Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

The management of advanced rectal cancer during COVID 19 pandemics. Experience report of a tertiary surgical unit

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Abstract. Objective. The access to surgical care has been limited throughout the world due to COVID-19 pandemics. This article aims to study the outcomes in locally advanced rectal cancer in our department, as a result of COVID-19 pandemics restrictions. Materials and methods. We included in the current study all patients who underwent surgery for locally-advanced rectal cancer in our department in 2019 (n=32, Group 1). We compared these patients with the patients operated after the resolution of the COVID-19 restrictions in 2020 (n=16, Group 2). All patients underwent long-course neo-adjuvant chemoradiotherapy. Results. The mean age of the patients was 64.5 years in Group 1 vs 65 years in Group 2 (p=0.99). In Group 1, the majority of the patients were clinically staged as cT3 (68.7%), similar to Group 2 (cT3 stage - 87.5%). The median time between neo-adjuvant treatment and the surgery was 8.4 weeks in Group 1 vs 11.1 weeks in Group 2 (p=0.009). During neo-adjuvant treatment, none of the patients in Group 2 were diagnosed with SARS-COV2 infection and none of the surgeries were delayed due to the viral infection. There were no significant differences between the two groups in terms of pathologic staging (p=0.77), but complete pathologic response rate was higher in Group 2 as compared to Group 1 (25% vs. 12%). Conclusion. Neo-adjuvant long-course chemotherapy is a safe treatment option for patients with locally-advanced rectal cancer even during the COVID-19. Increased time to surgery leads to a higher rate of complete pathologic response, but further studies are needed to assess long-term impact of this outcome.

Key Words: covid 19, rectal cancer, neoadjuvant treatment.

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Introduction

In the spring of 2020 the World Health Organization declared the coronavirus outbreak (COVID19) as a pandemic due to the rapid spread of the viral infection worldwide. Anti-epidemic measures included severe restrictions such as complete lockdown, social distancing, limitations of journeys (WHO Coronavirus pandemic 2020). All hospitals were assaulted by COVID-19 patients and were forced to change their specialization in order to treat infected patients. After the initial outbreak, different organizing measures were taken by each country in order to face the numerous infectious cases, but still be able to respond to other emergencies.

The access to surgical care has been limited throughout the world and this fact might impact the outcomes of the oncologic patients. In colon cancer, for example, the current guidelines recommend curative surgical treatment as soon as possible after diagnosis. Delayed surgery due to different reasons leads to delayed pathological staging and initiation of adequate adjuvant treatment. It has been shown that an increase in the time from the diagnosis to surgery from 16 to 37 days significantly impairs the 5- and 10-year survival rate in colorectal cancer patients. Furthermore, other authors demonstrated a 2-3 fold increase in the mortality rate in colorectal cancer patients when surgery was delayed up to 12 weeks from the diagnosis (Kaltenmeier et al 2019; Shin et al 2019).

Similar difficulties were encountered by patients with rectal cancer. The delay of the diagnosis and access to treatment has challenged the current "gold standard" recommendations and affected medical decisions (Skowrn et al 2020). Current surgical tactics in locally advanced rectal cancer are represented by either long-course neoadjuvant chemoradiotherapy (RCT) or short-course radiotherapy (SCRT) followed by complete excision of the rectum with intact surrounding layers, en bloc excision of mesorectal fat and lymphatic structures (Allegra et al 2014; Daval et al 2014). The surgery can be performed immediately after the SCRT or can be deferred up to 12 weeks after the other neo-adjuvant regimens. The new pandemic situation challenged the medical professionals to find the best treatment schedule in order to limit the exposure of frail oncologic patients to SARS-COV2, but at the same time to ensure the best oncologic outcomes.

