5</sup>. A study conducted by Giusti *et al.* showed MRI to be very reliable for preoperative evaluation of tumor infiltration of mesorectal fascia and the authors achieved 100% sensitivity and 100% specificity, whereas after adjuvant therapy the respective values were 100% and 67%<sup>9</sup>. Good results confirming the role of MRI have been reported in a trial performed by Vliegen *et al.* The authors report 100% sensitivity and 32%-59% specificity, indicating that the influence of post radiation fibrosis on overstaging led to somewhat lesser specificity<sup>18</sup>. A recent trial indicated the necessity of preoperative irradiation in selected patients with positive mesorectal fascia at

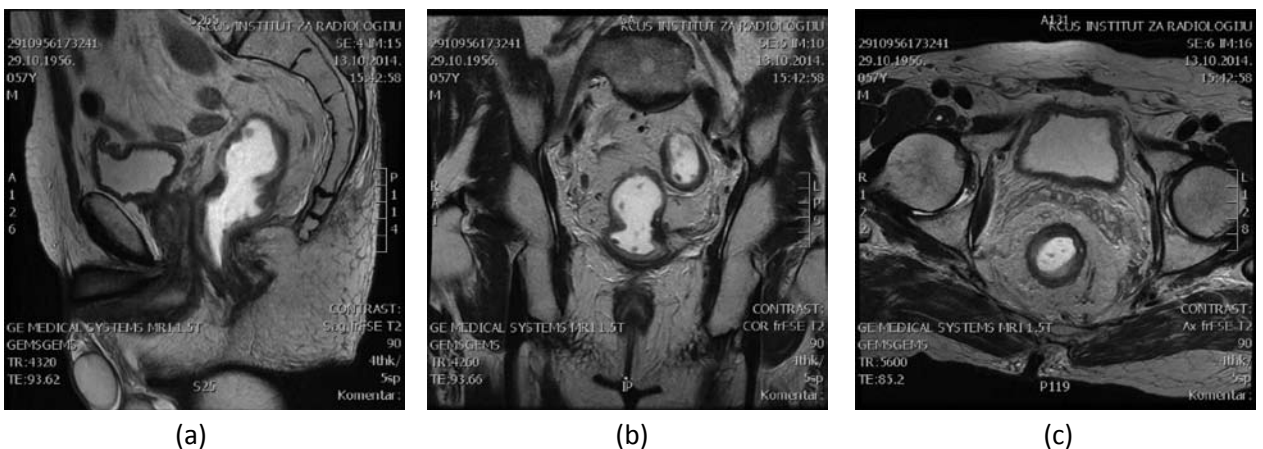
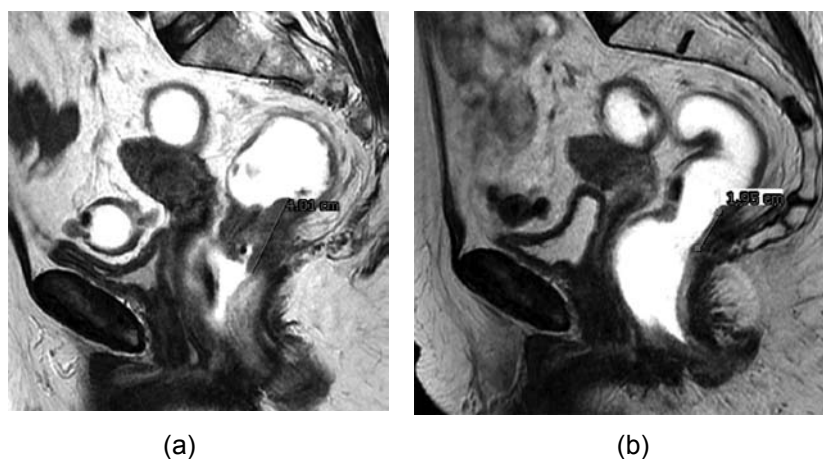


Fig. 2. Sagittal (a), coronal (b), and axial (c) T2w scans show regression of rectal carcinoma infiltration of mesorectal fascia following neoadjuvant therapy.



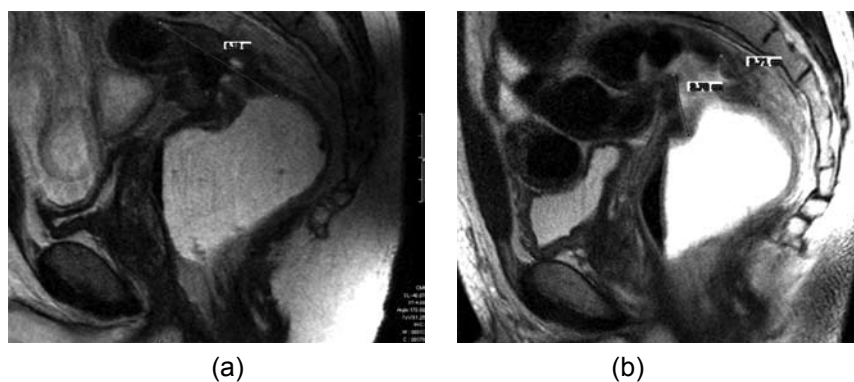
*Fig. 3. Sagittal T2w scans: (a) initial tumor infiltration of the middle portion of rectum; (b) tumor regression of the middle portion of rectum following chemoradiotherapy.*

