Acta Clin Croat 2024; 63:523-532

doi: 10.20471/acc.2024.63.04.10

Original Scientific Paper

TUMOR RESPONSE TO NEOADJUVANT LONG-COURSE CHEMORADIOTHERAPY DEPENDS ON THE RECTAL CANCER PATIENT GENDER

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SUMMARY – Our study aimed to analyze the correlation of cancer-related parameters with tumor regression grade (TRG) and disease-free survival (DFS) by gender in 192 rectal cancer patients operated on after neoadjuvant long-course chemoradiotherapy (LCCRT). Preoperative diagnostics revealed no significant gender differences in any clinical parameters other than obesity (p=0.031). We found that slightly overweight men had a lower incidence of distant metastases (p=0.042). The post-LCCRT pathologic finding showed that women had more positive lymph nodes (ypN, p=0.002) while no other pathologic parameter differed significantly between the genders. Overall, a poor response to therapy correlated with a shorter time to disease progression (p=0.002). Women achieved ypN0 in 50% of cases, but only 27% had a good TRG compared to 40.5% of men (p=0.073). Women had a worse DFS than men, even when complete response to therapy was achieved (p=0.003), and greater depth of residual tumor invasion (ypT, p=0.035) and higher ypN (p=0.002) correlated with shorter DFS. Positive resection margins (p<0.001), higher ypN stage (p=0.003), and poor TRG (p=0.025) correlated with shorter DFS in men. We conclude that women have a poorer response to LCCRT with the possibility that therapeutic approach to the neoadjuvant treatment of rectal cancer may be gender-specific.

Keywords: *Rectal cancer; Neoadjuvant chemoradiotherapy; Gender; Tumor regression grade; Disease-free survival*

Introduction

The incidence of rectum and rectosigmoid cancer was 1,439 cases (562 women), and mortality 712 cases (279 women) in Croatia in 2017; according to EU-27 estimates, in 2020 it will be even higher[1,2]. Unfortunately, both the incidence and mortality in Croatia still follow a steady growth trend[3].

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Received February 8, 2021, accepted March 4, 2021

In 2011, the University Hospital for Tumors standardized rectal cancer treatment protocols based on neoadjuvant therapy and total mesorectal excision surgery[4]. The clinical stage of the disease is determined by radiological magnetic resonance imaging (MRI) in preoperative diagnostics, which is the basis for multidisciplinary board decisions on therapy type and regimens. Depending on radiological cTNM stage and circumferential margin positivity, patients were selected for surgery, or neoadjuvant short/long course chemoradiotherapy (LCCRT) first[5]. Implementation of this approach along with respecting surgical standards of total mesorectal excision improved local disease control and overall survival in rectal cancer patients[6].

Neoadjuvant chemoradiotherapy has been used for over ten years for locally advanced rectal cancer. Despite many approaches aiming to stratify patients according to the likelihood and extent of response to that treatment, we still do not have a good selection model. Pathologic complete response (pCR) varies between 9% and 17%, with most patients (over 50%) having some degree of downstaging[7,8]. Based on the complete radiological response, there is a tendency for less extensive surgery or watch and wait approach[8,9].

In this observational, retrospective study, we analyzed a single-institution dataset on neoadjuvant rectal cancer and recorded clinical and demographic parameters for the rate of response to LCCR therapy, depending on gender.

Patients and Methods

The study included 192 consecutive patients with locally advanced rectal cancer undergoing neoadjuvant long-course chemoradiotherapy (LCCRT) with a radiation dose of 45 Gy combined with fluoropyrimidine-based chemotherapy. All selected patients received LCCRT at the University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Zagreb between January 2014 and December 2019, and were later surgically treated at the same facility.

From archived electronic medical files, we extracted demographic and disease-related data on age, gender, radiological status of tumor position from the anal verge, clinical TNM stage (cTNM) and circumferential resection margins (cCRM), as well as patient weight (kg) and height (m) to calculate body mass index (BMI, kg/m^2) and patient time to disease progression.

