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

What Rectal Cancer Patients May Be Able to Safely Avoid Radiation?

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Abstract

Purpose of Review Rectal cancers are treated with chemotherapy, radiotherapy, and surgery. While trials have illustrated the benefits of radiotherapy for locoregional control, recent investigations have questioned the need in select cases. This review seeks to understand why, how, and when radiation can be omitted from rectal cancer management.

Recent Findings Absolute contraindications of radiation include pregnancy, and relative contraindications include fertility concerns, sexual outcomes, autoimmune conditions, and prior radiation. Low-risk features of rectal cancer might warrant the omission of neoadjuvant radiation. MRI-directed therapy, chemotherapy alone, and immunotherapy may offer future ways to omit radiation.

Summary While radiation continues to be an essential component for rectal cancer treatment, there may be circumstances that it can be omitted. It is important to educate patients that not receiving radiation is a deviation from standard of care. In the future, we may see developments and changes in the treatment paradigm for rectal cancer.

Keywords Rectal cancer · Radiation · Radiation omission · Neoadjuvant therapy · Toxicity · Contra-indications

Introduction

Unlike the colon, the upper two-thirds of the rectum are partially covered with peritoneum and the distal one-third of the rectum lacks any peritoneal covering [1]. Thus, this lack of a serosal barrier facilitates rectal cancer invasion into adjacent structures, making surgical resection more difficult [2]. Therefore, compared to colon cancer, the local failure rate of rectal cancer is higher [3]. Given these anatomical differences, rectal cancers are treated with multimodality therapy with variations of chemotherapy, radiotherapy, and surgery, depending on the disease extent. In particular, radiation has historically played an active role to ensure local control, particularly for low-lying or extensive tumors. Prospective clinical trials have demonstrated the benefits of adjuvant and neoadjuvant chemoradiotherapy to decrease locoregional recurrence for patients with stage II or stage III rectal cancers even after high-quality total mesorectal excision (TME) [4, 5]. Additionally, these trials highlight that neoadjuvant radiation treatment not only improves locoregional control but also aids in preservation of sphincter function, decreases toxicity, and improves the quality of life compared to adjuvant treatment [3]. It is also important to note that neoadjuvant radiation is not indicated for most T1 or T2 N0 disease, and adjuvant radiation is only reserved for limited clinical contexts.

Recent developments in systemic therapy and surgical procedures have questioned the need for radiation in more select cases of rectal cancer. While multimodality treatment might result in a high chance of cure, ongoing research is investigating the necessity of all treatment modalities to prevent overtreatment and minimize toxicity [6, 7]. For example, while the addition of chemoradiotherapy is recommended for patients with transmural or node-positive rectal cancer, there are patients with favorable characteristics that may have only a marginal benefit from radiotherapy. To guide clinicians when discussing the utility of radiation in the treatment of rectal cancers, we provide a detailed overview of why, how, and when radiation can possibly be

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omitted in the treatment of rectal cancers. We include absolute and relative contraindications as well as new horizons in the rapidly changing landscape of optimal rectal cancer management.

Absolute Contraindications to Radiation

Pregnancy

Pregnancy is a major contraindication for delivering radiation for the treatment of rectal cancer [8, 9]. The incidence of cancer during pregnancy has been reported to be 1 in every 1000 pregnancies and colorectal cancer is the 7th most common type of cancer diagnosed in pregnancy with an estimated incidence of 1 in 13,000 pregnancies [10]. Additionally, this will become even more relevant with the alarming increase in rectal cancer diagnoses in younger patients [11].

When a diagnosis of colorectal cancer is made during pregnancy, a discussion among a multidisciplinary team is required to allow for safe delivery of treatment. Radiation therapy is not recommended to the pelvis during pregnancy as it can cause harm to the fetus and any fetal radiation should be measured during pregnancy. Radiation to the fetus can result in fetal malformation, disturbance in growth or development, carcinogenic effect, and even miscarriage [12]. Additionally, if neoadjuvant radiation is omitted and pelvic radiation is still needed following birth and rectal cancer management, it can be considered, but the patient should be counseled on the risk of infertility [13]. Regardless, pregnancy is an absolute contraindication to radiation and thus radiation should be omitted.

