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Age-related trends in colorectal cancer diagnosis: focus on evaluation of prehabilitation and rehabilitation programs

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Abstract: The increase in the prevalence of both colon and rectal cancer in recent years poses challenges for the medical system in terms of patient management and indirectly incurs significant financial burdens. Purpose: The aim of this paper is to track the changes in the prevalance of the colon and rectal cancer at a tertiary clinic in Romania over time and to identify complementary methods to improve the prognosis and quality of life of cancer patients. Material and methods: We conducted an observational, longitudinal, population-based study, including all patients newly diagnosed with colon or rectal neoplasia within the time frame from 1 January 2013 to 1 January 2024 in a tertiary medical clinic in Romania. For each case included in the study, we gathered demographic data (age at the time of cancer diagnosis, gender, place of origin), location of the tumor, duration until surgical intervention, alternative treatment methods employed (such as radiation or chemotherapy, and immunotherapy), and the length of survival. We also assess the feasiblity of physical prehabilitation and rehabilitation programs for inpatients diagnosed with malignant neoplasms of the colon or rectum. Results: The study found significant differences in patient ages and the execution of prehabilitation and rehabilitation practices between those admitted for colon and rectal cancer during the periods 2013-2018 and 2019-2023, with a notable shift in the prevalence of colon versus rectal cancer over these periods. Conclusions: Prehabilitation and rehabilitation practices for colorectal cancer patients are underdocumented or suboptimal, with recent improvements in documentation, especially for rectal cancer due to colostomy needs, and an observed increase in patient age due to COVID-19 pandemic protocols. Additional research and the development of standardized protocols are needed.

Keywords: rehabilitation programs, cancer, prehabilitation, personalized physical prehabilitation

1. Introduction

Colorectal cancer (CRC) represents a global medical system problem that requires prompt and efficient strategies for prevention, especially by addressing the modifiable risk factors and by better detection of premalignant lesions [1, 2]. In 2020, Globocan reported CRC as the 3rd most incident (1,931,590 cases, 10%) and the 2nd in mortality (935,173 cases, 9.4%), but the fearful part are the estimations that by 2040 the incidence will surpass 3.2 million new cases globally [1]. In Europe, the CRC sits in second place in terms of both incidence (520,000 cases in the year 2020) and mortality (250,000 in the same year) [3]. Even though the forecasts for 2024 show a decrease in the incidence of CRC in Europe, it is concerning that an increase in prevalence is estimated in the younger age group (25-49 years old) [4]. Romania also reports a similar trend in the incidence of this

malignancy [5]. In 2020, more than 13,000 cases of CRC were diagnosed (mostly in late stages), and more than 6,000 deaths due to this malignancy were recorded, despite the implementation of the Romanian Colorectal Cancer Screening Program (ROCCAS) in 2019 [6].

The onset age of CRC in the most cases is over 50 years old. A decrease in the incidence of colorectal cancer has been observed in older individuals and an increase among younger populations, especially during the last 30 years [7]. Cases occurring in individuals under 55 years old rose from 11% in 1995 to 20% in 2019. Additionally, there is a trend towards left-sided tumors, with the proportion of rectal cancer increasing from 27% in 1995 to 31% in 2019. Overall, colorectal cancer (CRC) mortality decreased by 2% annually from 2011 to 2020, but it increased by 0.5% to 3% annually in individuals under 50 years old [8].