From pathology reports, we extracted data on pathologic TNM stage of the residual tumor (ypTNM), status of all resection margins, lymphovascular/perineural tumor invasion, tumor deposits, and tumor regression grade (TRG). According to the American Joint Committee on Cancer (AJCC), tumor regression was classified as follows: (a) TRG0, pathologic complete response with no viable tumor cells; (b) TRG1, single or small groups of tumor cells; (c) TRG2, residual cancer outgrowth with fibrosis; and (d) TRG3, no tumor cells killed[10]. The surgery date was taken as the starting point of monitoring progression of the disease, and the last examination was performed in December 2020. Due to the retrospective nature of the study, some data are missing (indicated in tables).

The study was conducted following all applicable guidelines and rules, and patient identity was not recorded.

Data analysis

Data are shown as percentages, median and interquartile range. Binary variables were analyzed by χ^2-test with Yates correction available by Vassar Stats online calculator (http://vassarstats.net/tab2x2.html). For statistical analysis, we used Ryan modification of the AJCC classification where TRG0 and TRG1 are classified as good response to therapy, TRG2 (partial response), and TRG3 (poor response) as therapy-resistant tumors. Kaplan-Meier analysis and log-rank test were used to monitor disease-free survival (DFS). The nonparametric Spearman correlation test (correlation coefficient, r_s) was used to analyze parameters that could affect disease progression depending on gender (statistical software StatSoft 7.0, Tulsa, USA). The level of statistical significance was set at $p<0.05$.

Results

Our study included 71 (37.0%) women and 121 (63.0%) men, median age 63 (range 30-89) years. The clinical and histopathologic characteristics analyzed between genders are presented in Table 1. Although women were somewhat older at the time of surgery, with median age of 65 compared to 62 years in men,

Table 1. Gender differences in clinical and histopathologic characteristics of 192 patients with rectal cancer who underwent neoadjuvant long course chemoradiotherapy

Characteristic		**Total N (%)**	**Men n=121 n (%)**	**Women n=71 n (%)**	**$\chi 2$ p**	**p**
Age (years)/ median (IQR) ≤65 >65		63 (57-70) 110 (57.0) 83 (43.0)	62 (56-70) 74 (60.7) 48 (39.3)	65 (58-70) 36 (50.7) 35 (49.3)	1.42	0.232
Tumor position from anal verge (cm)/median (IQR) ≤5 >5 Unknown		5 (3.25-8) 99 (52.7) 89 (47.3) 4	5.5 (4-8) 60 (49.6) 61 (50.4)	5 (3-7) 39 (58.2) 28 (41.8) 4	0.96	0.327
Body mass index/ Median (IQR) <25 ≥25 Unknown		25.5 (23.0-28.0) 63 (42.0) 87 (58.0) 42	25.9 (23.7-27.7) 34 (35.0) 63 (65.0) 24	24.5 (22.6-28.0) 29 (54.7) 24 (45.3) 18	4.66	**0.031**
Clinical T stage (cT)	T2 T3 T4 Unknown	9 (5.0) 128 (71.1) 43 (23.9) 12	7 (6.1) 82 (71.3) 26 (22.6) 6	2 (3.1) 46 (70.7) 17 (26.2) 6	0.97	0.615
Clinical N stage (cN)	N0 N1 N2 Unknown	16 (8.9) 52 (28.9) 112 (62.2) 12	11 (9.6) 37 (32.2) 67 (58.2) 6	5 (7.7) 15 (23.1) 45 (69.2) 6	2.16	0.340
Clinical M stage (cM)	M0 M1	167 (87.0) 25 (13.0)	107 (88.4) 14 (11.6)	60 (84.5) 11 (15.5)	0.31	0.577
Clinical CRM	Positive Negative Unknown	94 (57.3) 70 (42.7) 28	78 (73.6) 28 (26.4) 15	42 (72.4) 16 (27.6) 13	0.01	0.991
Pathologic T stage (ypT)	yT0 yT1 yT2 yT3 yT4	23 (12.0) 12 (6.2) 45 (23.4) 106 (55.3) 6 (3.1)	17 (14.1) 9 (7.4) 30 (24.8) 64 (52.9) 1 (0.8)	6 (8.5) 3 (4.2) 15 (21.1) 42 (59.2) 5 (7.0)	8.01	0.091
Pathologic N stage (ypN)	yN0 yN1 yN2	125 (64.7) 43 (22.3) 25 (13.0)	90 (74.3) 19 (15.7) 12 (10.0)	35 (49.3) 23 (32.4) 13 (18.3)	12.44	**0.002**
Pathologic ypCRM	Positive Negative Unknown	33 (21.3) 151 (78.6) 8	20 (17.2) 96 (82.8) 5	13 (19.1) 55 (80.9) 3	0.01	0.920
Lymphovascular/ perineural invasion	Present Absent	38 (19.8) 154 (80.2)	20 (16.5) 101 (83.5)	18 (25.4) 53 (74.6)	1.67	0.196
Tumor regression grade	Complete (TRG0) Subtotal (TRG1) Partial (TRG2) Poor (TRG3)	23 (12.0) 45 (23.4) 78 (40.6) 46 (24.0)	17 (14.0) 32 (26.5) 48 (39.7) 24 (19.8)	6 (8.5) 13 (18.3) 30 (42.2) 22 (31.0)	4.83	0.184
Disease progression (months), median (IQR) Present Absent Unknown		20 (10-43) 79 (44.1) 100 (55.9) 13	24 (10-59) 44 (39.6) 67 (60.4) 10	15 (8-32.5) 35 (51.5) 33 (48.5) 3	1.94	0.163

