14. Issues in colorectal cancer survivors

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Abstract. Colon and rectal cancers (CRC) are very frequent and their incidence doubles with each successive decade of life beyond 50 years. Consequently, the absolute number of CRC patients is expected to grow substantially in the coming years as the population progressively ages. On the other hand, improvements in treatment are expected to increase the number of survivors in the near future. A better understanding of the late effects and health-care needs of long-term CRC survivors will thus be imperative and is the aim of this chapter.

Introduction

The incidence of CRC increases with age, mainly after 50 years, and the population is now progressively aging. An increasing number of people are therefore expected to develop this disease in the near future [1,2]. On the other hand, advances in detection (prevention and screening programmes), treatment (adjuvant and neoadjuvant regimens) [3-7], and even the improvement of
surgical techniques such as mesorectal excision are contributing to improved rates of survival. For all these reasons, we can predict that the number of survivors of CRC is very likely to increase in the coming years [4].

Many relevant issues related to the treatments for this disease, or related to or favoured by possible comorbidities in the target population (elderly people) [8], merit our attention due to their potential impact on the quality of life (QOL) of these patients. This chapter will discuss these issues and several strategies for helping to improve the QOL of survivors.

1. Issues related to treatment

   The treatment of CRC is often multidisciplinary and depends mainly on the location of the primary tumour (rectum or colon) and also on the stage of the disease at diagnosis. In general terms, the treatment modalities for early stages could include surgical resection and adjuvant chemotherapy for colon cancer and additional radiation therapy for rectal cancers. All three modalities might have lasting associated morbidities that could affect long-term function and QOL for survivors of disease after the cancer is treated. We will describe the effects related to each of these treatments.

   **Issues related to surgical procedure**

   The main curative treatment for CRC is still complete surgical resection [9]. This standard oncologic surgery consists of en bloc bowel resection (colon and/or rectum) with appropriate proximal and distal resection margins, the resection of the associated blood vessels, and more than 12 harvested lymph nodes [10,11]. Most of these surgical procedures are usually performed through an open vertical incision in the abdominal wall, a procedure called laparotomy. This kind of surgery has several risks that could be relevant for people surviving the disease.

   **a. Laparotomy**

   Several problems associated with laparotomy can occur in the short and long term. Although long-term complications are more relevant for survivors, problems secondary to surgery in the acute period can be very important and may require additional invasive procedures. The most frequent complications during this period include wound infections (3-26%), anastomotic leaks (2-10%), and intra-abdominal infections (2-5%). All of these can be severe and may require invasive procedures [12-14]. Long-term complications,
though, are the most relevant. Bowel obstructions, hernias of the abdominal wall, and functional problems are the three most frequent complications.

**a.1. Bowel obstructions secondary to surgery**

Early postoperative small-bowel obstruction is a common and serious complication after colectomy. Shin and Hong [15] analysed 504 patients who underwent colectomy for CRC. These patients were monitored, and those assessed to have an obstruction within the first 30 days after surgery and lasting for at least two days presented nausea, vomiting, and abdominal distension. Early postoperative obstruction, the most frequent complication during the early perioperative period, occurred in 8.1% of the patients. The authors showed that pelvic surgeries did not lead to a higher rate of early obstruction compared with colonic surgeries. Local remnant tumours and poor systemic condition were independent risk factors for this complication after colectomies for CRC. Obstruction is particularly relevant for survivors of CRC. This complication has the potential for tumour recurrence, which can reduce the patients’ QOL [16].

Jeong *et al.* [17] studied 2586 patients operated for a primary CRC. During the follow-up, 5% of the patients presented adhesive small-bowel obstructions. The observed incidence rate was 0.0013 per patient-month. Most patients (80%) were successfully treated in less than one week (range 1-22 days) by conservative procedures such as intestinal decompression with gastrointestinal tubes. The remaining patients needed a new surgical procedure due to strangulation or the lack of improvement. These results indicate that initial conservative management is recommended for these patients.

**a.2. Abdominal-wall hernia secondary to surgery**

Incisional hernia is a long-term complication of laparotomy. Its exact frequency varies according to different authors but is always near 10% [18,19]. In cases with infected surgical wounds, though, the rate can be as high as 20% [20]. This complication can lead to pain, limitation of patient activity, and possibly reparative surgery or emergency surgery for bowel strangulation. Only 50% of these hernias become evident within six months of the operation. The remainder appear well after recovery from surgery [21,22]. Millikan [21] reported that 100 000 repairs are performed annually in the USA, with a rate of recurrence of 5-10%. Incisional ventral hernia has many predisposing factors that might reduce the overall incidence of these hernias,
such as factors related to patients conditions, type of closure, and materials used.

