

Research Progress: Exploring the Long-term Survival Status of Colorectal Cancer Survivors

Abstract

The survival rate of colorectal cancer has significantly improved with advances in early screening and treatment strategies. Therefore, the long-term survival status of colorectal cancer survivors is of increasing concern, which can be summarized mainly in three aspects: quality of life, psychological status, and financial stress. In this article, we reviewed the quality of life of long-term survivors in the context of treatment modalities for colorectal cancer patients, including surgery, radiation therapy, chemotherapy, and wait-and-watch strategies, and separately summarized sexual functioning with long-term quality of life, which is easily neglected by clinical practice. In addition, we discussed the psychosocial problems and financial pressures faced by long-term survivors, analyzing the underlying factors that contribute to these challenges. In this review, long-term survivors of colorectal cancer often face persistent challenges such as chemotherapy-induced peripheral neuropathy, dry mouth, hair loss, intestinal dysfunction leading to frequent and urgent bowel movements, and incontinence. Additionally, they may struggle with ostomy care, body image dissatisfaction, sexual dysfunction, and a reduced quality of life. Psychosocial issues including distress, depression, and anxiety, as well as economic hardships due to treatment costs and potential job loss, further compound their situation. While these hardships cannot be quickly resolved, the review aims to offer a scientific basis for developing targeted intervention strategies, guiding researchers and practitioners in creating new support measures to address these multifaceted challenges.

Keywords: *Colorectal cancer, Long-term survivors, Quality of life, Psychological status, Financial stress*

Introduction

Based on GLOBOCAN's comprehensive analysis of 36 types of cancers across 185 countries and regions, colorectal cancer (CRC) accounted for 10.0% of new cases and 9.4% of deaths in 2020, ranking third and second in incidence and mortality rates, respectively.^[1] Despite a trend towards younger onset of CRC since the 21st century, with a growing number of early-onset cases diagnosed in individuals under 50, CRC survivors aged 65 and above still comprise three-quarters of the total cases, as reported by the American Cancer Society and the National Cancer Institute in 2022.^[2]

The treatment strategies for CRC have been continuously evolving, with surgery remaining the most common approach. In addition, chemotherapy, radiotherapy, immunotherapy, combination therapy, and a wait-and-watch strategy are also available. The choice of treatment strategy is influenced by factors such as the pathological stage and type of the tumor, as

well as the shared decision-making process between the patient and the medical team.^[3] For patients with stage I and stage II colon cancer, most receive surgery alone without chemotherapy or radiotherapy.^[2] Only some patients with high-risk stage II colon cancer and approximately two-thirds of patients with stage III colon cancer receive adjuvant chemotherapy after surgery to reduce the risk of recurrence. Over 60% of patients with Stage I rectal cancer opt for surgical treatment, of which approximately 50% receive neoadjuvant radiotherapy or chemotherapy before surgery. Most patients with Stage II and III rectal cancer adopt neoadjuvant radiotherapy and chemotherapy combined with surgical treatment. Nearly 50% of patients with Stage IV colon cancer and 30% of patients with Stage IV rectal cancer undergo surgery combined with chemotherapy and/or radiotherapy. Immunotherapy may also be an option for tumors with specific molecular profiles.^[4,5] In addition, there are increasing options for surgical treatment, with a growing emphasis on preserving

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organs and functions for the long-term benefits of patients. For instance, super minimally invasive surgery in the era of digestive endoscopy is a significant breakthrough compared to traditional open surgery and laparoscopic minimally invasive surgery. It emphasizes preserving the natural physiological state of the human body to the maximum extent while removing lesions without changing the original anatomical structure of the body.^[6] Its benefits to the long-term quality of life of CRC survivors remain to be further explored.

