

After the Treatment Phase of Colorectal Cancer Care: Survivorship and Follow-Up

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ABSTRACT

The number of long-term colorectal cancer (CRC) survivors has increased substantially over the past three decades due to both ongoing advances in early detection and improvements in cancer therapies. Adult survivors of CRC experience chronic health conditions due to normal issues associated with aging, which is further compounded by the long-term adverse effects of having had cancer and anti-cancer therapies. In addition, they are at a higher risk for CRC recurrences, new primary cancers, and other co-morbidities. This article will provide an overview of the clinical care of adult survivors of CRC. Epidemiologic data will be presented followed by a discussion of the approach to the care of long-term adult survivors of CRC, including surveillance of recurrences and new primary cancers, interventions to manage both physical and psychological consequences of cancer and its treatments, and strategies to address concerns related to unemployment and disability. Finally, we will explore the challenges of healthcare delivery, especially with respect to the coordination of follow-up between cancer specialists and primary care physicians, so as to ensure that all of the survivor's health needs are met promptly and appropriately.

Keywords: Colorectal Cancer; Survivorship Care; Surveillance of CRC

1. Introduction

In recent years, CRC has become one of the most commonly diagnosed cancers for both men and women globally [1]. Currently, there are approximately 150,000 new cases of CRC annually in the United States (US) alone where it accounts for 9% of all cancer deaths [2]. Age is a major risk factor for CRC, with 90% of sporadic CRC occurring after the age of 50 [3]. Among newly diagnosed CRCs, 39% of cases present with localized disease, and another 37% present with lymph node involvement. The majority of these patients are eligible for curative-intent surgery [4]. However, among the 20% of patients who present with metastatic disease, only those with isolated liver or lung metastases may be considered for curative-intent surgery. Over the past two decades, early detection and more effective treatments have resulted in an increasing number of CRC survivors in the US [5-7]. These survivors experience long-term effects of having had cancer therapy in addition to normal health issues related to aging. As patients transition away from regular specialist visits upon completion of active cancer treatment, primary care providers may be inadequately informed about surveillance of these patients and the complications that may arise from treatment leading to wide variation in care.

2. Risk of Recurrence

Surgical resection remains the primary treatment modality for CRC patients who present with localized disease. Unfortunately, more than 40% of patients who present with stage II or III CRC eventually relapse despite potentially curative surgery [8]. The majority of recurrences (>90%) develop within the first five years of diagnosis, and most commonly within the first three years [9]. Unlike colon cancers, rectal cancers have a higher rate of local recurrence after surgery due to the challenges of obtaining clear radial margins. The most important indicator of outcome after curative surgery is the pathological stage at presentation. According to the population-based SEER database, five-year survival rates for CRC range from over 90% for stage I disease to 8% for stage IV disease. Rectal cancer statistics are very similar, although slightly worse stage for stage than for colon cancer [10]. These data underscore the importance of vigilant follow-up after surgery.

3. Surveillance after Resection

Despite curative surgery and modern adjuvant treatment with chemotherapy and radiation therapy, more than 40% of patients who initially present with stage II or III CRC

will relapse. The main purpose of surveillance is to promptly identify patients who may still be cured by surgical intervention and to screen for second primary cancers. Numerous studies have shown that early detection of recurrences results in improved survival. For example, resection of localized recurrences that are limited to only the liver can lead to cure for some patients. Specifically, patients who undergo successful partial hepatectomy for limited hepatic metastases can achieve favorable long-term outcomes, with five-year survival rates approximating 40%. Similar results have also been reported in selected patients with lung metastases [11,12]. In addition, studies have shown that resection of asymptomatic rather than symptomatic recurrences is more likely to result in cure and portends a more favorable outcome after surgery [13-15].