Relative Contraindications to Radiation

Fertility and Sexual Outcomes

In addition to affecting the fetus, pelvic radiation can impact fertility and sexual function. This is especially important as up to 5% of colorectal cancers occur in women of reproductive age and radiation to the uterus might make future pregnancies nonviable [14, 15, 16]. In fact, women who receive more than 25 Gy in childhood or 45 Gy during adulthood to their uterus should receive clinical guidance and counseling about avoiding pregnancy [15]. Clinical practice guidelines recommend that fertility preservation be discussed with all patients at the time of diagnosis, as sperm banking, embryo/oocyte cryopreservation (the freezing of fertilized or unfertilized eggs), and ovarian transposition (a surgical repositioning of the ovaries away from the field of radiation) should be started in advance of treatment [17].

Additionally, while sexual outcomes of patients with gynecologic and prostate cancers have been investigated, there is a paucity of data regarding sexual outcomes in patients following treatment for rectal cancer. Preoperative radiation therapy in resectable rectal cancer has been shown to increase the likelihood of sexual dysfunction. In the Dutch Total Mesorectal trial comparing surgery alone to surgery with neoadjuvant radiation (25 Gy in 5 fractions) found that both men and women treated with radiation had significantly worse patient-reported sexual dysfunction compared to those not treated with radiation. More specifically, erectile and ejaculatory dysfunction was reported by approximately 80% and 72% of men, respectively, and dyspareunia and vaginal dryness were reported by approximately 59% and 57% of women, respectively. Only ejaculatory dysfunction was significantly associated with preoperative radiation at initial analysis [18]. At a 14-year follow-up analysis, there was a significantly higher prevalence of erectile dysfunction in those who received radiation compared to those who did not. There remained no difference in vaginal dryness and dyspareunia in women at 14-year follow-up [19]. However, in the Norwegian Rectal Cancer Registry, there was a significant difference in erectile dysfunction after radiation (86% in irradiated males versus 55% in non-irradiated males) [20] as well as vaginal dryness (50% in irradiated females versus 24% non-irradiated females) and dyspareunia (35% in irradiated females versus 11% non-irradiated females) [21].

While rates of sexual dysfunction after radiation for rectal cancer are high, a study aimed at understanding what radiation oncologists discuss with rectal cancer patients at initial consultation revealed that only 72% of men and 40% of women learned about sexual dysfunction as a possible side effect of radiation [22]. Moreover, a questionnaire asking how physicians and patients value sexual dysfunction determined that patients find learning about treatment-related sexual dysfunction more relevant than physicians [23].

In these studies, sexual dysfunction in men is synonymous with erectile dysfunction which leaves out major aspects of sexual dysfunction, such as anodysparania, which may be important to sexual minority men (SMM), which includes gay and bisexual men [24]. While the literature is sparse regarding how treatment affects sexual outcomes in SMM with rectal cancer, epidemiological studies have shown that colorectal cancer may be more common in SMM compared to heterosexual men [25]. Furthermore, colorectal cancer treatment has a more profound impact on mental health in SMM compared to heterosexual men [26]. This may be related to the effects of treatment on SMM sexual performance. A survey study by Boehmer et al. showed that SMM colorectal cancer survivors have increased hospital visits compared to heterosexual men which may be related to SMM concern of sore skin around the anal area [27].

Moreover, pelvic radiation has implications on gender-minority patients who have undergone or plan to undergo gender-affirming surgery. Colorectal cancer is one of the five most common diagnosed cancers in trans patients [28]. While there is little information on how to manage gender minority patients with rectal cancers, radiation prior to gender-affirming surgery could cause surgical complications during and following reconstruction. Thus, it is essential to counsel trans patients planning on getting gender-affirming surgery on the implications radiation treatment may have on their future surgical procedures [29]. Physicians must discuss neoadjuvant treatment with sexual minority men and transgender patients as radiation may impact sexual health outcomes and gender-affirming surgery. Further research is sorely needed to better understand the complex relationship between radiation and sexual and surgical outcomes in these underrepresented patient populations.