χ^2-test with Yates correction; IQR = interquartile range; CRM = circumferential resection margin; ypT = depth of invasion of residual tumor; ypN = lymph node status after; TRG = tumor regression grade

there was no statistically significant difference. About 52.7% of patients had low rectal cancer with less than 5 cm from the anal verge, the majority with clinical T3/T4 stage, and with more than three positive lymph nodes. Median BMI was 25.5 (range 16.9-39.5), and men were more likely to be overweight than women (χ^2=4.66; p=0.031). We did not detect a statistically significant difference in tumor position from the anal verge or radiologically defined TNM stage (cTNM) and cCRM between genders.

Analyzing correlations in the preoperative setting of all patients, we found that shorter time to disease progression significantly depended on the already present distant metastases (cM) (r_s=0.22; p=0.004), whereas correlation with more positive lymph nodes (cN) was not statistically significant (r_s=0.15; p=0.066).

Only 12.0% of rectal cancer patients achieved pCR to LCCRT without residual tumor (ypT0) and 6.2% near complete response (ypT1) with sporadic tumor cells invading the submucosa. Overall, only 24% of patients did not achieve any regression effect of therapy (TRG3). Based on post-LCCRT pathology reports, 50.7% of women had positive lymph nodes compared to 25.7% of positive lymph nodes in men (χ^2=12.44; p=0.002). There was no statistically significant difference in the pathologic ypT stage of residual tumor, presence of lymphovascular or perineural tumor invasion, pathologic CRM, or TRG according to AJCC criteria between women and men (Table 1). Twenty-seven (14%) patients had tumor deposits, i.e., 14 (85.7%) women and 13 (61.5%) men had disease progression.

Poor tumor regression on LCCRT significantly correlated with disease progression in patients with rectal cancer (r_s=0.24; p=0.002). Correlation analysis in the total cohort showed that positive lymph nodes were the strongest indicator of disease progression (r_s=0.35; p<0.001), together with the depth of residual tumor invasion (ypT) (r_s=0.22; p=0.003) and positive cCRM (r_s=0.23; p=0.003). Younger patients responded better to LCCRT (median age 62 *vs.* 64), especially men (mean age 61 compared to 65 years in women) (r_s=0.169; p=0.02).

Overall, women with rectal cancer had lower tumor response to LCCRT than men. Among patients with good tumor response, only 27.9% were women, while