Three meta-analyses examining intensive versus symptom-based surveillance strategies revealed a significant survival benefit from intensive follow-up of CRC [16-18]. However, the optimal combination and frequency of surveillance tests still remain unclear. Currently, the American Society of Clinical Oncology recommends history, physical examinations, and carcinoembryonic antigen (CEA) measurements every three months for at least the first three years in patients with stage II or III CRC, particularly if they are candidates for potential curative surgery or systemic therapy should a relapse be found. They should also undergo annual computerized tomography

(CT) scans of the chest and abdomen for the first three years. Routine CEA monitoring and CT scanning are not recommended beyond five years (see **Table 1**) [19].

In contrast, ongoing surveillance for stage I CRC other than routine colonoscopy is currently not recommended. Aggressive surveillance consisting of regular CEA measurements and imaging with chest x-rays or CT scans is not routinely performed, mainly because of a high cure rate of close to 95% with surgery alone. There has been a trial studying the salvage rates of stage I or IIA CRC patients who underwent routine screening with CEA, chest x-ray, and colonoscopy [20]. Although the salvage rates after recurrences detected by screening are quite high (37%), the overall number of recurrences detected in this study group was quite low (less than one percent of patients), and hence the absolute benefit of aggressive screening remains minimal [20].

4. Complications of Surgery

Surgical resection is the cornerstone of curative therapy for localized colon and rectal cancer. Morbidities in the immediate post-operative period after open colectomy include prolonged ileus, small bowel obstruction, intra-abdominal complications such as injury to adjacent organs, bleeding and infection [21,22]. Small bowel obstruction is the most common complication in the early postoperative period mostly because of the potential presence of inflammatory peritoneal adhesions [23,24].

Table 1. 2005 colorectal cancer surveillance guidelines from the American Society of Clinical Oncology (ASCO).

History and physical examination
Every three to six months for the first three years; every six months during years 4 and 5, then annually thereafter.
Carcinoembryonic antigen (CEA)
Serum CEA testing should be performed every three months for at least three years in patients with stage II or III colon or rectal cancer if they would otherwise be candidates for surgery or systemic therapy. Since adjuvant 5-FU-based therapy can falsely elevate the serum CEA, waiting until adjuvant therapy is finished to initiate surveillance is advised.
Computed tomography
Patients with colon or rectal cancer at higher risk of recurrence (stage III or stage II with multiple poor risk features) should undergo annual CT of the chest and abdomen for three years if they would otherwise be eligible for curative intent surgery.
Annual pelvic CT for three years should be considered for rectal cancer surveillance, particularly if the patient has not been treated with pelvic radiation therapy.
Colonoscopy
All patients with colon or rectal cancer should have a full colonoscopy in the preoperative or perioperative setting to document a cancer-free and polyp-free colon. Patients who present with an obstructing cancer should undergo full colonoscopy within six months of surgery. Repeat colonoscopy is recommended at three years, and if normal, every five years thereafter. For patients with high-risk genetic syndromes, the panel recommended that the screening guidelines of the American Gastroenterology Association be followed.
Flexible proctosigmoidoscopy, rectal cancer
For patients who have not received pelvic radiation therapy, direct visualization of the rectum with flexible proctosigmoidoscopy is recommended every six months for five years.

The majority of cases, however, resolves with conservative management alone [24]. Surgery is reserved for cases involving persistent obstruction (despite nasogastric tube drainage), high grade obstruction, or ischemic bowel. Most patients will also experience a slight increase in the frequency of their bowel movements, but some will have significant diarrhea. Bowel patterns usually return to normal after a period of adaptation over four to six months. A variety of intra-abdominal complications can occur during CRC surgery such as injury to adjacent organs and surgical site infection. Due to the close proximity of the colon to the spleen, the risk of splenic injury may be as high as 8% [25,26]. Intraoperative splenic injury is usually managed with splenic salvage (e.g. primary repair) with splenectomy being reserved for cases involving uncontrollable bleeding [27]. The effect of splenectomy on CRC outcomes following resection remains controversial at the present time [25, 28]. On the other hand, the incidence of injury to the small bowel ranges from one to three percent during colonic procedures [29,30]. Multiple enterotomies occurring in a short segment of bowel are repaired by primary segmentectomy with a primary anastomosis. In contrast, a single enterotomy involving the full thickness of the bowel wall is repaired in one or two layer closures. The rate of surgical site infection following CRC surgery ranges from one to 30% depending on the definition used and the specific type of procedure performed [31,32]. The risk of surgical site infection increases with preoperative blood transfusions, obesity, ostomy creation and placement of a drain [31]. Peri-operative mortality and hospital stays are significantly higher in patients with surgical site infection following CRC surgery [31].