In Cluj-Napoca, Romania, complete lockdown was deployed between 23th March and 5th May 2020. Our surgical unit usually treats trauma and oncological patients. During the lockdown, centralized care for oncologic patients was implemented and all patients usually addressing to our department were either referred to another hospital or surgical care was deferred. Thus, between 23th March and 1st June 2020 our department covered only emergency surgical patients and no oncological procedures were done. The hospital was completely reorganised by designing new patient circuits and the patients capacity was reduced due to the implementation of a surgical ward for suspected or confirmed COVID-19 patients. The admittance capacity was reduced with 30%, and the surgical activity during lockdown was reduced up to 20%- only emergency surgery. After the lockdown, oncological surgical care was reestablished at a capacity of 70% for patients who were deferred due to the pandemic.

This article aims to study treatment outcomes in locally advanced rectal cancer in our department, as a result of COVID-19 pandemics restrictions. We hypothesized that long-course neoadjuvant treatment can represent a risk factor for contacting the viral infection and that delay of surgery due to epidemic restrictions might impair oncological outcomes and can be associated with disease progression.

Materials and methods

After confirmed consent, we included in the current study all patients who underwent surgery for locally-advanced rectal cancer in our department between 2019 and 2020. The patients were separated into two groups: Group 1 - patients operated in prepandemic time (January-December 2019) and Group 2 - patients operated after the resolution of COVID-19 restrictions (June-December 2020). According to our clinical guidelines, real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) of nasopharyngeal swabs were done to all patients 24 to 48 hours prior to surgery.

Clinical and pathological data of the patients were extracted from our electronic records. Cancer staging was realized according American Joint Committee on Cancer (AJCC) statement, published since 2018. Middle and high rectal cancer patients with cT2N1, cT3-cT4 N0-1 tumors were included. We included also patients with cT2N0-N1 tumors located below 5 cm from anal verge, for whom neo-adjuvant therapy is considered standard of care. All patients underwent neoadjuvant long-course RCT followed by surgical resection according to current European guidelines recommendations. En bloc rectal resection with total mesorectal excision was performed by low anterior resection or abdomino-perineal resection. In all patients with low anterior resection and anastomosis, protective ileostomy was performed as standard. Complete pathologic response to neoadjuvant radiochemotherapy was defined as the lack of tumor cells on resected specimens at the pathological examination.

Statistical analysis was performed using Medcalc v18.11.6. Continuous data were expressed as median and interquartile range (IQR) and categorial data was expressed as number and percentages. ANOVA- Kruskal-Wallis test was used for the correlation between continuous and categorial data, while Chi-square test was performed for the correlation between categorial variables.

Results

Between January 2019 and December 2020, 48 patients with locally advanced rectal cancer underwent surgery in our department. The patients were divided into two groups, Group 1 - pre-pandemic (2019) which included 32 patients and Group 2 – during pandemic (2020) which included 16 patients.

The mean age of the patients was 64.5 years (IQR 60-68.5) in Group 1 and 65 years (IQR 57.5-70) in Group 2 (p=0.99). In Group 1, the majority of the patients were clinically staged as cT3 (68.7%), while 12.5% of the patients were cT2 and 18.8% cT4. In Group 2, we observed a higher percentage of patients in cT3 stage (87.5%), whereas 12.5% were cT2. No patient was staged as cT4 (p=0.17 for Group 1 vs Group 2, Table 1). The mean distance from the anal verge was 9.5 cm (IQR 7-10.5) in Group 1 vs 7.5 cm (IQR 4.7-10.5) in Group 2 (p=0.14).