Regarding therapeutic management, it presents particularities depending on the location (colon, rectum, or anus), histological type, clinical status of the patient at the time of diagnosis, and especially depending on the TNM staging. The European Society of Clinical Oncology provides different guidelines for all colorectal cancer sites (anus, rectum and colon – with or without metastases) [9-12]. In both colon and rectal cancer, surgical treatment with curative intent is considered the first-line approach for patients in early stages, eligible for surgical intervention, but there are certain differences in subsequent management [13]. For example, in cases of early rectal cancer (cT1N0), local excision via transrectal endoscopic microsurgery (TEM) or local radiotherapy is recommended as an alternative to the surgery. Local radiotherapy can be performed using brachytherapy or contact therapy. More advanced cases, including cT2c/T3a/b, require total mesorectal excision (TME) to minimize the risk of recurrence and involvement of locoregional lymph nodes. Patients with poor performance status, contraindicated for TME, may benefit from local excision via TEM [10, 14, 15]. In locally advanced rectal cancer, neoadjuvant chemoradiotherapy may be considered if the adverse effects do not outweigh the benefits. For patients with rectal cancer located in the upper part of the rectum (more than 12 cm from the anal margin), therapeutic management according to colon cancer protocols is indicated, without preoperative chemoradiotherapy [10, 14].

The 5-year survival rate for all types of colorectal cancer is around 65% [16]. However, it can reach up to 90% if diagnosed at a localized stage. Despite the years of life gained, CRC survivors experience persistent consequences of long-term treatment, with gastrointestinal (GI) symptoms being among the most common [17].

Given the large number of cases, along with the many methods of CRC treatment (surgery, chemotherapy, immunotherapy, and radiotherapeutic), a comprehensive approach is attempted through prehabilitation and rehabilitation programs for cancer patients, aiming to reduce mortality and morbidity, ultimately improving their quality of life [18, 19].

Prehabilitation encompasses a range of physical, psychological, nutritional, and educational approaches applied to the patient from the time of diagnosis until the initiation of treatment [19, 20]. Initially, the effectiveness of prehabilitation measures was analyzed in patients undergoing major surgeries, but later analysis expanded to the benefits of prehabilitation in non-surgical cancer patients, especially in gastrointestinal, pulmonary, and hematological conditions [18, 21]. Rehabilitation includes all complementary modalities, including psychological, nutritional, and physical aspects, aimed at optimizing cancer therapy and improving quality of life, initiated from the time of curative surgical intervention [22]. The aim of prehabilitation and rehabilitation programs is to improve the patient's life physically, psychologically, and spiritually. Obviously, in the case of oncology patients, the therapeutic approach must be in complex, multidisciplinary teams, personalized, and adjusted step by step throughout the entire process and based on previous outcomes [19-22]. Implementing rehabilitation and prehabilitation programs was affected during the COVID-19 pandemic, especially in the patients with cancer [23].

The main aim of this study was to examine a population of patients with colorectal cancer admitted to a tertiary clinic in Romania, comparing the patterns of evolution

between 2013-2018 and 2019-2023. Another purpose was to evaluate the types of rehabilitation/prehabilitation implemented for these patients, to explore the pitfalls, and to propose better interventions for patients suffering from CRC in order to enhance their quality of life.

2. Results

The age was significantly higher in patients with colon cancer as compared to patients with rectal cancer (63.4±11 vs 62.3±10.6; p=0.002).

Between 2013-2018 there were 1445 (52.4%) patients with colon cancer and 1315 (47.6%) patients with rectal cancer. Between 2019-2023 there were 518 (57.4%) patients with colon cancer and 385 (42.6%) patients with rectal cancer. The difference was statistically significant (p=0.01). The difference between the two timeframes is shown in the following figure (Figure 1).