Some patients present associated systemic diseases (chronic obstructive pulmonary disease, obesity, severe cardiopathies, immunodeficiencies, etc.) that favour or increase the risk of an incisional hernia. Hidalgo et al. [20] evaluated 72 high-risk patients (42 with CRC) selected for surgical intervention through median infra-umbilical laparotomy. During laparotomy, the preperitoneal space was dissected at a point where a low-molecular-weight polypropylene mesh was to be placed when closing the peritoneum. Meshes were about 7-8 cm wide with a variable length depending on the length of the surgical incision. Follow-up was 3-5 years. No noteworthy complications or operative mortality occurred, and no mesh required removal. In two patients who developed liver metastases and needed a second surgical intervention, the health of the abdominal wall and the absence of hernia were confirmed. None of the 72 patients developed an incisional hernia. These authors concluded that the prophylactic use of a low-molecular-weight polypropylene mesh in abdominal surgery may be useful for the prevention of incisional hernia.

Current controversies remain to be answered concerning the methods for repairing hernias (open versus laparoscopic procedure) and the types of fixation (partial- versus full-thickness abdominal muscular/fascial wall) necessary to stabilise the position of the mesh while tissue growth occurs [21].

b. Minilaparotomy

Ishida et al. [23] evaluated minilaparotomy, a minimally invasive alternative to laparoscopy, for performing curative resections of colon cancer. They studied the feasibility, safety, and early oncological outcome among 73 patients (first group), in whom a curative resection of colon cancer was performed via minilaparotomy (skin incision ≤ 7 cm) using specific instruments (North-bridge retractor system), and 94 patients (second group), in whom a similar procedure was performed without using specific instruments. These two groups did not differ in the incidence of postoperative complications, length of postoperative hospital days, or overall survival, although the second group had a higher frequency of prior abdominal surgery (38.3 vs. 21.9%; \( P = 0.03 \)) and a shorter median operating time required for a standard lymph-node dissection (120 vs. 135 min; \( P = 0.03 \)). The authors thus concluded that improved techniques and experience precluded the need of specific instruments for the performance of a curative colectomy and that minilaparotomy is a good alternative to laparoscopy.
c. Laparoscopy

Several studies, however, have demonstrated the advantages of laparoscopic surgery, another less aggressive surgical procedure [24-27]. Its smaller incisions lead to less pain, shorter length of stay, lower rate of incisional hernia, and probably less adhesion formation. Several randomised trials comparing this procedure with open incisions have demonstrated that patients who underwent laparoscopic resections recovered earlier with less need of blood support and lower morbidity. Some studies have even suggested a lower risk of tumour recurrence and death from any cause or from cancer-related causes [27]. More laparoscopically assisted surgical resections will likely be performed in the future. Minimally invasive surgery has multiple benefits, including a shorter hospital stay and less postoperative opioid use, without compromising long-term [27,28] outcomes or increasing the costs of health care [29].

Laparoscopic resection of the colon was first described in the nineties [30]. Although techniques and equipment were at first cumbersome, laparoscopic colectomy for benign and malignant conditions of the colon soon became a reality. Early reports of laparoscopic-assisted colectomy revealed a faster recovery from surgery and fewer surgical complications [31,32]. However, wound-site recurrence, which reached 21% in some studies, raised significant concerns about this technique [33].

A randomised controlled trial comparing the efficacy of laparoscopic-assisted colectomy with open colectomy found that patients having the former approach recovered faster, had less blood loss, and had lower morbidity ($P < 0.001$). Finally, the authors report that the probability of cancer-related survival was higher in the laparoscopic-assisted group ($P = 0.02$); the Cox model showed that the laparoscopic-assisted approach was independently associated with reduced risk of tumour relapse, death from any cause, and death from a cancer-related cause compared to open colectomy [24].

Another trial of the laparoscopic versus open approach for treatment of colon cancer has also been performed in North America. Regarding QOL issues, Weeks et al. demonstrated that the global QOL was significantly higher at two weeks following the laparoscopic approach compared to open surgery [25]. Additionally, the laparoscopic patients required significantly fewer days of parenteral and oral narcotics. Of note, however, is that no differences in QOL were demonstrated at two months following surgery. Importantly, survival and recurrence rates from this trial were not statistically different, which thus suggests that laparoscopic resections of colon cancer can be performed safely in appropriately performed operations [27].
Two recent meta-analyses reviewed the current literature on laparoscopic resection in rectal cancer. One meta-analysis showed that this approach was associated with lower morbidity but a longer operative time; wound infection, anastomotic leakage, and mortality were similar in both open and laparoscopic groups [34]. The other analysis revealed a reduction in length of hospital stay and time to first bowel movement and stomal function in patients who underwent laparoscopic surgery. Specifically, in the set of patients requiring abdominoperineal resection, laparoscopic patients required fewer parenteral analgesics and had a reduced rate of postoperative wound infection [35].