Thanks to the technological advancements in early screening, surgery, radiotherapy and chemotherapy, immunotherapy, as well as the continuous improvement of treatment strategies, the survival outcomes of CRC have been significantly improved compared to the past. According to the data reported by the American Cancer Society and the National Cancer Institute in 2022, the 5-year relative survival rate for CRC patients diagnosed from 2011 to 2017 reached 65%, an increase of approximately 15% compared to 40 years ago.^[2] With the improvement of survival rates, the long-term survival status of CRC survivors is becoming increasingly noteworthy. Therefore, this article summarizes research on the quality of life, economic pressure, psychological state, and other aspects of long-term CRC survivors, and provides a review of their long-term survival status, aiming to provide a reference for the development of targeted intervention strategies.

Quality of life

The internationally recognized and frequently used subjective quality of life assessment scales for patients with CRC include the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-CR29, and EORTC QLQ-CR38 questionnaires, as well as the 5-level EuroQoL 5-dimension questionnaire (EQ-5D-5L) and the 36-Item Short-Form Health Survey (SF-36).^[7-11] The assessment tools encompass the Low Anterior Resection Syndrome (LARS) scale for intestinal function, the International Prostate Symptom Score (IPSS) for urinary function, and the International Index of Erectile Function (IIEF) questionnaire along with the Female Sexual Function Index (FSFI) questionnaire for sexual function evaluation.^[7, 11] The quality of life addressed in the research report covers various aspects, including gastrointestinal, urinary, and sexual functions; physical, role, emotional, social, and cognitive functions; stoma care; economic pressure; and overall health status.

Surgical treatment and quality of life

Different surgical methods may affect the long-term quality of life of patients with CRC after surgery. Guren *et al.*^[12] found that the quality of life of patients with rectal cancer receiving abdomino-perineal resection (APR) was inferior to that of patients receiving low anterior resection. Koneru *et al.*^[13] believed that the presence of severe LARS after restorative proctocolectomy was the key to the difference in quality of life. The quality of life of patients with no or mild LARS was significantly higher than that of the APR group, while the quality of life of patients with severe LARS after surgery was similar to that of the APR group. However, a cross-sectional survey did not observe differences in the overall quality of life

scores of patients with mid-low rectal cancer after APR, low anterior resection with mechanical anastomosis, and low anterior resection with manual anastomosis. Only the perception of body image after APR was worse than the other two groups. The proportion of patients with severe LARS in the colorectal manual anastomosis group was significantly higher than that in the mechanical anastomosis group (83.3% vs. 56.6%, $p = 0.002$).^[14] Some research results also indicate that female patients with rectal cancer who undergo APR have a higher risk of dyspareunia (OR=2.61, 95%CI 1.00-6.85). Intestinal dysfunction after low anterior resection is associated with bladder storage difficulties (OR=1.64, 95%CI 1.01-2.65), urinary incontinence (OR=2.17, 95%CI 1.35-3.50), and decreased libido (OR=2.69, 95%CI 1.21-5.98).^[15] A recent meta-analysis has shown that after sphincter-preserving surgery for rectal cancer, intestinal dysfunction mainly affects social and emotional functions in quality of life, further impacting overall health status.^[16] A study on CRC survivors with an average survival time of ≥ 15 years found that although long-term survivors scored similarly to the control group in terms of fatigue, urination function, physical function, emotional health, and overall quality of life, intestinal dysfunction may still be a persistent issue.^[17]

To understand whether different tumor locations affect the quality of life of survivors after intestinal resection for CRC, comparative studies have emerged between colon and rectal cancer, as well as between left-sided and right-sided colon cancers. Keane *et al.*^[18] found that although about 50% of rectal cancer survivors who underwent low anterior resection exhibited severe Low Anterior Resection Syndrome (LARS), which is higher than the group with sigmoid colon cancer resection (25%) and the non-cancer matched control group (26%), the study did not observe differences in the quality of life among the groups. Univariate analysis revealed that the height of the anastomosis, stoma creation, and radiotherapy were all associated with severe LARS in rectal cancer survivors.^[18] Another study also emphasized that both colon and rectal cancer patients may face gastrointestinal functional issues after intestinal resection, with the proportions of LARS being 21% and 55%, respectively.^[19] Contrary to the findings of Keane *et al.*^[18] this study found that similar to patients with LARS after rectal cancer surgery, those with severe LARS after colon resection also reported a significant decrease in quality of life.^[19] A study specifically comparing the quality of life of CRC survivors after left-sided and right-sided colon resection found that the proportions of patients reporting severe LARS were 15.6% and 20.6%, respectively. The analysis revealed that, after adjusting for age and gender, the risk of severe LARS increased for patients who underwent right-sided resection compared to left-sided resection (OR 1.48, 1.03-2.13; $P = 0.035$).^[20] Buchli *et al.*^[20] also observed that severe LARS was associated with impaired quality of life.

