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COMPLETE PATHOLOGICAL RESPONSE FOLLOWING NEOADJUVANT CHEMORADIOTHERAPY IN LOCALLY ADVANCED COLORECTAL CARCINOMA

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Summary

Background: The prognosis of rectal cancer has improved with neoadjuvant treatment for locally advanced disease. Twenty percent of patients respond to treatment with complete pathological regression, which is clinically estimated with magnetic resonance imaging.

Aim: describe the properties of the pathological complete response group of patients at our institution

Materials and methods: 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.

Results: We identified 23 patients with complete pathological responses, of which, despite surgery, seven progressed. We recorded a higher proportion of female patients in that group and younger age of onset. MRI preoperatively was not yet predictive of a complete pathological response.

Conclusion: The proportion of patients with a complete pathological response is 16% in this cohort. All patients underwent surgery but did not receive consolidating therapy. About 30% progressed during the observed period.

KEYWORDS: *neoadjuvant therapy, rectal cancer, complete pathological response*

INTRODUCTION

Locally advanced rectal cancer (LARC) is a tumor invading or extending close to the mesorectal fascia(1). Neoadjuvant therapy (NT), which is used in treating LARC, primarily focuses on reducing the gross tumor volume and controlling the micrometastatic cancer-cell spread. That technique raises tumor resectability rates, sphincter-saving procedures, and downstaging. While the historical approach suggested the use of radiotherapy (RT) and fluorouracil (FU) after the surgery, current standards dictate the use of fluoropyrimidine-based chemotherapy, which is followed by surgery within 8-12 weeks(2). Many studies regarding patients treated with modalities

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Table 1.

Differences in clinical and pathohistological characteristics by gender of 192 patients with rectal cancer who underwent neoadjuvant long course chemoradiotherapy

Characteristics	**Total n (%)**	**Men N=121 n (%)**	**Women N=71 n (%)**	**X^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
Pathological 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
Pathological 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**
Pathological 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

X^2, Chi-square test with Yates correction; IQR, interquartile range; CRM, circumferential resection margin; ypT, depth of invasion of a residual tumor; ypN, lymph node status after LCCRT; TRG, tumor regression grade (data not yet published).

of neoadjuvant chemoradiotherapy (either *Long course chemoradiotherapy* (LCCRT) or *Short-course radiotherapy* (SCRT)) reported a significant decrease in the local recurrence rate(3–5). Furthermore, complete pathologic response (pCR), defined as the absence of cancer cells in the resected material, was found at a greater rate in the patients treated with neoadjuvant therapy(3,4,6). However, the correlation between pCR and disease-free (DFS) or overall survival (OS) rate remains unclear(4–6). While recent studies suggest better DFS following pCR(3,7–9), the OS results are still ambiguous(3). A relatively new therapeutic option emerged, called total neoadjuvant therapy (TNT), adding induction chemotherapy prior to the standard chemoradiotherapy. Meta-analysis suggests better DFS and OS with the use of TNT than with regular NT(2) this study aims to analyze the complete pathological and clinical response to the NT chemoradiotherapy treatment.

MATERIALS AND METHODS

This study is a single-center experience from Croatia, the city of Zagreb. The data were collected retrospectively between January 2019 to August 2020. Hundred and fifty patients (94;63% male) with rectal cancer (diagnoses C20) were treated at the surgical department of University Hospital for Tumors, University Hospital Center Sestre Milosrdnice. The patients who underwent neoadjuvant chemo+/-radiotherapy long-course chemoradiotherapy preoperatively were included. Our patients were operated on electively with different surgical techniques. Postoperatively, depending on the oncologist's decision, some patients received adjuvant chemotherapy. We collected clinical data regarding the patient's age, sex, BMI, date of admission, laboratory findings, the neoadjuvant protocol, the time gap between neoadjuvant therapy and surgery, and the type of operation. The aim was to describe the population with the complete pathological response: magnetic resonance staging and restaging, type of surgery, progression, disease-free interval, and pathology report with circumferential resection margin (CRM)(10).

