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RADIATION THERAPY AND RADIATION THERAPY INNOVATIONS IN COLORECTAL CANCER (PP LEE AND AC RALDOW, SECTION EDITORS)

Toxicity Management in the Era of Changing Treatment Paradigms for Locally Advanced Rectal Cancer

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Abstract

Purpose of Review Treatment paradigms for locally advanced rectal cancer have evolved over the last several decades. Patients now have several different "standard" options with different radiation courses, sequencing of treatment modality and in some scenarios potentially avoidance of surgery. In this context, an updated understanding of treatment toxicity is needed to help patients make informed decision regarding their treatment.

Recent Findings The RAPIDO study showed no difference in cumulative rate or grade of toxicity between short and long course radiation. Based upon our experience, patients with short course radiation tend to present with acute symptoms 1–2 weeks after completion of radiation, while those receiving long course chemoradiation have symptoms towards the end of treatment. Treatments that may be helpful particularly for short course radiation toxicity include Bentyl (dicycloverine) and steroids.

Summary The most common toxicities from radiation are due to bowel and rectal inflammation leading to diarrhea, cramping, and urgency. The combination of surgery and radiation can exacerbate these symptoms. The most common late toxicity in patients receiving doublet chemotherapy is neurotoxicity. Rates of infertility differ in men versus women; all efforts for fertility preservation should be completed prior to initiation of any therapy.

Keywords Rectal cancer · Radiation toxicity · Trimodality therapy · Enteritis · Proctitis

Introduction

Treatment paradigms for locally advanced rectal cancer have evolved over the last several decades. After the publication of the German Rectal Trial in 2004 [1], the main standard of care in the USA was long course chemoradiation, surgery, followed by adjuvant 5-FU-based chemotherapy. More recently, there has been a shift to completing chemotherapy upfront via a strategy of total neoadjuvant therapy (TNT) with the goal of maximally downstaging the primary tumor, improving rates of chemotherapy completion and gaining early control of micro-metastatic disease. Some TNT regimens use chemotherapy before versus after radiation, and radiation can be delivered over 5 weeks (long course chemoradiation) or 1 week (short course radiation). The TNT strategy has resulted in some patients achieving a complete response to chemotherapy and radiation, such that they may be able to avoid surgery. Given the multiple available treatment options, there has been increasing emphasis on patient choice of therapy, based upon values regarding treatment logistics, desire for organ preservation, and other factors. To help patients make the most informed decision, an accurate understanding of treatment toxicity, and ways to mitigate them, is needed. In this work, we will review toxicities associated with treatment for rectal cancer, with a focus on radiation toxicity, and discuss management strategies.

This article is part of the Topical Collection on *Radiation Therapy and Radiation Therapy Innovations in Colorectal Cancer*

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Treatment Toxicities

Pelvic radiation-related toxicity depends on several factors: radiation dose delivered, radiation modality, total treatment time, patient and tumor anatomy, and radiation sensitivity of the patient. Based upon our current cumulative knowledge base, the last factor, radiation sensitivity, is often unknown until the patient completes therapy with (or without) a certain degree of toxicity. Furthermore, the addition of radio-sensitizing chemotherapy can exacerbate toxicity, and whether a patient undergoes surgery can also alter gastrointestinal toxicities as well as affect time to recovery. Despite these complicating factors, categorizing radiation toxicity is important. Radiation toxicity is generally divided into two categories: acute and late. Acute toxicities include those that occur during, or shortly after treatment. Identifying acute toxicities is more straightforward since patients are followed closely during therapy, and particularly those on clinical trials are often have detailed symptom documentation. Late toxicities begin months after completion of therapy and can last or appear over the rest of an individual's lifespan; they can be irreversible. Late toxicities are harder to capture since patients are no longer attending appointments for treatment, and some are lost to follow-up. The acute and late toxicities we discuss with our patients receiving radiotherapy for rectal cancer are listed in Table 1.

Focusing on recently published studies, RAPIDO was a randomized trial comparing a strategy of TNT starting with short course radiotherapy versus "standard" treatment of neoadjuvant long course chemoradiation and adjuvant