A retrospective cohort study on rectal cancer suggested that compared to laparoscopic surgery, robot-assisted surgery, and transanal surgery were associated with a reduced rate of permanent stoma after low anterior resection (OR 0.39; [95% CI 0.25 - 0.59] and OR 0.35; [95% CI 0.22 - 0.55],

respectively).^[21] Among stoma patients, 45.4% experienced complications related to the stoma, which could manifest as high stoma output, skin complications, and parastomal hernia, among others.^[21] A study with an average follow-up of over 10 years found that among CRC survivors post-surgery, those with stomas had more early complications, but in the long term, the incidence of complications between stoma and non-stoma patients tended to be consistent. Common early complications included bleeding and postoperative infection, while common long-term complications included hernia, urinary retention, bleeding, skin complications, and intestinal obstruction. Stomas were associated with long-term fistula formation (OR 5.4; 95% CI 1.4-21.2), and in stoma survivors, fistulas were related to a decrease in health-related quality of life ($P < 0.05$).^[22] Recent research indicates that the long-term quality of life for patients with permanent stomas due to low rectal cancer may be worse than for non-stoma patients, affecting various aspects of daily life and interpersonal relationships.^[23] However, this conclusion may not apply to all age groups. Orsini *et al.*^[24] surveyed the quality of life of rectal cancer patients after total mesorectal excision (TME) using the SF-36 questionnaire and EORTC QLQ-C38 questionnaire. With a median follow-up of 3.4 years, the study found that the presence or absence of a stoma had little impact on the quality of life for elderly patients aged 70 and above.

Radiotherapy and quality of life

Radiotherapy is commonly used in the treatment of rectal cancer, and both preoperative neoadjuvant radiotherapy and postoperative adjuvant radiotherapy can increase the risk and severity of bowel dysfunction. Guren *et al.*^[12] noted that patients who received radiotherapy exhibited more severe symptoms in terms of abnormal bowel movements, urgency, and incontinence. Bruheim *et al.*^[25] in their cohort study, also reached similar conclusions, finding that patients who underwent radiotherapy experienced increased bowel frequency, higher rates of fecal incontinence (49% vs. 15%, $p < 0.001$), greater use of sanitary pads (52% vs. 13%, $p < 0.001$), higher rates of urinary incontinence (9% vs. 2%, $p = 0.001$), and poorer social functioning compared to those who did not receive radiotherapy. Additionally, studies have found that preoperative neoadjuvant radiotherapy is associated with urinary difficulties (OR = 1.63, 95%CI 1.09 - 2.44), dyspareunia (OR = 2.76, 95%CI 1.12 - 6.79), decreased libido (OR = 2.22, 95%CI 1.09 - 4.53), and reduced sexual activity (OR = 0.55, 95%CI 0.30 - 0.98).^[15] Furthermore, pelvic radiotherapy can lead to chronic proctitis, which is a significant risk factor for chronic pain. Chronic pain can result in functional limitations and negatively impact the quality of life of CRC survivors.^[3]

Chemotherapy and quality of life

In a cohort study based on 562 patients with stage II and III CRC, chemotherapy was associated with poorer long-term (≥ 5 years) quality of life, particularly among survivors younger than 70 years old at the time of follow-up. Chemotherapy may cause symptoms such as taste disorders, anorexia, and hair loss, and is associated with decreased physical, role, and cognitive functions. For CRC survivors aged ≥ 70 years,

chemotherapy was significantly associated with dry mouth and hair loss.^[26] A prospective cohort study by Vardy *et al.*^[27] found that about half of patients with localized CRC had cognitive dysfunction within 2 years of diagnosis, while the incidence of cognitive dysfunction in the healthy control group was 13%-19% ($P < 0.001$). However, researchers observed no significant difference in the proportion of cognitive impairment between long-term CRC survivors (with an average follow-up time of 9 years) and the control group (16 vs. 8%).^[28] Currently, multiple studies have shown that the impact of chemotherapy on cognitive function in CRC survivors is negligible.^[27, 29, 30]