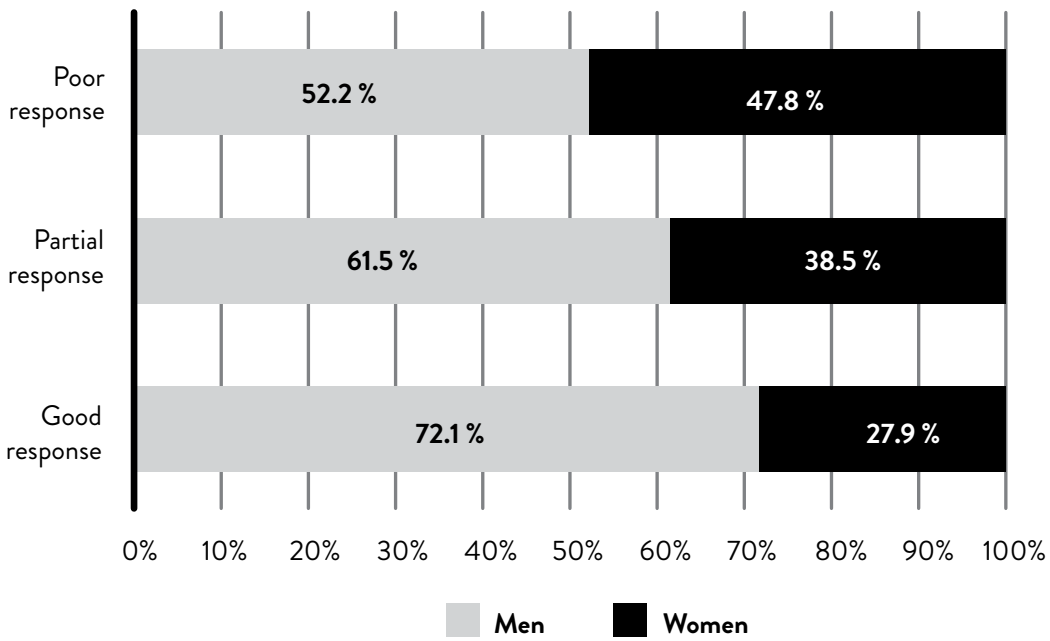

Fig. 1. Gender difference in tumor regression grade (TRG) after long-course chemoradiotherapy using Ryan modification of TRG (χ^2=4.78; p=0.073).

Table 2. Correlation analysis of clinical and histopathologic factors in men and women with rectal cancer who underwent neoadjuvant long course chemoradiotherapy

Characteristic	Men N=121	Women N=71
Progression *vs.* age	r_s=-0.17 p=0.079	-
Progression *vs.* cT	r_s=0.19 p = 0.069	-
Progression *vs.* cN	r_s=0.29 **p=0.003**	-
Progression *vs.* cM	r_s=0.18 p=0.062	r_s=0.26 **p=0.036**
Progression *vs.* ypT	r_s=0.18 p=0.069	r_s=0.26 **p=0.035**
Progression *vs.* ypN	r_s=0.29 **p=0.003**	r_s=0.38 **p=0.002**
Progression *vs.* ypCRM	r_s=0.34 **p<0.001**	-
Progression *vs.* tumor regression grade	r_s=0.22 **p=0.025**	r_s=0.24 p=0.053
BMI *vs.* cM stage	r_s=-0.21 **p=0.042**	-
BMI *vs.* cT and cN stage	r_s=-0.18 p=0.091	-
BMI *vs.* good response to therapy	-	r_s=-0.24 p=0.08

r_s = Spearman correlation coefficient; BMI = body mass index; cTNM = radiologically assessed TNM stage; ypTNM = pathologically assessed TNM stage on residual tumor; ypCRM = pathologically assessed circumferential resection margin

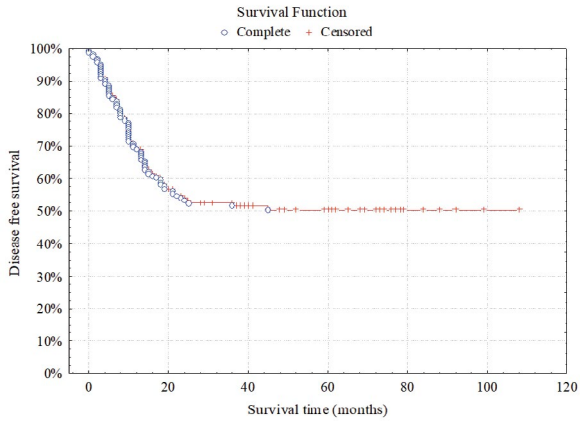

Fig. 2. Overall five-year disease-free survival Kaplan-Meier curve of colorectal cancer patients.

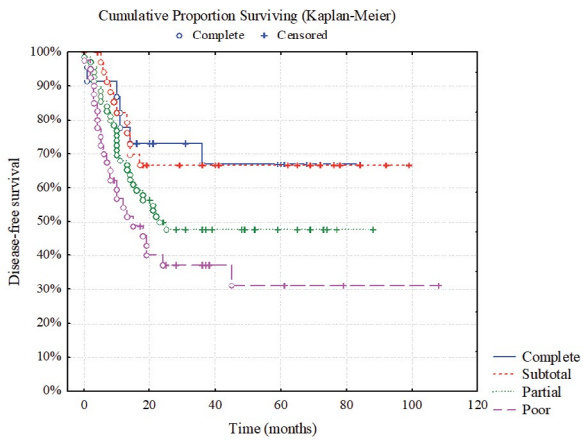

Fig. 3. Five-year progression-free survival according to degree of tumor regression after long-course chemoradiotherapy in colorectal cancer patients (χ^2=10.47; p=0.015).

among patients with poor response, 47.8% were women (Fig. 1).