the time of diagnosis<sup>19</sup>. It can be stated with certainty that MRI has emerged as the dominant modality of pelvic imaging in rectal cancer and high sensitivity in depicting mesorectal fascia<sup>20</sup>. That is why we used it in our study as a reference method for evaluation of tumor response of rectal carcinoma following neoadjuvant therapy. Our results showed tumor regression from mesorectal fascia following chemoradiotherapy in 70.5% of cases (Wilcoxon test,  $p=0.002$ ) (Figs. 1 and 2). In 80.3% of cases, there was a reduction of tumor length (Wilcoxon test,  $p=0.006$ ) (Figs. 3 and 4). Our results are comparable to the results reported by Topova *et al.* on 69.5% tumor response to neoadjuvant therapy<sup>21</sup>. In our study, the mean tumor length prior to neoadjuvant therapy was 5.4 (2.3-15) cm. The mean reduction of tumor length following neoadjuvant therapy was 3.56 (0.3-4.1) cm. The results of our study showed that a large number of patients with tumor infiltration of mesorectal fascia benefited from neoadjuvant therapy and underwent transition from inoperable to operable stage. Unfortunately,

neoadjuvant therapy is not beneficial for all patients due to different tumor response, which is an independent prognostic factor for rectal carcinoma<sup>22</sup>. MRI evaluation of rectal carcinoma following neoadjuvant therapy proved correct in 100% of the cases regardless of post irradiation fibrosis. Despite the known limitations created by post irradiation fibrosis, MRI is a sovereign modality that enables evaluation of high accuracy and topographic relation between lateral extension of the tumor and mesorectal fascia. MRI is very useful for careful selection of patients who will benefit from neoadjuvant therapy, and therefore avoid inadequate therapy that implies insufficient or excessive medical treatment.

### Conclusion

Magnetic resonance imaging is an important tool in the evaluation of tumor infiltration of mesorectal fascia, based on which patients are selected for appropriate treatment option for rectal carcinoma. MRI



*Fig. 4. Sagittal T2w scans: (a) tumor infiltration of the middle portion of rectum prior to chemoradiotherapy; (b) tumor regression of the middle portion of rectum after chemoradiotherapy.*

reliably evaluates the effects of neoadjuvant therapy which contributes favorably to the outcome of treatment for this disease.

## References

1. Maier A, Fuchsjäger M. Preoperative staging of rectal cancer. *Eur J Radiol.* 2003;47:89-97.
2. Tang R, Wang JY, Chen JS. Survival impact of lymph node metastasis in TNM stage III carcinoma of the colon and rectum. *J Am Coll Surg.* 1995;180(6):705-12.
3. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumour spread and surgical excision. *Lancet.* 1986;2:996-9.
4. Willett CG, Badizadegan K, Ancukiewicz M, Shellito PC. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? *Dis Colon Rectum.* 1999;42:167-73.
5. Kapiteijn E, Marijnen CA, Nagtegaal ID. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* 2001;345:638-46.
6. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet.* 1993;341:457-60.
7. Taylor FGM, Swift RI, Blomqvist L, Brown G. A systematic approach to the interpretation of preoperative staging MRI for rectal cancer. *AJR Am J Roentgenol.* 2008;191:1827-35.
8. Brown G, Kirkham A, Williams GT, Bourne M, Radcliffe AG, Sayman J, *et al.* High-resolution MRI of the anatomy important in total mesorectal excision of the rectum. *AJR Am J Roentgenol.* 2004;182:431-9.
9. Giusti S, Bucciante P, Castagna M, Fruzzetti E, Fattori S, Castelluccio E, *et al.* Preoperative rectal cancer staging with phased-array MR. *Radiat Oncol.* 2012;7:29.
10. Glimelius B, Grönberg H, Järhult J, Wallgren A, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in rectal cancer. *Acta Oncol.* 2003;42:476-92.
11. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials. *Lancet.* 2001;358:1291-304.
12. Glimelius B, Holm T, Blomqvist L. Chemotherapy in addition to preoperative radiotherapy in locally advanced rectal cancer: a systematic overview. *Rev Recent Clin Trials.* 2008;3:204-11.
13. Glimelius B. Pre- or postoperative radiotherapy in rectal cancer: more to learn? *Radiother Oncol.* 2001;61:1-5.
14. Sebag-Montefiore D, Stephens RJ, Steele B. Preoperative radiotherapy *versus* selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet.* 2009;373:811-20.
15. Frykholm GJ, Glimelius B, Pählman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum.* 1993;36:564-72.
16. Glimelius B, Isacson U, Jung B, Pahlman L. Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose-response effect favoring preoperative treatment. *Int J Radiat Oncol Biol Phys.* 1997;37:281-7.
17. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, *et al.* Preoperative *versus* postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351:1731-40.
18. Vliegen RF, Beets GL, Beets-Tan RG. Mesorectal fascia invasion after neoadjuvant chemotherapy and radiation therapy for locally advanced cancer: accuracy of MR imaging prediction. *Radiology.* 2008;246(2):454-62.
19. Goh V, Halligan S, Bartram CL. Local radiological staging of rectal cancer. *Clin Radiol.* 2004;59:215-26.
20. Torkzad MR, Pahlman L, Glimelius B. Magnetic resonance imaging (MRI) in rectal cancer: a comprehensive review. *Insights Imaging.* 2010 Sep;1(4):245-67.
21. Topova, L, Hellmich, G, Puffer, E, Schubert, C, Christen N, Boldt T, *et al.* Prognostic value of tumor response to neoadjuvant therapy in rectal carcinoma. *Dis Colon Rectum.* 2011;54(4):401-11.
22. Garajová I, Di Girolamo S, de Rosa F, Corbelli J, Agostini V, Biasco G, *et al.* Neoadjuvant treatment in rectal cancer: actual status. *Chemother Res Pract.* 2011;2011:839742. doi:10.1155/2011/839742.PMID:22295206, PubMed Central PMCID: PMC3263610.