Neurotoxicity is a common side effect of chemotherapy for CRC, mainly manifesting as numbness, commonly seen with oxaliplatin. Its neurotoxicity is dose-dependent.^[31] The effects of this toxicity may persist for a long time. A meta-analysis showed that the prevalence of peripheral neuropathy was 58%, 45%, 32%, and 24% at 6 months, 1 year, 2 years, and 3 years after chemotherapy, respectively.^[32] Chemotherapy-induced intestinal dysfunction usually manifests as diarrhea, but chemotherapy-related diarrhea usually resolves spontaneously and has less long-term impact on quality of life.^[33]

Wait-and-watch strategy and quality of life

The wait-and-see strategy, as a new treatment option, is a non-surgical treatment plan that requires patients to undergo strict and regular monitoring and follow-up. Since its first report in 2004, its impact on patients' survival outcomes and quality of life has attracted much attention.^[34] A high-quality clinical study that included 880 patients with rectal cancer showed that the 2-year cumulative local recurrence rate was 25.2% (95% CI 22.2-28.5%) and the 5-year overall survival rate was 85% (95% CI 80.9-87.7%) in patients who adopted a wait-and-see strategy after clinical complete response. The 5-year disease-specific survival rate could reach 94% (91-96%).^[35] A prospective study included 278 patients with rectal cancer who achieved a clinical complete response or near-complete response after neoadjuvant chemoradiotherapy or neoadjuvant radiotherapy. During the 24-month follow-up period, 221 patients (80%) adopted a wait-and-see strategy, 18 patients (6%) underwent local resection, and 39 patients (14%) received TME. The study found that about one-quarter of patients who adopted the wait-and-see strategy reported severe intestinal dysfunction and more than half of male patients had severe or moderate erectile dysfunction. Female sexual function and satisfaction also decreased compared to previous levels.^[11] Despite this, patients who adopted the wait-and-see strategy generally had a better quality of life than those who received additional surgical treatment.^[11]

Sexual function and quality of life

A study in the Netherlands used the sexual function subscale of the EORTC QLQ-CR38, and among the 1,371 CRC survivors who responded, 1,359 had undergone surgical treatment. The study found that male rectal cancer survivors had higher rates of erectile (54% vs. 25%, $p < 0.0001$) and ejaculation problems (68% vs. 47%, $p < 0.001$) compared to colon cancer survivors. The incidence of sexual pain in female

rectal cancer and colon cancer survivors was 30% and 9%, respectively, which was significantly higher than that in the normative population (0%, $p=0.001$).^[36] In a study by Bregendahl *et al.*^[15] 72% and 53% of female rectal cancer survivors reported vaginal dryness and sexual pain, respectively, and 69% of the respondents indicated a decrease or absence of sexual interest. Although sexual health problems are common among CRC survivors, communication and discussion between patients and doctors about this aspect are inadequate.^[37, 38] Factors limiting medical workers from asking about related issues may include time constraints during consultations or a lack of knowledge about the treatment of sexual dysfunction. Enhancing the initiative of consultations and awareness of referral resources may be the key to addressing this issue.^[38] Although studies have confirmed that patients experience changes in sexual function and face sexual health problems during the diagnosis and treatment of CRC, data in this area are still scarce, and more long-term, interventional studies are needed to provide strategies and scientific evidence for improving sexual function and quality of life.^[39]