Increasingly more laparoscopically assisted surgical resections of colon and rectal cancers will likely be performed in the future; however, with the laparoscopic approach, the performance of appropriately indicated and safe resections of cancers remains a priority.

d. Other issues related to surgical procedures

1. Bowel changes and dysfunction

The goal in the treatment of rectal cancer should be recovery from the disease with the best faecal continence and QOL. Certainly, one of the functions of the rectum is the storage of faecal material. Whenever the rectum is resected for cancer, the storage capacity of the replacement, which is the colon (i.e., usually the descending or sigmoid colon), is much reduced. Consequently, more-frequent, clustered, and/or incomplete bowel movements can appear. On the other hand, because of possible nerve damage from surgery or radiation therapy, the functioning of the anal sphincter may be further affected, and the degree of incontinence may worsen.

Radiation therapy also has a role in these kinds of symptoms. In fact, Kollmorgen et al. [36] found that adjuvant chemoradiotherapy for rectal cancer had a major long-term detrimental effect on bowel function, as explained later in this chapter. This study did not find a significant correlation between the level of the anastomosis and postoperative stool frequency or incontinence. Previous trials had demonstrated such a correlation, with lower anastomoses being associated with greater stool frequency and more incontinence [37-39]. These contradictory results may be partly due to the selection criteria used in the study, which were not used in the previous investigations. Short-term follow-up, during which the greatest deterioration in bowel function occurs, was not performed, and patients who had sutured colo-anal anastomoses or who had extensive resections, dysfunctioning stomas, or clinically significant anastomotic leaks were excluded. In these groups, very low anastomoses may be more common, and postoperative...
function may be even worse [37-39]. Various studies have also detected that bowel function is often compromised in the early postoperative period after anterior resection, with frequent bowel movements and faecal incontinence. Bowel function improves over the ensuing one to two years, and this improvement correlates well with increasing capacity of the "neorectum" [40-42].

Franco et al. [43] tried to compare QOL and manometric results in patients treated with neo-adjuvant chemotherapy and rectal low-anterior resection (LAR). They recruited 50 patients with advanced (T3-T4) rectal cancer who underwent neo-adjuvant chemotherapy. Forty-one patients subsequently underwent LAR with or without a colonic pouch. QOL was evaluated by questionnaire after a few months, and the patients later underwent manometric evaluations measuring resting, squeeze, and rectal compliance. The manometric results and the scores from the questionnaire agreed in 75% of the patients. Patients with a hypotonic sphincter had a good QOL if a LAR with pouch had been performed compared to the patients without a pouch. The authors concluded that performing LAR with a colonic pouch after neoadjuvant chemotherapy in patients with a hypotonic sphincter improves QOL. Preoperative anorectal manometry could thus select patients who would benefit from pouch construction to avoid a deterioration in QOL.

Chatwin et al. [44] tried to evaluate clinical outcomes and QOL in terms of anal function, among others, after LAR for rectal cancer. They evaluated 43 patients with low rectal cancers. Twenty-seven were not given adjuvant radiotherapy, and 16 received preoperative adjuvant radiotherapy of 1.6 Gy twice daily for 13 days. Twenty-three patients reported normal defecation (53%), nine had incontinence of flatus (21%), five had occasional minor soiling (12%), two had frequent major soiling (5%), and four had total faecal incontinence (9%). The authors concluded that despite the reported faecal dysfunction most patients were satisfied with their QOL. The authors strongly recommended counselling at the time of operation as a means of contributing to personal satisfaction. Most patients prefer a sphincter-sparing procedure, although they need to understand that bowel dysfunction may also occur.

Although the location of the anastomosis is very relevant for maintaining function, defecatory problems can occur as a result of surgical trauma or the effects of radiation therapy on the anal sphincter and associated nerves, even in cases in which a sphincter-preserving procedure has been performed. A low anastomosis is more associated with a higher frequency of defecation and faecal leakage and incontinence than a higher anastomosis. Although these are the most frequent symptoms after surgery for rectal cancer, some degree of diarrhea or constipation and excessive flatus have also been described. All these issues could impact the patients’ QOL.
2. Ostomy issues in survivors

Intestinal ostomy is a surgical procedure for treating several benign or malignant diseases, but rectal cancer is the most common reason for a person to undergo this kind of surgery [45]. Many patients undergo ostomy each year, and every effort is made to preserve intestinal integrity [46,47]. This therapeutic approach can be either temporary or permanent and creates many challenges for QOL and maintenance of function. In colostomy and ileostomy surgeries, normal bowel function is interrupted, and waste is passed through the abdominal wall via an opening called a stoma into an appliance that must be emptied periodically [46,47].