All patients underwent neoadjuvant RCT followed by surgery. The median time between neo-adjuvant treatment and the surgical procedure was 8.4 weeks in Group 1, as compared to 11.1 weeks in Group 2 (p=0.009). During neo-adjuvant treatment, none of the patients in Group 2 were diagnosed with SARS-COV2 infection and none of the surgeries were delayed due to the viral infection. The delay in surgical treatment was secondary to epidemic restrictions in all patients. The pathologic assessment of the resected specimens revealed mean tumor relics of 2.5 cm (IQR 1.5-2.6 cm) in Group 1 vs. 2 cm (IQR 1-2.5 cm) in Group 2 (p=0.07). There were no statistically significant differences between the two groups in terms of pathologic staging (p=0.77), but complete pathologic response rate was higher in Group 2 as compared to Group 1 (25% vs. 12%) (Table 1). Of the patients with complete pathologic response in Group 2, one was clinically staged as cT2N0 (3 cm from the anal verge), while the rest were locally advanced. In Group 1, all patients with complete pathologic disease had stage III disease. A single patient in Group 1 had a positive resection margin, while in Group 2 all surgical margins were negative.

Discussions

Since February 2020, the COVID-19 outbreak continues to challenge the European healthcare system. Despite the restrictions and decreased access to healthcare, we observed similar clinical staging of the patients with rectal cancer who presented to our department. Furthermore, although there was an increased time between neo-adjuvant treatment and surgery as a consequence of the epidemic restrictions in 2020, higher rates of pathological complete response were observed. Respecting distancing measures and hospitals protocols led to safe administration of neo-adjuvant RCT, without increasing the risk for SARS-COV2 infection.

In rectal cancer, neoadjuvant treatment is recommended as the standard of care specifically in locally advanced cases (cT3-cT4, N0-1+). Improved local outcomes were demonstrated in all types of strategies. Treatment delivery can be done by short course radiotherapy (SCRT, 5Gy/fraction/day, 5 fractions) with immediate or 4-8 weeks delayed surgery or by long course RCT (2Gy/fraction/day, 25 fractions) with 6-10 weeks delay to surgery. The Stockholm III trial demonstrated higher rate of complete pathologic response and less toxicity using the long course RCT followed by 6-8 weeks delayed surgery as compared to

Table 1. Clinical-pathological differences between groups

Parameter	Group 1 Before Pandemic (2019)	Group 2 During pandemic (2020)	P
Number of patients	32	16	
Sex	M-75% F-25%	M-62.5% F-37.5%	
Age, years **Median (IQR*)**	64.5 (60-68.5)	65 (57.5-70)	0.99
Distance from the anal verge, cm **Median (IQR)**	9.5 (7-10.5)	7.5 (4.7-10.5)	0.14
Clinical staging at presentation	cT2-12.5% cT3-68.7% cT4-18.8%	cT2-12.5% cT3-87.5% cT4-0	0.17
AJCC Staging**	I-6.2% II-9.4% III-75% IV-9.4%	I-6.2% II-6.2% III-87.5 IV-0	0.6
Median distance to surgery, weeks **Median, (IQR)**	8.4 (7.5-10.2)	11.1 (9.4-12.5)	0.009
Tumor relics dimension, cm **Median (IQR)**	2.5 (1.5-2.6)	2 (1-2.5)	0.07
Pathologic staging	ypT0-12% ypTis-4% ypT1-4% ypT2-24% ypT3-40% ypT4-16%	ypT0-25% ypTis- 0% ypT1- 0% ypT2=32.2% ypT3=31.2% ypT4-12.5%	0.77

*IQR- interquartile range **AJCC: American Joint Committee on Cancer

SCRT (Erlandsson et al 2017). However, SCRT can be an option in frail patients to reduce environmental exposure to the viral infection.

In the era of COVID-19 pandemic the main concern is represented by respecting the anti-epidemic measures such as isolation and avoiding unnecessary travel. Prolonged in-hospital stay for receiving neoadjuvant treatment can be a factor of exposure for oncologic patients. Also, alteration of the treatment schedule due to anti-epidemic measures or crowded hospitals by infected patients may contribute to poor oncologic outcomes. Although traditionally the use of long course RCT followed by surgery at 6-10 weeks was the preferred treatment due to a better downstaging and treatment response than SCRT, in 2020 some hospitals shifted the trend (Romesser et al 2017). Their aim was to limit patients' exposure to COVID-19 treating hospitals and to avoid immunosuppression by postponing chemotherapy. Adopting a SCRT strategy allows the patients to reduce hospital visits (Mirnezami et al 2020). In this context, some authors suggested that SCRT followed by delayed surgery (5-13 weeks) may be a good option for patients with locally-advanced rectal cancer as recent studies have shown that the likelihood of sphincter preserving surgery and negative margins rates are similar between immediate and delayed surgery (Bujko et al 2014).