Psychological health

Many CRC survivors indicate that it is difficult to return to a healthy state after treatment, and the fear of disease recurrence may increase their risk of developing mental health problems.^[2, 40] The prevalence of anxiety, depression, and distress reported by CRC survivors varies widely among different studies, which may be related to inconsistent use of measurement tools and methodological differences. In a prospective survey of 1,966 CRC survivors, psychological distress was classified as the presence of anxiety, depression, or somatization of mental state, and the study found that the incidence of psychological distress among survivors five years after diagnosis of CRC was 42%.^[41] In a report by Chambers *et al.*^[42] only 5% of people reported severe mental health problems five years after diagnosis. Although the relevant research and reports are very limited, the existing research results indicate that a considerable proportion of long-term survivors of CRC suffer from psychological distress such as anxiety and depression.^[43]

Dunn *et al.*^[41] found that male survivors of CRC were more likely to have mental health problems ($p < 0.001$) compared with women, and the study suggested that young men with low education levels and insufficient social support might be the focus of targeted intervention. In another five-year longitudinal study on patients with rectal cancer, although no significant difference in mental health status between men and women at the same time point was observed in the SF-36 scale, the study found that the mental health status of women improved over time, while that of men hardly changed within five years.^[44]

A study with an average follow-up time of 11 years on rectal cancer survivors found that survivors with permanent stomas reported worse mental health status on the SF-36 scale compared with the control group without stomas.^[45] CRC patients who undergo permanent stoma surgery usually face

psychological challenges, which are often related to post-operative adjustment and adaptation to bodily changes. To improve the quality of life of this group, attention should be paid to several elements, including support for personal values, inner peace, interconnectedness of social emotions, and a sense of belonging.^[46]

Economic pressure

Research reports indicate that approximately 40% (ranging from 7% to 80%) of CRC survivors face economic pressure, and CRC-related economic pressure is associated with reduced quality of life (OR=2.54, 95% CI 1.62-3.99).^[47-49] A study by Mo *et al.*^[50] showed that more than half of the survivors of stage I-III CRC bear a heavy economic burden, and factors such as being young, having a low annual family income, being unemployed, receiving chemotherapy, and having insufficient social support are all associated with economic pressure ($p<0.05$). Economic pressure is related to reduced survival rates and poorer quality of life, possibly due to the fact that the financial burden reduces patients' compliance with treatment, thereby affecting their quality of life and survival outcomes.^[51]

Conclusion

In the era of multi-disciplinary comprehensive diagnosis and treatment and individualized precision therapy, we cannot only focus on survival benefits while ignoring the long-term quality of life of CRC survivors. Long-term survivors of CRC may not only experience complications such as chemotherapy-related peripheral neuropathy, dry mouth, hair loss, but also face intestinal dysfunction (manifesting as frequent bowel movements, urgency, and fecal incontinence), issues with colostomy bag care, dissatisfaction with body image, abnormal sexual function, and other health-related quality of life impacts. They may also encounter psychosocial problems (such as distress, depression, anxiety, etc.) and economic pressure due to treatment costs and unemployment. This article provides a comprehensive review of the long-term survival status of CRC survivors from several perspectives, including the impact of different treatment options (including surgical treatment, radiation therapy, chemotherapy, and watch-and-wait strategies), as well as the influence of gender, age, and the presence or absence of colostomy on long-term quality of life and mental health status. Although it is difficult to improve their problems in a short period, this provides researchers and medical workers in the field of CRC with a direction for effort.

Cancer itself and its treatment have significant impacts on the health and quality of life of CRC survivors. Therefore, it is crucial to provide them with high-quality, comprehensive and coordinated clinical follow-up medical guidance and care. We should not only focus on the physical impacts but also take into account the psychological and social aspects while making personalized adjustments based on the treatment needs and conditions of each patient. Although current clinical follow-up care still lacks comprehensive guidance, we are increasingly aware of the importance of teaching CRC survivors health management strategies. The American Cancer Society has

developed care guidelines for CRC survivors to help them minimize the adverse effects of the long-term living conditions of CRC.^[3] It is believed that there will be more and more health guidance strategies in the future, assisting in improving the long-term survival status of CRC.

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Conflict of interest

None.

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Ethics statement

None.

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