Ostomy is an unpleasant surgery. In many cases this procedure leads to intensified distress for patients who will inevitably suffer from physical and emotional problems, isolation, and fear of cancer recurrence or death. The stoma is usually red and swollen and may cause stress as a consequence of skin irritation and rash around the ostomy site (76%), pouch leakage (62%), bad odour (59%), reduction in pleasurable activities (54%), and depression or anxiety (53%) [46].

The procedure impacts negatively on the patients’ QOL. Most patients report significant limitation in physical activity after their ostomy. Social and family relationships are also affected, although these improved over time. A patient’s family must learn how to cope with the new situation, and the patients may complain about their relationships with their intimate partners [45]. A study by Brown and Randle [48] showed that patients with stomas tend to worry about sexual issues, especially in the early postoperative period, leading to a further deterioration of their QOL. Symms et al. [49] reported that almost half of patients who were sexually active before ostomy became inactive after this procedure. The passage of time is the most important factor in adapting successfully to life after ostomy. As the study by Ohman [50] has shown, many problems such as anxiety from faecal leakage, offensive odour, bowel noise, and loss of libido can decrease over time. Counselling and evaluation of sexual health after recovery from surgery are important.

After an abdominoperineal resection, the presence of a permanent colostomy has a strong influence on survivors. Stoma-related problems are common. In a series of 203 patients with end sigmoid colostomies, the 13-year actuarial risk of paracolostomic complications was 58%. Paracolostomic hernia was the most common complication (36% at 10 years). Other stoma-related complications may occur in survivors, including stomal prolapse (12%), skin-related problems (e.g., excoriation) (12%), and stenosis of the stomal opening (7%) [51]. Several studies have demonstrated a decreased health-related quality of life (HRQOL) in patients with stomas. US war
veterans with stomas were surveyed using the City of Hope Quality of Life-Ostomy questionnaire. Qualitative analysis was performed on the basis of the City of Hope QOL for Ostomates format of HRQOL (physical, psychological, social, and spiritual). For colostomic patients, family and spousal relationships were frequently considered important in the psychological category, while sexual relationships were important in the social category. The authors concluded that awareness of patients' social, psychological, and medical status allows surgeons to identify those likely to have problems and to use resources to help these patients [52].

Ostomic patients depend on the integrity of their peristomal skin to maintain a normal lifestyle. Peristomal-skin problems are thought to be common and may interfere with the use of ostomic pouching systems. These problems constitute a special category not commonly seen by dermatologists. Loss of skin integrity may be related to chemical injury, mechanical destruction, infectious conditions, immunological reactions, and disease-related conditions. Peristomal irritant dermatitis caused by skin contact with ostomic effluent is by far the most ordinary condition seen [53]. Mechanical trauma, infection, and aggravation of pre-existing skin diseases are also seen. Allergic contact dermatitis, which is often cited as the cause of peristomal skin problems, appears to be a rare condition with an estimated prevalence of only 0.6%. Despite the importance of the integrity of peristomal skin, the topic is poorly described in the literature. Existing publications suggest that although peristomal skin disease can be diagnosed and treated, additional information on both patients and physicians is necessary to optimise patient care [54,55]. In a survey of almost 400 ostomates, 51% had skin problems (e.g., rashes) and 36% had leakage; 80% reported some change in lifestyle. In addition to reports of complications, several studies have compared postoperative psychosocial adjustment and QOL in ostomic and nonostomic patients, including concerns about sexuality, limitations of activity, and bowel function.

It is important that clinicians make use of referral of patients to enterostomal therapists who are able to address both the physical and psychosocial sequelae of having a stoma. Their consultation is valuable throughout the course of survivorship from preoperative to short- and long-term periods. Stomal support groups exist in many communities and are another resource [45].