RESULTS

Our previous manuscript analyzed 192 patients who underwent neoadjuvant therapy for rectal cancer (data not yet published). Table 1. Depicts the cohort characteristics.

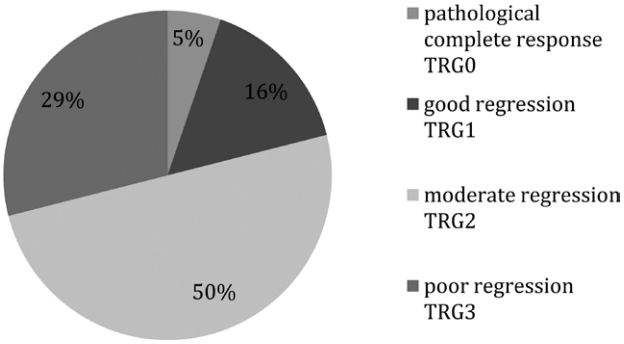

Figure 1. Proportions of patients who underwent neoadjuvant chemotherapy according to pathological response after the therapy.

This paper focuses on patients with complete pathological responses to treatment. In our cohort, all underwent surgery. Sixteen percent of patients had a complete pathological response (Figure1).

Therefore we analyzed the pre and post-treatment magnetic resonance characteristics which did not correlate with the complete pathological response rate (9/23, Table.2).

In comparing those who progressed during the follow up period and those who did not after having a complete pathological response, it seems the surgery was more radical (1 abdominoperineal resection vs 6 and 6 resections without anastomosis formation), relatively more female patients progressed and patients who progressed were younger.

DISCUSSION AND CONCLUSIONS

In the subcohort analysis of neoadjuvant rectal cancer patients with complete pathological response, we noticed the imperfect correlation of clinical staging based on magnetic resonance after neoadjuvant treatment with postoperative pathological findings. In a recent literature review, more accurate estimations were achieved(11), even for estimating the complete pathological criteria if MR-derived methods were used(12).

Combining chemotherapy and radiotherapy before surgery is the standard for treating locally advanced rectal cancer. The advantages of preoperative therapy are better control of micrometastasis, and better tolerability than similar treatment

Table 2.

Characteristic of pathological complete response patients according to whether they progressed or not during the observed period

		Progression (number of patients)	No Progression (number of patients)
Age (years)		56(30-69)	61(44-79)
Gender	female	3 (42,9%)	3
	male	4 (57,1%)	13
Distance from anal verge (cm)		7,55(4,8-10)	5,89(1-12)
mrTNM (before therapy)			
	T4	4	4
	T3	2	13
	T2	0	0
	T1	1	0
	T0	0	0
	N2	4	
	N1	3	
mrCRM (before therapy)	positive	5	14
	negative	2	2
mrTNM (post therapy)	T4	1	0
	T3	0	9
	T2	0	2
	T1	0	2
	T0	6	3
	N2	1	4
	N1	0	3
mrCRM (post therapy)	positive	1	4
	negative	6	12
Surgery	Anterior resection (AR)	6	6
	Hartmann	0	3
	Miles	1	6
	AR plus ileostomy	0	1
Disease free interval (months)		21(1-36)	54(7-84)

after surgery, hence allowing increased dose intensity and potentiality to downstage tumor and improve the possibility of curative resection(13). The base of most regimens is 5-fluorouracil, lately in combination with oxaliplatin. Most of the patients in this study were included during the long course standard and did not have heterogeneity in therapy schemes (five weeks of radiotherapy with concomitant 5-FU-based therapy during weeks one and five).