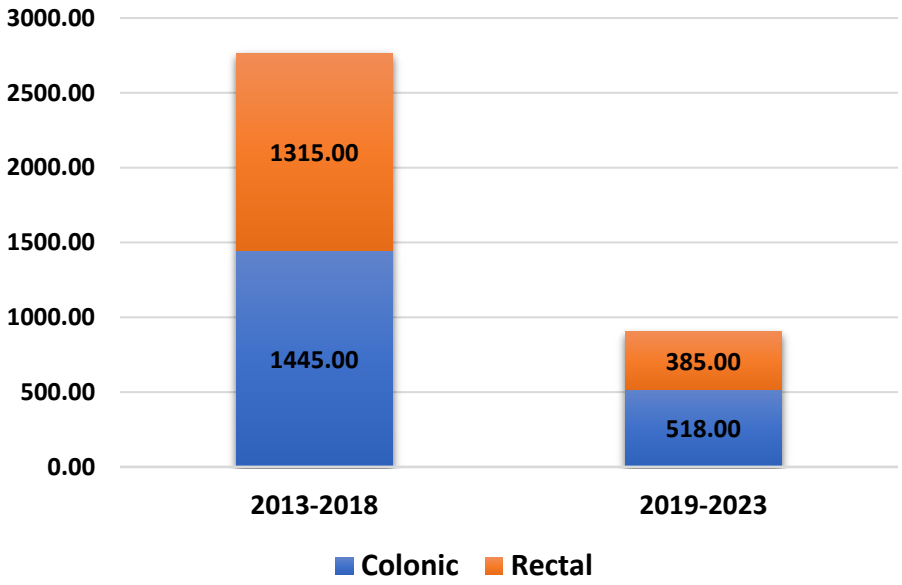

Figure 1. Differences between the two timeframes regarding the total number of colon and rectal cancer diagnosis

The age differences between the study groups is presented in the following table (Table I).

Table I. Differences between the median age in the study groups

	2013-2018	2019-2023	P (significance value)
Age - colonic cancer	62.6±11.2	65.7±10.1	<0.05
Age - rectal cancer	61.9±10.8	63.9±9.8	<0.05

The detailed information regarding the execution of medical interventions of prehabilitation and rehabilitation (early and late rehabilitation) is described in the following figure (Figure 2). We observed a significant shortfall in the execution of these essential interventions during both evaluated timeframes (acknowledging the possibility that certain interventions may have been administered but not adequately documented in the patient records). There were significantly more patients without any written information about pre-/rehabilitation practices (p<0.001) during the 2013-2018 timeframe compared to 2019-2023. This difference may be attributed to the lower number of treated patients and the stricter documentation rules imposed during the COVID-19 pandemic.

During the 2019-2023 timeframe, statistically significantly more pre-/rehabilitation practices were conducted for patients with rectal cancer compared to those with colon cancer. This difference primarily stems from the necessity of explaining the colostomy and its associated nursing care.