Therapeutic procedures may not only treat disease but also affect patient QOL. Therefore, QOL should be measured in order to assess the impact of disease and therapeutic procedures. To identify clients' problems, the assessment of several dimensions of QOL, including physical, spiritual, economic, and social aspects, is necessary. To address these issues, we
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conducted a qualitative study to explore QOL and its dimensions in ostomic patients referred to the Iranian Ostomy Association. Fourteen patients were interviewed about their QOL dimensions by purposeful sampling. Data were gathered by semistructured interviews and analysed using the content-analysis method. Nine main themes emerged, including physical problems related to colostomy, impact of colostomy on psychological functioning, social and family relationships, travel, nutrition, physical activity, sexual function, and religious and economic issues. The findings of the study identified a number of challenges in QOL for patients with ostomy. The results can be used by providers of health care to create a supportive environment that promotes better QOL for their ostomic patients [45].

3. Sexual dysfunctions

A growing body of evidence suggests that the prevalence of sexual dysfunction among men and women is high following treatment for CRC [56-59]. Several descriptive cross-sectional and longitudinal studies of CRC survivors have concluded that overall health-related HRQOL after treatment is good, although many survivors, even those who reported good QOL, also report significant difficulties in sexual functions.

Sexual function is one element of QOL that may be significantly damaged following treatment for rectal cancer, but its incidence and contributing risk factors are generally poorly understood. An increasing number of studies have recently reported sexual dysfunction following treatment of rectal cancer. The lack of a standard definition of sexual dysfunction, though, complicates matters. The absence of sexual activity can be used as a surrogate marker for sexual dysfunction, but this is confounded by an individual's desire and opportunity for sexual activity and may not be an accurate reflection of physiological functionality [56-59].

Sexual problems are associated with surgical and radiation therapies that affect the pelvic tissues and/or organs and their innervation. In males, the main sexual problem is erectile dysfunction related to disruption of the parasympathetic nerve and ejaculatory difficulties (inability to ejaculate or retrograde ejaculation) secondary to injury to sympathetic nerves [60]. A conventional resection of rectal cancer in men is associated with postoperative impotence and retrograde ejaculation, or both, in 25-100% of cases [61-63]. The incidence of these problems is higher in older men and in men who underwent an abdominoperineal resection (removal of the rectum and placement of a permanent colostomy) compared to those who underwent an anterior resection [62,63].
In females, the most common postoperative sexual problem is dyspareunia, which may include loss of vaginal lubrication and inability to achieve orgasm. Because both symptoms are very difficult to measure, sexual activity is used as a surrogate marker. Various studies have found that among those women who were sexually active before surgery, 47-86% remained sexually active after surgery. Other studies have demonstrated that this number is related to the kind of procedure patients have undergone. After sphincter-preservation surgery, 55-58% of women remained sexually active, but only 10-39% were active after an abdominoperineal resection [60-64].

Havenga et al. [62] surveyed 54 women after total mesorectal excision with autonomic-nerve preservation for rectal cancer (44 LAR, 10 abdominoperineal resection). Ninety-five percent of women remained interested in sex, 86% remained sexually active, 85% continued to experience vaginal lubrication during arousal, and 91% maintained their ability to achieve orgasm postoperatively. In all these cases of men and women, the best possible outcome is achieved by careful sharp dissection with preservation of the pelvic autonomic nerves.

Marijnen et al. [65] evaluated the QOL of 990 patients with rectal cancer who did or did not undergo preoperative short-term, high-dose radiation therapy prior to rectal excision. At three months after surgery, patients who underwent preoperative radiotherapy reported significantly reduced daily activity. Both men and women receiving preoperative radiation therapy reported a significant decrease in sexual activity, although HRQOL was not otherwise affected. Relatively nonspecific problems such as changes in level of sexual activity, a lack of sexual enjoyment, and alterations in body image have also been identified in both men and women following treatment for CRC.

Lee et al. [66] evaluated the effects of surgery for rectal cancer on postoperative voiding and sexual function over time. Data from 28 male patients who underwent autonomic nerve-preserving surgery for rectal cancer were retrospectively analysed. Operations were performed between October 2005 and July 2007, and all patients were followed-up for more than three years. Preoperatively, all patients underwent urodynamic studies, including uroflowmetry, and were assessed for their International Prostate Symptom Score (IPSS). The evaluation of sexual function consisted of an Erectile-Function domain score from the International Index of Erectile Function (IIEF-EFD) and an Ejaculation domain score from the Male Sexual Health Questionnaire (MSHQ-EjD). Data from uroflowmetry and the questionnaires were examined. At three years postoperation, the prostate volume was similar to the preoperative value \((P = 0.727)\). No statistically significant postoperative changes were found in the average maximum flow rate (15.9 ml/s vs.
16.2 ml/s, \( P = 0.637 \) and the post-void residual urine volume (34.7 ml vs. 36.8 ml, \( P = 0.809 \)). No statistically significant differences were observed in the IPSS (13.2 vs. 12.2, \( P = 0.374 \)). However, even though pelvic autonomic-nerve preservation was performed, a significant proportion of rectal-cancer patients suffered from sexual dysfunction, and the average IIEF-EFD and MSHQ-EjD scores were lower postoperatively for three years (25.1 vs. 16.1 and 28.3 vs. 14.2 respectively, \( P < 0.001 \)). The authors concluded that voiding function was not affected after autonomic-nerve-preserving surgery for rectal cancer, but sexual function was significantly aggravated. We recommend that the baseline genitourinary function should be evaluated before treatment for male patients with rectal-cancer, and penile rehabilitation is necessary for their QOL after treatment.