Spearman correlation analysis by gender (summarized in Table 2) revealed a positive correlation of pathologic ypT (r_s=0.26; p=0.035) and ypN stage (r_s=0.38; p=0.002) after LCCRT with disease progression in women, while only ypN stage remained correlated with DFS in men (r_s=0.29; p=0.003). Significant correlations were only found in men between positive resection margins and disease progression (r_s=0.34; p<0.001), and between higher BMI and lower incidence of distant metastases (r_s=-0.21; p=0.042). In addition, better tumor regression after LCCRT was an indicator of better DFS in men (r_s=0.22; p=0.025), while in women it did not show a statistically significant correlation (r_s=0.24; p=0.053).

Overall, the five-year DFS rate of rectal cancer patients after LCCRT was 50% (Fig. 2) with median time to progression of 19.5 months (interquartile range 10-43 months). Figure 3 shows that patients with complete (TRG0) and subtotal (TRG1) cancer regression had a far better DFS rate than partial (TRG2) and poor responders (TRG3) (χ^2=10.47;

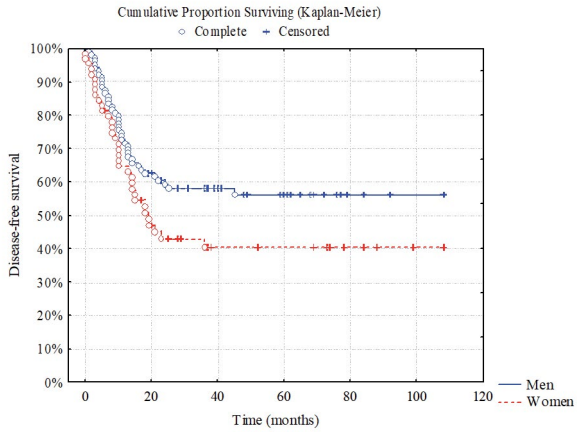

Fig. 4. Kaplan-Meier disease-free survival curve by gender (log-rank test WW=-7.95 test statistic=-1.88, p=0.061).

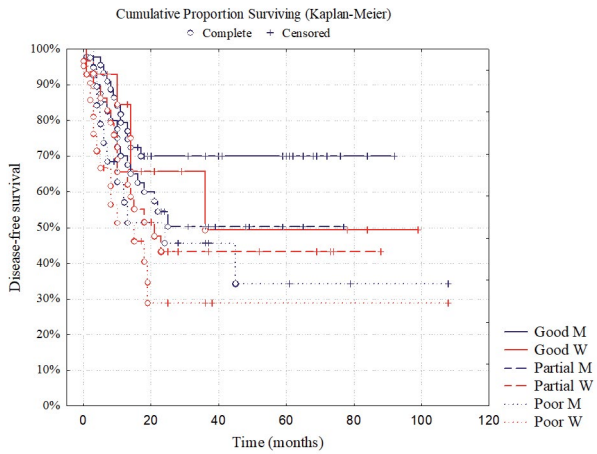

Fig. 5. Kaplan-Meier disease-free survival curve in colorectal cancer patients according to degree of tumor response to long-course chemoradiotherapy (good, partial, or poor) by gender (men (M) and women (W)) (χ^2=12.1; p=0.033).

p=0.015). Women had disease progression more often than men (51.5% *vs.* 39.6%), and the Kaplan-Meier curve showed a five-year DFS rate of 40% for women and 56% for men (log-rank test WW=-7.95, test statistic=-1.88, p=0.061) (Fig. 4). Comparing patient DFS with tumor response to LCCRT depending on gender, we observed that women who achieved complete response to therapy (TRG0) had a poorer five-year DFS rate than men (χ^2=12.1; p=0.033) (Fig. 5).