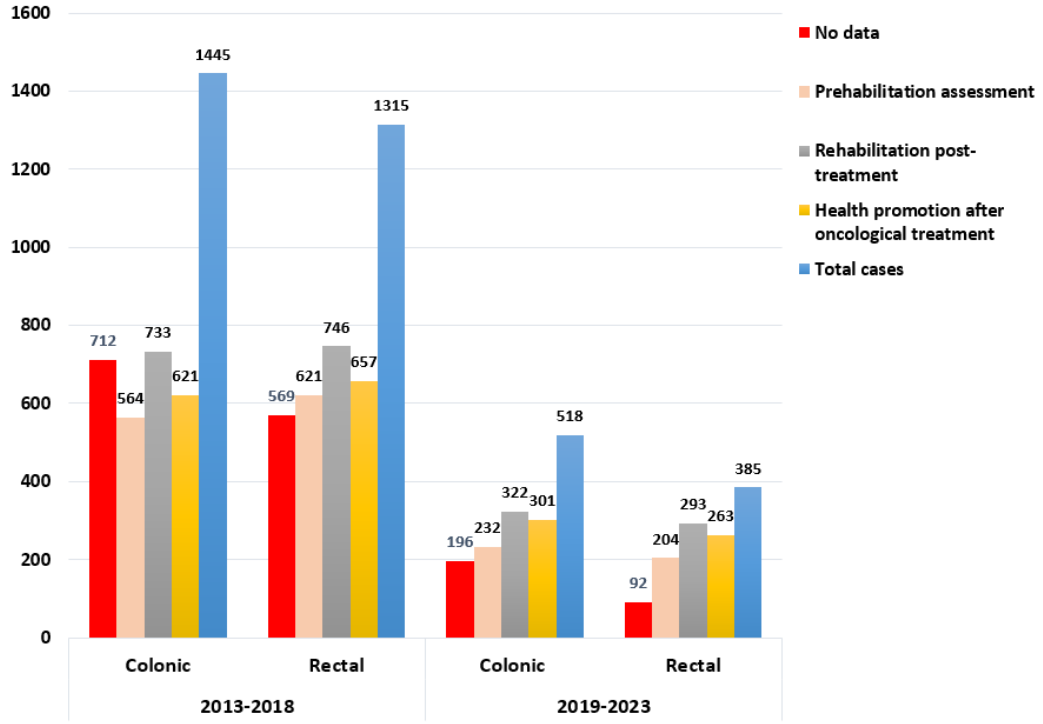

Figure 2. Documented services of pre-/rehabilitation offered to cancer patients diagnosed and treated in the two timeframes

3. Discussion

The increased prevalence of CRC, on an upward trend, poses challenges for the long-term management of these patients. Alongside the rising survival rate, there is a desire to improve the quality of life for patients and to reintegrate them into society as early as possible. Prehabilitation and rehabilitation come to the aid of these patients as complementary treatment methods aimed at improving their health status. Both approaches encompass physical, psychological, nutritional, and educational interventions [24]. However, conclusive evidence on the feasibility and financial viability of multimodal prehabilitation remains scarce, so more rigorous research is essential to achieve standardization in this area [20, 24, 25, 26]. Recent studies emphasize that age is a very important parameter to be kept in mind, along with the racial differences, when discussing the deficits and quality of life [27].

In the XXth century the incidence of CRC in individuals under the age of 50 has been rising at a rate of 2% per year. This increase in new cases of colorectal neoplasia among young adults is particularly concerning, especially considering the overall decrease in CRC frequency [28]. In our study, when we analyzed the age of colon cancer diagnosis over the periods 2013-2018 compared to 2018-2023, we found a statistically significant increase for the latter timeframe. These results do not follow the worldwide trendline of finding less colorectal cancer in general, at a younger age of diagnosis [29]. This fact can be explained by the difficult access to medical services during the COVID-19 pandemic (evidenced by the reduced number of hospitalizations), and by the diagnosis of rectal neoplasms with a higher degree of severity, at a more advanced stage. Also, during the lockdown period of the pandemic, access to screening colonoscopy was almost stopped

in the hospital where we conducted the study. In line with other studies, we obtained a statistically significant difference regarding the age at which they were diagnosed with neoplasia: higher for colon neoplasm and lower for rectal cancer [30].

We found there was a reduction in the number of newly diagnosed cases compared to the previous period, which is similar to previous reports, which state that the COVID-19 pandemic has induced alterations in how CRC patients present, resulting in a transient decrease in overall incidence due to deferred diagnoses [31]. Also, after the ending part of the pandemic, the endoscopic units did not yet achieve the same level of workload as before [32]. However, there has been a rise in patients requiring emergency admission or presenting with symptoms, after the resolution of the COVID-19 pandemic [31]. In our study, the lower numbers in patients admitted in the 2018-2023 timeframe could be explained by the fact that this period included the pandemic, during which access to medical services was partially restricted in Romania, leading to the diagnosis of patients in more advanced stages of the disease and consequently at an older age at the time of diagnosis. Also, the profile of patients admitted to the CF Clinical Hospital was slightly changed in 2020-2021, because the clinic had to solve cases of patients with acute hepatitis A and E and HIV-related infections (thus reducing the potential situations of finding CRC even more).

In our study, there were clearly insufficient documented practices of prehabilitation and rehabilitation in patients suffering from both colon cancer and rectal cancer. This aspect was also reported in one of our previously published studies [23], irrespective of the cancer type treated in our tertiary clinic. While in 2019 it was published the first International RCT describing the multimodal prehabilitation in colorectal cancer [19], in Romania, data on rehabilitation is scarce [33], and there has been little discussion about prehabilitation, which is nearly nonexistent. This is still an issue even worldwide. Recent systematic reviews on prehabilitation note significant heterogeneity among studies with varying levels of evidence and a lack of clinical outcomes, concluding the need for more studies to identify the optimal screening and prehabilitation program before implementation [34].