In our series of patients, long course RCT remained as standard during the pandemics. In 2019, our surgical unit operated 32 patients with locally advanced rectal cancer who underwent preoperative RCT, with a mean time to surgery of 8.4 weeks. Due to the drastic anti-epidemic strategies and change of hospital profile, in 2020 only 16 cases of locally-advanced rectal cancer underwent surgery in our department. The mean time to surgery after finishing neoadjuvant treatment was 11.1 weeks in 2020, with a supplementary delay of 3-5 weeks above the time recommended by current guidelines in rectal cancer surgery. We observed similar staging at diagnosis of rectal cancer for both years and no significant differences between these groups in terms of pathological outcomes (p=0.77). Moreover, the rate of complete pathological responders was higher when the surgery was delayed as in the second group.

Although most of the authors recommend the SCRT regimen in order to limit patients' visits to hospital during these times, we consider that long course RCT with delayed surgery is the best option even in this scenario. When comparing the results of SCRT to long course RCT, several reports showed that the local outcomes are better, with a rate of complete pathological response up to 30%, and lower toxicity in favor of long course RCT. Reduction of the toxicity and better response to treatment can also lead to lower need for repeat hospital visits, less exposure

to contagious environments and better adherence to treatment. Furthermore, if complete response is achieved, a watch and wait strategy can be employed, aiming to reduce the surgery related morbidity (Pucciarelli et al 2013; Kauff et al 2017).

The long term effect of delayed surgery remains questionable. In the GRECCAR-6 trial, no differences in oncological outcomes at 3 years were observed between patients who underwent surgery at 7 weeks vs 11 weeks. Our delay to surgery was 11.1 weeks in Group 2, while in Group 1 the delay was 8.4 weeks. According to the GRECCAR-6 trial, at 7-8 weeks the effect of neoadjuvant treatment is maximum, but further delay up to 11 weeks does not impair pathological outcomes and 3 year overall survival. Further results of this trial are still expected to be published (Lefevre et al 2019).

The newest approach in locally-advanced rectal cancer, as shown by RAPIDO trial, is represented by SCRT followed by total neo-adjuvant chemotherapy and surgery (without adjuvant treatment). Preliminary results on 912 patients were promising, showing a rate of complete pathologic response of 30.1% in the experimental group as compared to 17% in the current standard of care group. However, concerns remain during the pandemic, as this treatment leads to 18-weeks of continuous immunosuppression secondary to the chemotherapy (Bahadoer et al 2020).

Conclusion

Neo-adjuvant long-course chemotherapy is a safe treatment option for patients with locally-advanced rectal cancer even during the COVID-19 pandemics if preventive measures are followed. Increased time to surgery leads to a higher rate of complete pathologic response, but further studies are needed to assess long-term impact of this outcome.

Acknowledgement

This paper was realized within the Doctoral Research Project no. 4107/01.10.2017, which runs with the financial support of "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.

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Citation	Andras D, Caziuc A, Cucoreanu C, Binţinţan V, Seicean R, Drașovean R, Scurtu R, Hopîrtean C, Popescu T, Coman I, Dindelegan G. The management of advanced rectal cancer during COVID 19 pandemics. Experience report of a tertiary surgical unit. HVM Bioflux 2021;13(2):77-81.
Editor	Antonia Macarie
Received	8 May 2021
Accepted	27 May 2021
Published Online	15 June 2021
Funding	Doctoral Research Project no. 4107/01.10.2017
Conflicts/ Competing Interests	None reported