Table 1 Acute and late toxicity from radiotherapy for rectal cancer

Categories	Acute toxicity	Late toxicity
Common	- Bladder inflammation causing burning, frequency, spasm, discharge, bleeding - Inflammation of bowel causing cramping and diarrhea - Inflammation of rectum and anus causing pain, spasm, discharge, bleeding - Tiredness - Depression of blood counts leading to increased risk of infection and/or bleeding - Disturbance of menstrual cycle (female only)	- Ovarian damage causing infertility, sterility, or premature menopause (female only)
Uncommon	- Skin changes: redness, irritation, scaliness, blistering, or ulceration, coloration, thickening, and hair loss - Vaginal discharge, pain, irritation, and bleeding (female only) - Nausea	- Bowel damage causing narrowing or adhesions of bowel with obstruction, ulceration, bleeding, chronic diarrhea or poor absorption of food elements and may require surgical correction of colostomy - Bladder damage with loss of capacity, frequency or urination, blood in urine, recurrent urinary infections, pain, or spasm which may require urinary division and/or removal of bladder - Bone damages leading to fractures - Changes in skin texture and/or coloration, permanent hair loss, and scarring of skin - Vaginal damage leading to dryness, shrinkage, pain, bleeding, or sexual dysfunction (may result in pain with intercourse) (female only) - Scarring of the vaginal wall; narrowing of the vaginal cavity (female only) - Impotence (loss of erection) or sexual dysfunction (male only) - Testicular damage causing reduced sperm counts, infertility, sterility, or risk of birth defects (male only)
Rare		- Bowel complications requiring surgical procedure - Pelvis and hip fracture
Extremely Rare	- Severe diarrhea and dehydration requiring hospitalization	- Cancers caused by radiation - Rectal or urinary bleeding requiring transfusion or surgery - Nerve damage causing pain, loss of strength or feeling in legs, and/or loss of control of bladder or rectum - Fistula between the bladder and/or bowl and/or vagina - Swelling of genitalia or legs
Children		- Disturbances of bone and tissue growth - Bone damage to pelvis and hips causing stunting of bone growth and/or abnormal development - Secondary cancers developing in the irradiation area

chemotherapy [2••]. The primary endpoint was 3-year disease-related treatment failure, defined as locoregional failure, distant metastasis, new primary colorectal tumor, or treatment-related death. There were a total of 920 patients enrolled. The experimental arm of short course TNT had lower rates of disease-related treatment failure at 3 years (23.7% vs. 30.4%), mostly driven by distant metastases. The initial study reported rates of acute toxicity. Notably, rates of Grade 3 + toxicity were 48% during TNT for the experimental arm. In the standard arm, 25% and 35% had Grade 3 + toxicity pre- and post-operatively [3]. For both groups, diarrhea was the most common Grade 3 + toxicity pre-operatively (18% experimental vs. 9% standard), and neurotoxicity was the most common post-operatively in those receiving adjuvant chemotherapy (16%). The study authors recently published on quality of life and late toxicity [4••] reporting on patients who did not experience disease-related treatment failure. Measurement indices included the validated EORTC QLQ-C30, QLQ-CR29, QLQ-CIPN20, and lower anterior resection syndrome (LARS) questionnaires. There were no significant differences observed between the two groups, which were reassuring in demonstrating that short course TNT did not increase late toxicity as compared to the historical standard regimen. Notably however, late toxicity rates were overall high. Major LARS occurred in ~ 65% of patients. At 6 months post-treatment, approximately 56% of patients in both groups continued to experience toxicity, which declined to approximately 30% at 3 years. Neurotoxicity, presumably from oxaliplatin chemotherapy, was the most commonly reported toxicity.

Owing to the fact that there are more younger patients diagnosed with colorectal cancer, and their treatments may differ from older patients whose comorbidities may preclude them from receiving full intensity trimodality therapy, investigators at Fox Chase compared rectal cancer treatment toxicity between patients ≥ versus < 65 years [5••]. Of a total 123 patients, the older subset had higher rates of hematologic toxicity and hospitalization but no difference in non-hematologic toxicities.

Together, these studies, among many others, suggest that a substantial subset of patients experience high degrees of toxicity, often long-lasting, after treatment for rectal cancer.

Management Strategies

The main toxicities of treatment are gastrointestinal with symptoms caused by radiation enteritis (injury to small and large intestines) and proctitis (injury to rectum and anal canal). Acutely, no additional diagnostic work-up is needed if symptoms are consistent; however, in the late/chronic setting, endoscopy and biopsy should be performed to rule out other etiologies. In the acute setting, management includes anti-diarrheal medications such as imodium (loperamide) or lomotil (diphenoxylate/atrophine). Opioids, in addition to helping with pain, can also slow down bowel movements.

Given the results of the RAPIDO study above, and due to the COVID-19 pandemic increasing the need for hypofractionated radiotherapy, more patients are treated with short course radiation therapy. With this regimen, patients must be informed that radiation treatment toxicity usually happens *after* treatment is over, usually beginning approximately 1–2 weeks later. For this reason, a post-treatment check-up around that time is highly recommended, since patients often start chemotherapy a couple weeks after radiation, which can exacerbate gastrointestinal toxicities. Bentyl (dicycloverine), an anti-spasmodic medication can be helpful with symptoms of tenesmus, and the dose we would recommend is 20 mg QID. Proctofoam can also help with symptoms of radiation proctitis, although needs to be directly inserted into the anal canal which can be uncomfortable/difficult for patients. Anecdotally, some colleagues empirically prescribe dexamethasone for patients receiving short course radiotherapy for 2–3 weeks, at a dose of 4 mg BID, although that is not our institution practice. Between short course and long course chemoradiation, we counsel patients that acute toxicities from long course chemoradiation occur during treatment, are generally more predictable with smaller range between patients, and are easier to manage as patients are seen for on treatment visit. In contrast, there is a wider range of variation in toxicity from short course radiation with some patients experience very little toxicity and some with quite severe sub-acute toxicity as above. Fortunately, these side effects are mostly transient (however can be highly distressing). This difference in toxicity presentation may help patients choose between radiation regimens.