Prehabilitation can lead to improved functional capacity, as determined by the 6-minute walking test both preoperatively and postoperatively, as well as a lower number of postoperative complications and emergency hospitalizations. However, the number of readmissions could potentially increase within the prehabilitation cohort [20]. Regarding the studies on the utility of prehabilitation programs, they have shown that patients who underwent such programs had a significantly shorter hospital stay after colorectal cancer surgery compared to those who did not follow these programs [35, 36]. Furthermore, an extensive study has shown that prehabilitation should be considered as one of the routine care methods even for patients at high-risk undergoing planned surgeries for the colon and potentially for the rect. It is essential to maximize outcomes through frequent monitoring of progress to identify non-responders or non-adherent individuals as early as possible [24]. However, the results are not consistent, with a recent comprehensive study concluding that there was no effect of prehabilitation and physical rehabilitation after colorectal cancer surgery on short-term self-assessed physical recovery [37], or in general [38], on hospital stay duration [39].

The concepts of prehabilitation are new, and studies conducted to date use different prehabilitation protocols. Moreover, there is a lack of agreement regarding the diagnosis of frailty in cancer patients, nor a standardized prehabilitation protocol [40]. Additionally, a multimodal approach presents more benefits compared to a unimodal approach [41]. Recent studies have shown that multimodal prehabilitation programs, including exercise regimens, dietary guidance, emotional counseling, and interaction between these components, could be effective in reducing postoperative complications [24]. Other recent research has demonstrated a clinically relevant reduction in both complications and hospitalization duration following the implementation of comprehensive prehabilitation regiment for those receiving surgery for colorectal cancer [40, 42].

In our study, we noted a notable deficiency in the documentation of prehabilitation during both assessed periods. However, we observed a significantly higher number of

patients lacking any documented information regarding pre-/rehabilitation practices ($p<0.001$) during the 2013-2018 period compared to 2019-2023. This disparity may be explained, as previously suggested, by the reduced patient volume and better documentation requirements enforced during the COVID-19 pandemic. These enhanced practices were implemented in fact everywhere worldwide, along with strict regulations related to the pandemic [43].

Another interesting observation from our study is the fact that, in the period from 2019 to 2023, there was a statistically significant increase in the implementation of pre-/rehabilitation practices for patients with rectal cancer compared to those with colon cancer. This variance primarily arises from the need to address colostomy and its related nursing care requirements. The most recent Enhanced Recovery After Surgery (ERAS) guidelines incorporate prehabilitation as a preoperative strategy, but with low/moderate levels of evidence and strengths of recommendation [39, 44].

Physical prehabilitation can be achieved through the implementation of resistance or aerobic training, at various intensity intervals, and with specific frequencies. Other intervention methods include respiratory muscle training and pelvic floor muscle training. The effectiveness of these exercises can be quantified by assessing health-related quality of life (HRQoL) using questionnaires such as the Short Form Health Survey (SF-36) or the European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30). Functional capacity can be evaluated using the 6-minute walk test. The Comprehensive Complication Index (CCI) can be used to assess postoperative complications. The Gastrointestinal Quality of Life Index (GIQLI) is an indicator of gastrointestinal impairment perceived by the patient [39, 45]. These questionnaires were not used in the cohorts of patients from our study, as there was no documentation for such use in our patients' records.

Significant barriers to the implementation of prehabilitation are primarily associated with the complexity of the intervention, its relatively unknown nature, and limited evaluation within research environments. The need for clear and unambiguous evidence, however, contradicts implementation challenges, even within the research context, due to negative attitudes of skeptical professionals towards prehabilitation, limited organizational flexibility, conflicting guidelines (e.g., strict timing of surgery), and patient cognitions (e.g., the need for sedentary behavior in illness) [42]. Therefore, creating photo/video materials that include prehabilitation measures, feasible for execution at home, may represent a solution in these situations [46, 47].