There are three major surgical options for rectal cancer including a local excision, a sphincter-sparing procedure (SSP) and an abdominoperineal resection (APR). Local excision is used to treat rectal cancers with non-aggressive features (e.g., T1 lesion, less than 3 cm in diameter). A SSP includes resection of the sigmoid colon and rectum with a primary anastomosis between the descending colon and rectum or anal sphincter. An APR, on the other hand, involves resection of the sigmoid colon, rectum, and anus, and the construction of a permanent colostomy. Most patients, however, will require the latter two surgical options due to deeply invasive tumors that cannot be treated with local excision. Overall, long-term quality of life after an APR has been shown to be very similar to a SSP [33,34]. Research has demonstrated that patients who undergo an APR may experience more depression and negative changes in body self-image due to the need for a permanent colostomy [35]. However, in a prospective study comparing patients who received a SSP versus an APR, quality of life was shown to be worse in patients who underwent a SSP with an anastomosis within 5 cm

of the anal verge due to high rates of fecal incontinence and increased stool frequency. Thus, an APR should be the procedure of choice for patients with rectal cancer involving the anal sphincter musculature or rectovaginal septum, poor continence preoperatively, or pre-existing diarrhea, where a low anastomosis would result in fecal incontinence [36]. Additional factors that increase the risk of fecal incontinence include radiation administered preoperatively or postoperatively and concurrent chemoradiotherapy in the peri-operative period [37,38]. Fecal incontinence can be treated with medications to decrease stool frequency, pelvic floor exercises to strengthen the abdominal wall muscles, and surgery [39-41].

Pelvic dissection during colorectal surgery may potentially lead to urinary problems and sexual dysfunction resulting in infertility. The incidence of voiding difficulty is highest among those who have undergone an extensive pelvic dissection and APR [42]. Up to 12% of patients may have persistent urinary dysfunction beyond the 20-day postoperative period [42]. Similarly, sexual dysfunction post-proctocolectomy depends on the extent of the dissection of the pelvic nerves. Additional predisposing factors include advanced age, radiation, APR, and total mesorectal excision [43-45]. On average, 30% to 40% of previously sexually active patients reported sexual dysfunction following treatment [46]. Unfortunately, physicians seldom address sexual dysfunction at the time of CRC treatment or during follow-up care. There are currently many therapies available for men (including testosterone replacement and various intracavernous pharmacologic therapies), highlighting the fact that these problems can be addressed effectively if given the opportunity [47,48].

A significant number of CRC patients require either a temporary or permanent colostomy. Patient undergoing ostomy surgery must adapt to a new pattern of fecal elimination and to a significant alteration in body image. An ostomy has many complications including skin irritation, lack of bowel control, as well as negative effects on social, emotional and sexual function. In particular, patients may experience concerns regarding their self-image and difficulties with sexual intimacy. Patients should be counseled to empty the pouch regularly and prior to sexual intercourse. These issues may decrease overall quality of life of CRC survivors and contribute to higher rates of depression. Therefore, these issues warrant attention and follow up while providing survivorship care [49, 50].