## Sažetak

## MAGNETSKA REZONANCIJA ZA PROCJENU UČINKA NEOADJUVANTNE TERAPIJE KOD REKTALNOG KARCINOMA

*A. Sofić, Z. Vukobrat-Bijedić, A. Husić-Selimović, N. Šehović, D. Bulja, Dž. Eminagić, M. Banjin i A. Đuran*

Iako totalna mezorektalna ekscizija u odnosu na druge kirurške pristupe smanjuje pojavu lokalnog tumorskog recidiva, on je još uvijek veoma čest, osobito kada postoji tumorska infiltracija cirkumferentne reseksijske margine. Mezorektalna fascija je važan prognostički i dijagnostički čimbenik. Može se reći da mezorektalna fascija predstavlja cirkumferentnu reseksijsku marginu ako se kao kirurški pristup koristi totalna mezorektalna ekscizija. Tumorska infiltracija mezorektalne fascije zahtijeva prijeoperacijsku neoadjuvantnu terapiju kako bi se smanjio rizik od pojave tumorskog recidiva. Cilj ove studije bio je pokazati važnost visoko rezolucijske faze magnetske rezonancije (*high-resolution phased-array MRI*) kao tehnike izbora u prijeoperacijskoj procjeni učinaka neoadjuvantne terapije kod lokalno uznapredovalog rektalnog karcinoma. U ovo prospektivno komparativno istraživanje bio je uključen 51 bolesnik s lokalno uznapredovalim rektalnim karcinomom koji je infiltrirao mezorektalnu fasciju. Svi bolesnici su podvrgnuti MRI skeniranju dva puta, prije i poslije neoadjuvantne radiokemoterapije. Rezultati dobiveni pomoću MRI prije i nakon neoadjuvantne radiokemoterapije uspoređeni su s ciljem procjene regresije tumorske dužine i regresije tumorske infiltracije mezorektalne fascije. Svi bolesnici s karcinomom rektuma koji su podvrgnuti neoadjuvantnoj terapiji imali su podjednaku spolnu distribuciju i prosječnu dob od 51 (32-81) godine. MRI rezultati su pokazali da je kod 36 (70,5%) slučajeva nakon radiokemoterapije došlo do povlačenja tumora i oslobađanja mezorektalne fascije, pri čemu je Wilcoxonov test pokazao značajne razlike u prijetjerapijskom i poslijeterapijskom MRI nalazu ( $Z=-3,162$ ,  $p=0,002$ ) u smislu regresije tumorske infiltracije mezorektalne fascije. Kod 41 (80,3%) bolesnika došlo je do smanjivanja tumorske dužine, pri čemu je Wilcoxonov test pokazao razlike u prijetjerapijskom i poslijeterapijskom MRI nalazu ( $Z=-2,754$ ,  $p=0,006$ ) u smislu smanjivanja dužine tumora. Prosječna dužina tumora bila je 5,4 (2,3-15) cm. Prosječno smanjenje dužine tumora nakon radiokemoterapije bilo je 3,56 (0,3-4,1) cm. Poslijeterapijski MRI rezultati potvrđeni su patohistološki kod svih 36 bolesnika koji su nakon neoadjuvantne terapije imali od tumora slobodnu mezorektalnu fasciju nakon operacijskog zahvata. MRI je važan u procjeni tumorske infiltracije mezorektalne fascije, na osnovi čega se provodi odabir bolesnika za odgovarajući terapijski tretman rektalnog karcinoma. MRI pouzdano procjenjuje učinke neoadjuvantne terapije koja utječe na bolji ishod liječenja ove bolesti.

Ključne riječi: *Rektalni tumori – terapija; Magnetska rezonancija, snimanje; Neoadjuvantna terapija*