Chronic Radiation Enteritis

Management of chronic radiation enteritis is dependent upon symptoms. Usually, dietary modification is the first step, although this usually takes some trial and error. For symptoms of diarrhea and urgency, we instruct patients to avoid foods that are high in fiber. Even if the patient did not previously have lactose intolerance, we have found that asking patients to try limiting dairy indicate can be helpful. Probiotics have recently garnered high levels of interest due to emerging data on the role of the gut microbiome in colorectal cancer. A recent meta-analysis of trials suggested that probiotics may be effective in ameliorating radiation-induced diarrhea [6], so we sometimes suggest to patients to try probiotics (either in food or drink or pill form).

The mainstay of medical management includes anti-diarrheal agents and for patients with evidence of small intestinal bacterial overgrowth, antibiotics can be curative.

Among anti-diarrheal agents, we generally use Imodium and loperamide.

For patients with severe refractory symptoms, we advise discussion of colostomy if they do not have one already. This can be upsetting to patients and in some ways make them feel like they have "failed" treatment, particularly if one of the goals of therapy was to avoid surgery and/or creation of a permanent colostomy. However, for those who have such severe gastrointestinal symptoms—particularly incontinence and urgency—that they are essentially homebound due to needing to be in proximity of a bathroom, having a colostomy can significantly improve quality of life.

Chronic Radiation Proctitis

In addition to the above, for symptoms of rectal pain, tenesmus, or bleeding, sucralfate enemas can be helpful. In a randomized trial of sulfasalazine plus prednisolone versus sucralfate enema, the response and toxicity profile of sucralfate enemas was superior [7], and another study showed that these responses tend to be durable [8]. For symptoms of obstructive due to radiation strictures, stool softeners may also be used.

Some patients experience persistent bleeding. Several endoscopic methods can be used to treat bleeding, the most common being argon plasma coagulation, which has been shown in several series to have efficacy rates upwards of 80% [9–11]. Other endoscopic methods including bipolar electrocoagulation with heating probe, radiofrequency ablation, band ligation, and formalin therapy. The success of these interventions is highly operator dependent, and there have been no large, randomized studies comparing the different methods. For patients with strictures, dilation with balloon can be highly effective. Finally, as above, colostomy creation should be discussed.

For all patients with chronic gastrointestinal symptoms, we recommend follow-up with a gastroenterologist and occasionally physical medicine and rehabilitation (PM&R), the latter particularly for musculoskeletal symptoms including stricture. These specialists can provide exercises for patients to perform on a regular basis at home and assess progress with specific metrics, rather than relying solely on symptomatic reporting.

Fertility

A complete discussion of radiation-induced fertility and sexual toxicity is outside the scope of this piece; however, the topic is highly important, especially given the increasing number of young patients diagnosed with rectal cancer. Unfortunately, the ovaries are highly sensitive to radiotherapy, and all pre-operative and definitive doses used in rectal cancer will cause permanent infertility in women. While ovarian transposition is an option, internal radiation scatter cannot be eliminated and depending on placement of the ovaries, they may still not be spared sufficiently to prevent infertility. As such, for women interested in having future biologic children, we recommend egg harvesting prior to initiation of any therapy. This can be accomplished within several weeks. For men receiving radiotherapy, we quote the risk of infertility of approximately 20%. Therefore, sperm banking is recommended to maximize the probability of having biologic children. Conversely, for those who do not wish to have more children, contraception is advised during and after radiation therapy.

For females, the most common side sexual side effects of pelvic radiation are vaginal dryness and stricture which can lead to dyspareunia (pain with intercourse). For the former, we recommend the use of topical estrogen. Vaginal strictures/stenosis can be irreversible however they are preventable. We strongly advise all female patients to use a vaginal dilator starting 4–6 weeks after completion of pelvic radiotherapy. We advise use 3 times weekly, for 15–30 min, with the largest comfortable dilator size. Dilator use can also be supplanted with sexual intercourse. The most critical window for dilator usage to prevent strictures is about 3 months to 1 year after completion of radiotherapy.

For men, the dose of radiation used in rectal cancer is generally lower than nerve tolerance and thus is unlikely the cause of erectile dysfunction. However, rates of sexual dysfunction in men after rectal surgery are high because peripheral nerves controlling sexual function are frequently sacrificed during total mesorectal excision. In a study of 343 men who underwent surgery for rectal cancer, the incidence of sexual dysfunction was approximately 70% and close to 80% in those undergoing lateral lymph node dissection [12]. Age was a significant predictor of erectile dysfunction which was more common in older males.

Conclusion

As treatment paradigms for rectal cancer continue to evolve, careful examination of side effects, particularly late toxicity, is critical. It is important for clinicians to be transparent with patients about the toxicities of treatment when counseling about options. This includes conveying to patients the wide range of toxicities experienced, that these are sometimes unpredictable, and occasionally irreversible. A young patient advocate once conveyed to me that many patients "are so worried about surviving their cancer, and then so grateful to be alive, that they do not even think to ask about toxicity until it's too late." Finally, new treatment for toxicities are needed or, at the very least, larger comparator studies of currently existing therapies allowing for more informed decision-making regarding treatment options.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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