5. Complications of Radiation

Patients treated with pelvic radiation for rectal cancer may develop complications including acute and chronic radiation proctitis, pelvic fractures and second malignancies. Acute radiation induced proctitis usually manifests

within six weeks of radiation therapy and is caused by direct damage to the rectal mucosa. The majority of cases resolves upon discontinuation of radiation therapy and does not require any treatment [51,52]. Chronic proctitis, however, usually presents within one year of radiation exposure, but it can occur anytime up to 30 years after radiation exposure [53,54]. Symptoms of proctitis include diarrhea, rectal urgency, pain and obstruction. CRC survivors should be made aware of these side effects so they can seek prompt medical attention if these symptoms develop. Colonoscopy is typically recommended to exclude other causes of proctitis. Management is tailored to the specific symptoms and their intensity.

Pelvic radiation may also predispose patients to bone loss and fractures. Other risk factors include concurrent chemoradiation, use of steroids, heparin, thyroid hormone therapy, and lack of estrogen [55]. As a result, patients who are at risk should undergo regular monitoring of bone density and should be advised to seek appropriate treatments for osteopenia and osteoporosis [55,56]. Radiation associated secondary malignancies are extremely rare and the magnitude of risk remains unclear. A large retrospective cohort study of patients undergoing pelvic radiotherapy for vulva, cervix, uterus, anus and rectosigmoid cancer showed that pelvic radiation was associated with an increased risk of secondary leukemia [57]. There are currently no studies examining the specific risk of secondary malignancies after radiation treatment for rectal cancer.

6. Complications of Systemic Therapy

A number of specific chemotherapeutic agents can be administered in the adjuvant setting following CRC resection in order to decrease the risk of relapse. Options include 5-fluorouracil (5-FU), capecitabine, and oxaliplatin. Fortunately, most of the common treatment-related toxicities, such as diarrhea, mucositis, febrile neutropenia, and hand-foot syndrome, are temporary and are usually quickly reversible upon treatment discontinuation. The agent 5-FU is frequently used and represents the second most common cause of chemotherapy-induced cardiotoxicity. Risk factors include the infusional form of 5-FU, pre-existing coronary artery disease, and concurrent administration of anthracyclines and/or radiation [58,59]. Cardiac symptoms range from chest pain, arrhythmias, pericarditis, to acute pulmonary edema, but almost all of these typically resolve soon after discontinuation of 5-FU [60]. Re-challenging patients with history of cardiac toxicity remains controversial. Other common acute side effects associated with 5-FU include hand-foot syndrome, which is also known as plantar-palmar erythrodysesthesia. Patients may initially present with tingling sensations in the palms and soles, but this can be followed by sym-

metrical erythema and swelling that involve mostly the fat pads of the distal phalanges [61]. Severe cases may result in functional impairment. Fortunately, hand-foot syndrome resolves within 2 to 4 weeks after cessation of therapy. For patients who develop severe reactions, the only remedy is to either omit the chemotherapy completely or reduce the dose in subsequent cycles in order to prevent worsening of this potentially debilitating symptom [62].

One of the most notorious long-term side effects of CRC chemotherapy is oxaliplatin-induced peripheral neuropathy. Symptoms include numbness, tingling and cold-induced pain. Two distinct syndromes have been reported with oxaliplatin: an acute neurosensory complex, which can appear during or shortly after the first few chemotherapy infusions, and a cumulative sensory neuropathy, with distal loss of sensation and dysesthesias [63]. Over 10% of patients will still report mild persistent neuropathy at four years after treatment. For patients who have severe symptoms, treatment with anti-convulsants, such as gabapentin, along with a concomitant referral to occupational and physical therapy may be beneficial, although the evidence to support such an approach is lacking [64].