Discussion

Our retrospective study included patients with locally advanced rectal cancer who underwent neoadjuvant LCCRT to downstage the tumor before surgery, and results showed a poorer treatment outcome in women than in men.

Although we have noticed fewer women referred to LCCRT in clinical practice, our data correspond to the latest data from the Croatian Cancer Registry[1]. They report that 39% of total rectal cancers in Croatia occur in women, with a similar percentage of regional spread and mortality as in men, especially after the age of 65. The literature cites several reasons why women with rectal cancer will not be treated with neoadjuvant therapy, e.g., difficulty obtaining circumferential resection without tumor, the higher rate of dissemination of the disease in women, women older than 80 years, etc.[7,11-13].

According to our data, the MRI screening criteria are the same for both genders, and preoperative diagnostics did not reveal significant gender differences in any of the clinical parameters (age, tumor position from the anal verge, clinical TNM, positive circumferential margins). Most clinical parameters, based on radiological MRI alone, were not predictors of tumor response to LCCRT or disease progression, other than positive lymph nodes in men and pre-existing distant metastases in women. Other studies did not detect gender differences in rectal cancer pre-treatment diagnostics either[7,11]. Today, more precise radiomics algorithms are being developed that could predict the pCR based on MRI data before treatment, and estimate which patients only need post-LCCRT monitoring[14,15].

The overall five-year DFS rate of 50% obtained in our research is consistent with the published literature[1,6]. The patient median age at the time of surgery (after LCCRT) was 63 years, and women were slightly older than men, which is consistent with the literature[6,11,12]. Younger patients responded better to LCCRT, especially men. Some studies also report

better response to therapy in younger patients (<55 years), particularly in younger women compared to men[16-18]. The proposed protective effect of estrogen in premenopausal women is one of the key factors that we could not consider in our study because the median age of women was 65 years[18].

About 12% of our patients achieved complete pathologic response to neoadjuvant chemoradiotherapy, whereas only about 25% did not achieve any tumor down-staging effect. Our results are consistent with others and confirm the existing claims that a higher TRG (complete or subtotal) after LCCRT represents a favorable long-term outcome[5-7,13,19,20]. Results from other studies show that complete pathologic response is achieved in 7% to 32% of cases[5-7,12,13,15,19-21]. Some differences in the literature on the prognostic value of TRG occur since there are five classification TRG systems[10,13,22]. A lot of studies investigate predictive factors for good response to LCCRT but the current ability of clinical, biochemical, or pathologic parameters to predict response to chemoradiotherapy is weak[21,23-26].

Our results show for the first time that women had worse five-year DFS than men, even in cases where they achieved complete response to therapy (TRG0). Although women achieved pathologic ypN0 resection in 50% of cases, only 27% of them had good response to therapy. Greater depth of invasion of the residual tumor (ypT), more positive lymph nodes (ypN), and tumor deposits present after LCCRT were likely parameters for poor DFS in women. More positive lymph nodes and positive resection margins indicate a shorter DFS in men. Contrary to our result, some authors found the female gender to be a favorable factor for colorectal cancer survival but the data are inconsistent. Better overall survival was found in women younger than 55, whereas women older than 65 had poor survival[16,17].

Radiation therapy is associated with reduced local recurrences of rectal cancer but also with possible severe toxicity and an increased rate of complications during surgery. Leucovorin, which is added in combination with 5-FU to enhance the effect of radiation by binding fluorouracil to an enzyme, could prolong the toxic effect of radiation and cause greater tissue damage. This effect could be more pronounced in women with lower BMI[27,28]. The National Comprehensive Cancer Network (NCCN) guidelines recommend preoperative chemoradiotherapy for patients with the clinical T3/N0 disease, as about 20% of these patients have positive lymph nodes in the pathologic finding[5]. Sarasqueta *et al.*[11] observed a longer interval between the first visit and the diagnosis in women, and in the case of an interval greater than three months, women had higher disease dissemination rates than men. Thus, NCCN guidelines address that complete perioperative therapy should not exceed 6 months[5].

Recent findings suggest that non-sex-related cancers in men and women should be considered biologically different[28]. According to Toh *et al.*[29], rectal cancers with high microsatellite instability (MSI-H) are more common in women but a high immunogenic response in such cancers has no protective role against early dissemination. MSI-H rectal cancers show resistance to chemoradiotherapy and have a better prognosis on neoadjuvant chemotherapy[30,31]. Given all of the above, it is obvious that we need better markers to stratify patients to LCCRT to achieve greater benefits for patients.