In light of the improving prognosis for patients with rectal cancer, the quality of functional outcomes has become increasingly important [67,68]. Large multicentre studies show that urogenital dysfunction remains a common problem after treatment for rectal cancer, despite the good functional results achieved by expert surgeons. More than half of patients experience a deterioration in sexual function, consisting of ejaculatory problems and impotence in men and vaginal dryness and dyspareunia in women. Urinary dysfunction occurs in one-third of patients treated for rectal cancer, with surgical nerve damage being the main cause. Radiotherapy appears to have a role in the development of sexual dysfunction, without affecting urinary function. Pelvic autonomic nerves are especially at risk in cases of low rectal cancer and during abdominoperineal resection. Data concerning nerve damage during laparoscopic surgery for resection of rectal cancer are needed. Structured education of surgeons on pelvic neuroanatomy, and systematic registration of identified nerves, could well be the key to improving functional outcome for these patients. Meanwhile, patients should be informed of all associated risks before their operation, and their functional status should be evaluated before and after surgery [67,68].

4. Urologic dysfunctions

Bladder dysfunction has been reported to occur in 7-68% of patients after resection of low rectal cancer, although its incidence is generally around 30% in most reports [69]. This kind of dysfunction includes various symptoms such as incomplete bladder voiding, mictional urgency, overflow or stress incontinence, loss of bladder sensation, dysuria, and chronic infections of the urinary tract. As with sexual dysfunction, most of these difficulties have a neurogenic origin related to parasympathetic denervation. After an abdominoperineal resection in men, 50% will have a neurogenic bladder, but
with recovery within 3 to 6 months after surgery in most cases [69,70]. Also as with sexual problems, the incidence is higher in elderly people, due to the presence of benign prostatic hypertrophy (particularly in this age group), which contributes to urologic dysfunction.

Another associated cause of these problems is mechanical: surgery can cause an angulation that contributes to these symptoms. These dysfunctions are more often associated with abdominoperineal resection than with anterior resection [71]. Once again, favorable outcomes may be achieved by careful sharp dissection with preservation of pelvic anastomotic nerves [71].

**Issues related to radiation therapy**

Several randomised studies have evaluated the role of radiation therapy and chemotherapy as adjuvant treatments in rectal cancer. After these trials, two consensus conferences, one American (NIH Consensus Conference 1990) and the other German (German Cancer Society Consensus Conference 1998), concluded that the combination of radiation therapy and chemotherapy was the preferred adjuvant treatment for patients with rectal cancer stages II and III [72-78]. Radiation therapy decreases local recurrence, and chemotherapy based on fluoropyrimidines increases survival at five years by 10-15%.

Kollmorgen *et al.* [36] have assessed the long-term effect of postoperative chemoradiotherapy on bowel function in a retrospective way. They studied patients undergoing anterior resection for Astler-Coller stage B2 or C rectal carcinoma who were given postoperative radiation therapy with chemotherapy. One hundred patients were suitable for inclusion and participated in a telephone questionnaire; 41 patients had postoperative chemoradiotherapy, and 59 did not. Both groups were well matched for basal characteristics. The authors found that the group receiving chemoradiotherapy had more bowel movements per day than the other group (median of 7 vs. median of 2, \( P < 0.001 \)); the former group had higher frequencies of "clustering" of bowel movements (42% vs. 3%, \( P < 0.001 \)), nocturnal movements (46% vs. 14%, \( P < 0.001 \)), occasional or frequent incontinence (39% and 17% vs. 7% and 0%, \( P < 0.001 \)), pad use (41% vs. 10%, \( P < 0.001 \)), and an inability to defer defecation for more than 15 minutes (78% vs. 19%, \( P < 0.001 \)). The group that received chemoradiotherapy also had liquid stools, used antidiarrheal medications, had perianal skin irritation, was unable to differentiate stool from gas, and needed to defecate again within 30 minutes of a movement significantly more often than the group that did not receive chemoradiotherapy. From these findings, the authors concluded that adjuvant postoperative chemoradiotherapy for rectal carcinoma has a major long-term detrimental effect on bowel function.
Bowel function after radiation therapy, then, is an important functional issue. Several studies have found consistent results showing that bowel function in patients, as measured by frequency, urgency, evacuation, sensation, and/or continence, is impaired after radiation therapy when compared with patients not treated with radiation.