7. Psychosocial Sequelae

As expected, cancer survivors generally experience more psychological impairment when compared to the general population, including slow adjustment to physical changes, persistent fears of cancer recurrences or developing a new cancer, and problems with re-integration into social relationships. Specifically, CRC survivors may experience psychosocial distress related to a progressive decline in anorectal function (including increased stool frequency, more fecal incontinence and decreased rectal compliance) and having an ostomy which leads to reduced social, emotional, sexual and occupational functioning. A survey of CRC survivors revealed that 7% of patients still suffered from psychosocial distress at 12 months post-diagnosis [65]. In this particular study, initial distress at six months post-diagnosis, multiple comorbidities, and the lack of social supports were found to be associated with increased distress at 12 months. Another study revealed that a higher rate of depression is still persistent at five years in comparison to the general population. Furthermore, females, African Americans, patients with two or more co-morbid conditions or patients with restricted physical and social functioning were found to exhibit more depressive symptomatology [66]. These results suggest that CRC survivors may benefit from regular depression screening during their survivorship care.

Many CRC survivors also experience difficulties with

social relationships and unemployment. Some patients have to reduce their time at work because of treatment or residual physical and psychological effects from their cancer [67]. A study in 2000 revealed that 18% of CRC survivors were not able to work in comparison to only 10% of non-cancer controls matched by age and gender. Furthermore, approximately 30% of patients were limited with respect to the type and amount of work that they could do, which could lead to demotion or denial of promotion [68]. Specifically, a prospective cohort study of non-metastatic CRC patients revealed that although most employed patients successfully returned to work, CRC survivors with lower socioeconomic status and advanced age were at higher risk of leaving the labor force than their non-cancer counterparts [69].

8. Coordination of Care

Due to advances in screening and therapeutic strategies, many patients diagnosed with CRC today will not necessarily die as a direct result of their malignancy. In fact, the proportion of patients who will be cured of their cancer is expected to increase over the next several decades. Preliminary studies indicate that second primary cancers and potentially preventable conditions, such as heart disease and diabetes, have become the greatest threats to life for many cancer survivors. Studies have also found that only 32% of adult survivors receive survivor-focused care and only 18% receive advice about future disease prevention. Failure to engage in such routine medical follow-up represents a missed opportunity for early detection, prevention, risk modification and optimal management of late effects [70]. Recent studies have revealed that follow-up of the primary malignancy may shift attention away from other medical needs. For example, studies indicate that survivors of CRC compared with matched controls were less likely to receive treatment for chronic conditions, such as ischemic heart disease. Patients followed exclusively by family physicians underwent fewer surveillance tests for cancers, while those seen primarily by oncologists obtained less non-cancer related care [71]. This finding suggests that there may be a lack of clarity surrounding the relative roles that primary care physicians, specialists, and patients play in cancer survivorship care planning.

To address this, a variety of care models have been proposed in order to improve coordination of care between specialists and primary care physicians. A committee established by the Institute of Medicine (IOM) recommended that “patients completing their primary treatment should be provided with a comprehensive care summary and follow-up plan that is clearly and effectively explained”. This document is known as the Survivorship Care Plan and it is meant to be an important tool

to facilitate communication between primary care physicians and oncologists in light of the uncertainties about physician roles and responsibilities which can lead to deficiencies in care. However, most health care providers have found it difficult to alter the way they care for cancer survivors due to the weak evidence base in survivorship care, remuneration challenges and workload burden [72]. Therefore, more efforts are still required to further determine the most essential elements of survivorship care.

9. Conclusion

The transition from active treatment to post-treatment care is known as survivorship care. It involves surveillance for cancer spread, recurrence, or second cancers; prevention of recurrent or new cancers; and assessment of medical and psychosocial late effects; and interventions for the consequences of cancer and its treatment. Failure to engage in such routine medical follow-up represents a missed opportunity for early detection, prevention, risk modification and optimal management of late effects. Although progress has clearly been made in this area over the last few years than previously, there is still much room for improvement. Further research is needed in identifying the essential elements of care that have a positive impact on morbidity, mortality and quality of life of all cancer survivors. In addition, the health care community needs to be educated about the importance of survivorship care [72]. In order to ensure that the gains from recent diagnostic and treatment advances are not lost, the consistency and quality of cancer and non-cancer related follow-up among adult survivors of cancer must be optimized.

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