The most significant limitation of this study was the shift in the profile of hospitalized patients, adapted to the epidemiological needs during the COVID-19 pandemic. Another limitation of this study is the lack of standardized information in patients' medical records regarding prehabilitation/rehabilitation procedures performed. Last but not least, the absence of an electronic registry of examined information could have led to errors related to the recording of information extracted by the study team members.

The implementation of integrating prehabilitation into the core components of therapeutic management programs for colorectal neoplasia encounters challenges related to the complexity of procedures, the need for material and human resources, as well as the lack of standardized protocols. Further studies are needed to evaluate the feasibility of implementing longer-duration prehabilitation protocols [42, 48]. We have conceptualized a framework for designing future studies that will explore both rehabilitation and prehabilitation interventions, building upon the insights provided by Heil TC et al. (2023) [49]. Therefore, for future randomized controlled trials assessing the impact of rehabilitation and prehabilitation, it is imperative that research teams develop comprehensive databases. These should include a wide array of clinical predictor variables (e.g., frailty scores), patient-reported outcome measures (e.g., quality of life questionnaires), and detailed algorithms for the interventions involved in prehabilitation and rehabilitation.

4. Materials and Methods

The study was designed as a retrospective, observational, population-based study, and it adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies. The study was previously approved by a local Institutional Review Board of the CF Clinical Hospital, from 2023.

We selected all cases hospitalized in a tertiary medical clinic in Romania (the CF Clinical Hospital from Cluj-Napoca) from January 1, 2013, to January 1, 2024, who were diagnosed with colon and rectal neoplasia during that hospitalization. Demographic data (age at cancer diagnosis, gender), neoplasm localization, and survival duration were collected for each case entered into the study.

Inclusion criteria: All patients hospitalized from January 1, 2013, to December 31, 2023, from the moment they were diagnosed with rectal or colon neoplasia, and subsequently all hospitalizations were analyzed until December 31, 2023. We included all patients aged over 18 and all stages, from early localized lesions to advanced metastatic disease, with or without other comorbidities.

Exclusion criteria: All patients not diagnosed with colon and/or rectal neoplasm during this time interval. All patients were already diagnosed with colon and/or rectal neoplasia at the initiation date of this study (January 1, 2013). We excluded all individuals under the age of 18 from this study.

Dynamically, we tracked the course of each patient included in the study, from the moment of the first diagnosis of rectal and/or colon neoplasia, then the moment of surgical intervention, and subsequently the periodic oncological monitoring, in order to indirectly assess the survival duration. Each patient in the study adhered to treatment protocols aligned with national guidelines. Their treatment regimen encompassed neoadjuvant chemoradiotherapy, subsequent adjuvant therapy, and various surgical interventions, as necessary.

For both timeframes, we recorded practices of prehabilitation, rehabilitation and practices of health promotion after the oncological treatment (for each cancer localization). If there were no recorded data describing these hospital practices, the patients were labeled with ”no data”.

Statistical analysis was conducted utilizing MedCalc® Statistical Software version 22.006 (MedCalc Software Ltd, Ostend, Belgium; 2024). Data were presented as figures and tables, using median of age, frequencies, and percentages, consistent with standard practice for reporting quantitative data. Group comparisons were executed using the chi-square test, with a p-value <0.05 indicating statistical significance.

5. Conclusions

Clinical practices of prehabilitation and rehabilitation remain suboptimal or inadequately documented for patients with colorectal cancer. However, there is an encouraging trend toward improved documentation of these practices, particularly among patients with rectal cancer, who require special attention due to the necessity of colostomy. The age of patients admitted for colorectal cancer has increased in recent years compared to the period 2013-2018, largely due to clinical practices imposed by the COVID-19 pandemic. Encouragingly, during the 2019-2023 timeframe there were conducted statistically significantly more pre-/rehabilitation practices for patients with colorectal cancer compared to the 2013-2018 period. Future studies will contribute to the establishment of definitive guidelines that delineate the precise algorithms for prehabilitation and rehabilitation in colorectal cancer and beyond, thereby improving the prognosis and quality of life of these patients, while simultaneously alleviating the financial burden on the healthcare system.

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