In fact, all patients had a long course of chemoradiotherapy in the complete pathological response group. In their randomized controlled study, Huang et al.(13) stated that they have not found any significant differences in 3-year or 5-year overall survival, disease-free survival or total death linking that to possible adverse effects of neoadjuvant chemotherapy, such as attenuation of immunity and delay of timely curative treatment. However, the same study supported that neoadjuvant chemotherapy contributes to a lower rate of distal, especially the liver, metastasis but resulted in a similar local recurrence rate. Banwell et al.(14) showed that SCRT significantly reduced local recurrence compared to surgery-alone patients. However, the distant metastasis in SCRT was unexpectedly greater than in LCCRT, which included the most locally advanced tumors. With the introduction of the RAPIDO protocol, the situation with possibilities of neoadjuvant treatment became even more complex(15).

About 60% of patients with complete pathological response in our cohort circumferential margin became negative after the treatment on clinical magnetic resonance imaging and in all pathology. Banwell et al.(14) stated that CRM suggests collinearity of more locally advanced tumors leading to more difficult resection rather than poor quality surgery. In this study, he focused on the quality of surgery. They validated the quality of the surgery by comparing positive CRM in resected tissue. The study involved 240 patients treated with surgery alone; 90 received SCRT, and 91 received LCCRT. Considering the type of operation, tumor location within the rectum, or quality of mesorectal excision, unlike the previous reports with whom they had compared, they have not defined the parameters mentioned above as risk factors for adverse survival outcomes. The same study acknowledged the previous cognition that CRM was not independently predictive of local recurrence but was predictive of systemic disease recurrence.

Time to surgery after neoadjuvant therapy has stretched from 8 weeks to 10 to 12 weeks post-therapy. Sloothaak et al.(16) evaluated 1549 pa-

tients with rectal cancer and showed that delaying surgery by 10 to 11 weeks from the end of chemoradiotherapy was associated with the highest chance of pathologic complete response. We also use this time frame in our standard protocol.

Caprici et al.(17) failed to detect an advantage in their study of 566 patients in clinical outcomes for 127 patients treated with adjuvant CT after neoadjuvant CT and surgical procedures. The two opposed groups, with and without adjuvant CT, were homogenous. Surprisingly, they showed that patients treated with postoperative CT compared with those without a worse relative risk for cancer death. The benefit of consolidating chemotherapy appears in more trials(16). In our cohort, adjuvant chemotherapy was not given to patients with complete response, as the inclusion dates precede the possible change in practice. Furthermore, we did not opt for the wait-and-watch approach in any of the patients either. The surgery is justified until we achieve more precise clinical staging on magnetic resonance preoperatively.

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Sažetak

POTPUNI PATOLOŠKI ODGOVOR NAKON NEOADJUVANTNE KEMORADIOTERAPIJE LOKALNO UZNAPREDOVALOG KARCINOMA REKTUMA

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Uvod: Prognoza raka rektuma poboljšana je neoadjuvantnim liječenjem lokalno uznapredovale bolesti. Dvadeset posto pacijenata reagira na liječenje potpunom patološkom regresijom, što se klinički procjenjuje magnetskom rezonancijom(MR).

Cilj: opisati svojstva skupine pacijenata s patološkim potpunim odgovorom u našoj ustanovi

Materijali i metode: Svi odabrani pacijenti primili su LCCRT u KBC-u Sestre milosrdnice, Zagreb, između siječnja 2014. i prosinca 2019. te su kasnije kirurški liječeni u istoj ustanovi.

Rezultati: Identificirali smo 23 pacijenta s potpunim patološkim odgovorom, od kojih je, unatoč operaciji, sedam imalo progresiju bolesti. U toj skupini bilježimo veći udio bolesnica i mlađu dob pri dijagnozi. Magnetska rezonanca prije operacije nije bila pouzdan pokazatelj potpunog patološkog odgovora.

Zaključak: Udio pacijenata s potpunim patološkim odgovorom je 16% u ovoj kohorti. Svi pacijenti su operirani, ali nisu primili konsolidirajuću kemoterapiju. Oko 30% je imalo progresiju bolesti tijekom promatranog razdoblja.

KLJUČNE RIJEČI: *neoadjuvantna terapija, karcinom rektuma, potpuni patološki odgovor*