We noticed that BMI differed significantly between the genders. Although it only showed a trend towards statistical significance with poor DFS in women, we would like to draw attention to this. Overweight men had a significantly lower incidence of distant metastases, and fewer positive lymph nodes when diagnosed with rectal cancer. As far as women are concerned, there is a trend of poorer response to chemoradiotherapy in those with lower BMI. Liu *et al.*[32] report on better DFS after LCCRT in overweight patients. Similar to our results, Park *et al.*[33] report fewer lymph node metastases and better overall survival in patients with visceral obesity while Aldaqal *et al.*[34] found a higher TNM stage in underweight colorectal patients. Although obese individuals have an increased risk of developing colorectal cancer, the association of BMI with colorectal cancer remains complex and debatable. For example, Carr *et al.*[35] found a significant relationship between BMI and MSI-H in women, and others found improved survival of overweight (not obese) patients with stage IV colorectal cancer[36,37]. According to Bull *et al.*[38], obesity is associated with several metabolic changes but none of them explains the association between adipocytes and colorectal cancer. They point out that the waist-to-hip ratio is a better risk criterion

for colorectal cancer in women due to peripheral fat storage. Excess adipose tissue can be a source of mesenchymal stem cells inducing radio-resistance, can amplify the effect of radiation by creating additional free radicals, or merely serves as energy in the body needed during aggressive therapy[39,40].

The main limitation of our study was its retrospective nature, single-center experience, and twice as many men than women in the cohort. Nevertheless, our results raise several questions that indicate the need of further analysis. It would certainly be necessary to determine whether there is a coherent longitudinal gender difference in the time elapsed from the first visit to the diagnosis; and whether there is a gender-sensitive screening for rectal cancer or some genotype differences that can be used in the preselection of patients for neoadjuvant therapy.

Conclusion

Our results indicate that women have poorer responses to LCCRT. In any case, more information is needed but there is a possibility that therapeutic approach to the neoadjuvant treatment of rectal cancer could be gender-specific.

Acknowledgments

The researchers S. R. and I. K. participate in the COST Action CA17118.

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Sažetak

TUMORSKI ODGOVOR NA NEOADJUVANTNU KEMORADIOTERAPIJU OVISI O SPOLU BOLESNIKA S RAKOM REKTUMA

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Cilj našeg istraživanja bio je analizirati utjecaj karakteristika raka rektuma sa stupnjem regresije tumora (*tumor regression grade*, TRG) i preživljavanjem bez povrata bolesti (*disease-free survival*, DFS) ovisno o spolu kod 192 bolesnika operiranih nakon neoadjuvantne kemoradioterapije (*long-course chemoradiotherapy*, LCCRT). Prijeoperacijska dijagnostika nije otkrila značajne razlike u spolu u bilo kojoj kliničkoj karakteristici osim pretilosti (p=0,031). Primijetili smo da blago pretili muškarci rjeđe imaju udaljene metastaze (p=0,042). Patološki nalaz nakon LCCRT pokazuje da žene imaju više pozitivnih limfnih čvorova (ypN, p=0,002), dok se niti jedan drugi patološki parametar ne razlikuje značajno. Sveukupno, loš odgovor na terapiju korelira s kraćim vremenom do povrata bolesti (p=0,002). Žene su postigle ypN0 u 50% slučajeva, ali samo 27% imalo je dobar TRG u usporedbi s 40,5% muškaraca (p=0,073). Žene su imale lošiji DFS od muškaraca čak i kad su postigle potpun odgovor na terapiju (p=0,003), a viši ypT (p=0,035) i ypN (p=0,002) stadij i prisutni tumorski depoziti koreliraju s kraćim DFS-om u žena. Pozitivni rubovi resekcije (p<0,001), veći ypN (p=0,003) i loš TRG (p=0,025) koreliraju s progresijom bolesti u muškaraca. Možemo zaključiti da žene imaju slabiji odgovor na LCCRT te postoji mogućnost da bi terapijski pristup neoadjuvantnom liječenju raka rektuma mogao ovisiti o spolu.

Ključne riječi: *Rak rektuma; Neoadjuvantna kemoradioterapija; Spol; Tumorski odgovor na terapiju; Preživljenje bez bolesti*