The Swedish Rectal Cancer randomised controlled trial [79] has shown that preoperative high-dose radiotherapy improves survival and decreases local recurrence in patients who underwent anterior resection for rectal cancer. The trial also found that the median frequency of bowel movements was higher in the group receiving radiotherapy and surgery compared to the surgery-only group (20 vs. 10 bowel movements per week, \( P < 0.0001 \)). Also, urgency, voiding difficulties, and incontinence for loose stools were more common in the radiation group (all \( P < 0.0001 \)). In terms of QOL, 30% of the radiation group stated that their social life was impaired because of bowel dysfunction compared to 10% of the surgery-only group (\( P < 0.01 \)). Dehni et al. [80] found similar results that the irradiated group had more diarrhea (39% vs. 13%, \( P = 0.005 \)) and more nocturnal defecation (36% vs. 15%, \( P = 0.03 \)) compared with the nonirradiated group.

Pucciarelli et al. [81] evaluated the long-term complications after preoperative chemoradiotherapy for rectal cancer. They recruited 123 consecutive patients with locally advanced mid-low rectal cancer who underwent preoperative chemoradiotherapy. Complications were defined as late if they occurred more than 6 months after surgery. At a median follow-up of 95 (range, 56-160) months, 50 late complications occurred in 41 patients, 21 of whom required surgery. Several of these complications were clearly related to chemoradiotherapy and were significantly associated with the total dose of radiation delivered (\( P < 0.05 \)). These authors concluded that late morbidity after this treatment is relevant and related to the radiotherapeutic dose used.

In a study of men with symptoms of radiation damage 2-6 years after radiation therapy for prostatic carcinoma, resting anal pressure and anal sphincter length were significantly decreased compared with age-matched controls [82]. Significant reductions in rectal capacity and compliance have also been found [83]. Histologic examination of specimens from patients who underwent a proctectomy for radiation injury commonly revealed hypertrophy of the muscularis mucosae and the muscularis propria, with degeneration of both Meissner's and Auerbach's plexi, and significant damage to the tissues surrounding the anus and rectum [84]. All these problems could contribute to long-term changes in bowel function. Magnetic resonance imaging of the pelvis after radiation therapy has demonstrated alterations in the signal from striated muscle, with thickening of the perirectal fascia and presacral space [85]. All these physiologic and pathologic changes evolve over a prolonged period.
In a study of 20 patients who underwent preoperative radiation for rectal carcinoma, the anal-sphincter pressures had not decreased when measured four weeks after the radiation was completed [86]. Furthermore, histologic examination of the excised specimens revealed only minimal changes. A different study reported nine patients who underwent postoperative radiation therapy after anterior resection [87]. Although the selection criteria for this study were not stated, the neorectal capacity and compliance were lower in these patients than in patients who had not undergone radiation therapy. With all these aspects in mind, we must conclude that radiation therapy, although with benefits, can have potentially serious late effects for the survivors of rectal cancer. Acute complications are discussed in detail in another chapter of this book. For all these survivors who underwent radiation therapy, the evaluation of morbidity, pelvic-floor function, and QOL is important.

Globally, delayed radiation toxicities have been reported several times and include radiation enteritis (4%), small-bowel obstruction (5%), and rectal stricture (5%), in addition to the bowel, sexual, and urinary dysfunction discussed earlier that may be aggravated by radiation-induced injuries to pelvic nerves.

Nathanson et al. [88] evaluated patients with rectal cancer 2-8 years following surgical resection with preoperative radiation, postoperative radiation, or no radiation. The postoperative radiation group had more episodes of clustered bowel movements ($P < 0.02$) than either the preoperative radiation group or the no-radiation group. The authors attributed the adverse effects of postoperative radiation therapy to irradiation of the neorectum, which is spared when radiation is given preoperatively.

**Issues related to chemotherapy**

Many patients with CRC have been treated with oxaliplatin in combination with fluoropyrimidines in the adjuvant or neoadjuvant context. This combination is generally well tolerated. The secondary effects most often reported have been haematologic, rarely exceeding grade 3, digestive (such as nausea, vomiting, diarrhea, etc.), mucositis, early-onset cold-induced dysesthesias, and a cumulative peripheral sensory neuropathy. These symptoms are acute, leading to a delay of cycles or even a cessation of chemotherapy, except for neuropathy.

**a. Neurosensory syndrome**

The occurrence of peripheral sensory symptoms was noted during the first phase I clinical trial [89]. The symptoms reported can be separated into two
distinct categories: a cold-induced dysesthesia with a rapid onset of hours to days following treatment, and a late-onset cumulative sensory neuropathy observed after multiple cycles of therapy. Acute onset is common (80-85% of patients); in fact, it is the most common form of acute neuropathic toxicity. It appears within hours of infusion and is usually short-lived without any sequelae. It is rarely debilitating since patients can adapt by avoiding cold stimuli.

The temporary loss of awareness of breathing is relatively uncommon but is probably the most alarming symptom. Patients must be warned about these symptoms and their transient nature prior to the administration of chemotherapy. Acute oxaliplatin-associated neurotoxicity can result in other disturbing symptoms such as visual-field cuts, blurred vision, and ptosis [90]. A dose-limiting peripheral sensory neuropathy occurs in 10-15% of patients after a total cumulative dose of 780-850 mg/m² [91-93]. This neuropathy begins as a persistent paresthesia after multiple cycles of oxaliplatin. A physical examination detects decreases in proprioception, vibration perception, and fine-point discrimination. The patients complain about difficulty in writing and the impairment of such fine manipulations as buttoning a shirt. The duration of these symptoms increases with an increase in the number of cycles. A 25% reduction in dose is thus recommended when these symptoms become persistent between cycles. Cessation of treatment is recommended in cases where worsening symptoms lead to functional impairment.

This syndrome is reversible in most cases after discontinuation of the treatment, with a median time of recovery of 15 weeks. These symptoms, however, sometimes persist and reduce the QOL of the survivors, with a perception of increased difficulty with current or daily activities. These patients generally have received a cumulative dose higher than 780 mg/m² [91-93]. The combination of oxaliplatin with 5-FU is associated with persistent neuropathy in 48% of these patients.

Due to stringent guidelines for dose modification, only a small proportion of patients experience serious functional impairment. However, as the cumulative dose of oxaliplatin increases, patients are more likely to experience paresthesia due to a cumulative sensory neuropathy. In patients who receive more than six cycles of chemotherapy (projected maximum cumulative dose given every three weeks of 780 mg/m²), the neuropathy can become persistent and affect the subject's ability to perform routine activities of daily living. Oxaliplatin-associated cumulative sensory neuropathy is slowly reversible in most patients [91-93].

Oxaliplatin-related neurotoxicity has no standard treatment. A variety of strategies have been employed to prevent or treat neurotoxicity to oxaliplatin [92,94,95], including treatment with carbamazepine, gabapentin, alpha lipoic acid, amifostine, glutathione, or celecoxib. The largest study of oxaliplatin-
related neurotoxicity is the retrospective analysis by Gamelin et al. [96]. It evaluated the benefit of infusing magnesium and calcium prior to administration of oxaliplatin in 96 patients compared to 65 patients who did not receive magnesium/calcium. The percentage of patients with grade 3 distal paresthesia was lower in the Ca/Mg group (7% vs. 26%, \( P = 0.001 \)), and acute symptoms such as distal and lingual paresthesia were much less frequent and severe in the Ca/Mg group. The authors concluded that Ca/Mg infusions seemed to reduce the incidence and intensity of acute oxaliplatin-induced symptoms and might delay cumulative neuropathy.

Despite these data, a large, randomised trial will be required to clarify the link between acute, transient symptoms and the likelihood of development of chronic sensory neuropathy, and to confirm whether strategies such as Ca/Mg infusions reduce the neurotoxicity without impacting on anti-tumour efficacy. Optimising the QOL of cancer survivors is of paramount importance, and continued research on oxaliplatin will help achieve this goal while also providing further progress in clinical benefit outcomes.

**Conclusion**

The number of long-term survivors from CRC (> 5 years after diagnosis) continues to rise and increasing attention to the health problems and needs of this population has appeared. Many CRC survivors could return to a normal functioning after the completion of treatment and could live relatively without symptoms. However, cancer and its treatments can also provoke a wide spectrum of physical and psychological problems without improvement with time, which can affect the patients’ QOL.

Although it is necessary more research to better understand these problems, the identification, surveillance and management of survivorship issues is a very relevant part of a survivorship care plan which would allow cancer survivors to be aware about the problems they are expected to present and the adequate strategies they could begin to alleviate and mitigate the impact of these long-term issues can have in their lives.

**References**

Colorectal cancer survivors