Autoimmune Systemic Condition

Autoimmune systemic conditions, including collagen vascular disease (CVD) and inflammatory bowel disease (IBD), are relative contraindications for radiation. Through initiation of the pro-inflammatory cascade, radiation may lead to higher rates of toxicity in patients with these disorders. A meta-analysis of 18 articles ($n=621$), 10 with CVD ($n=417$) and 8 with IBD ($n=204$), demonstrated that the incidence of grade ≥ 3 toxicity in CVD patients was 11.7% and 6.1% for acute and late toxicities, respectively, and incidence of grade ≥ 3 toxicity in IBD patients was 14.0% and 10.2% for acute and late toxicities, respectively [30]. The authors concluded that CVD and IBD are not absolute contraindications to radiation therapy and should not preclude RT for curable cancer therapy. Irritable bowel disease, which includes Crohn's disease and ulcerative colitis, is a risk factor for colorectal cancer [31, 32]. While CVD and IBD are not an absolute contraindication to radiotherapy, they still can lead to toxicity and it is important to consider how radiation may impact toxicity in rectal cancer patients with these comorbidities.

Pelvic Reirradiation

Patients who present with rectal cancer may have undergone prior pelvic radiotherapy for colorectal cancer as well as for prostate, cervical, and other pelvic cancers [33, 34, 35]. Radiation to a previously treated anatomic region poses many challenges especially if the cumulative dose is high to normal tissues. Several retrospective studies have investigated the possibility of reirradiation for recurrent rectal cancer in patients who did and did not receive previous radiotherapy [36, 37, 38]. These studies illustrated that while prior pelvic radiation is not an absolute contraindication, patients with rectal cancer who have had received prior radiation may receive reirradiation to lower doses ranging from 30 to 39 Gy with more potential to experience significant late toxicity [36, 37, 38]. Thus, efforts should be made to avoid or minimize radiation if possible when reirradiating the pelvis for patients with rectal cancer.

Low Risk Features

Omission of neoadjuvant radiation may be recommended if patients with rectal cancer are at a low risk of recurrence given favorable prognostic features. Low risk is defined as: negative circumferential radial margins at least 2 mm, a proximal lesion that is at least 10 cm from the anal verge, no nodal metastases, and no MRI-detected extramural vascular invasion [39, 40••]. While patients might be able to omit neoadjuvant radiation, at least 22% or more may require subsequent adjuvant therapy given pathological features [7]. Adjuvant therapy is associated with worse toxicity compared to neoadjuvant chemoradiotherapy and worse outcomes.

A study comparing short-course preoperative radiation and initial surgery with potential postoperative chemotherapy sought to understand the role of radiation in the management of rectal cancers. Patients received short-course neoadjuvant radiotherapy (25 Gy in 5 fractions) or initial surgery with adjuvant chemoradiotherapy (45 Gy in 25 fractions with concurrent 5-fluorouracil) if indicated for margins that were less than 1 mm. Eligible patients had rectal cancers at least 15 cm from the anal verge with no evidence of nodal involvement. The primary outcome was local recurrence. The authors noted a relative reduction of local recurrence at 3 years of 61% with short-course preoperative radiotherapy compared to no preoperative radiation (HR 0.39, 95% CI 0.27–0.58, $p<0.0001$). Additionally, the authors observed a relative improvement in disease-free survival of 24% for patients receiving neoadjuvant radiation (HR 0.76, 95% CI 0.62–0.94, $p=0.013$). There was no difference in overall survival between the two arms. The authors concluded that this trial provides evidence to use preoperative radiation therapy for the treatment of rectal cancers [41].

However, other ongoing studies continue to investigate the use of preoperative radiation. The ongoing Surgery Alone In Low Rectal cancer (SAILOR) trial is investigating whether radiation can be omitted for tumors located within 6 cm of the anal verge. The trial is using MRI to aid with identification of resectable low-lying rectal tumors. Patients are randomized to (1) standard of care (neoadjuvant radiation (45 Gy) with chemotherapy followed by a abdominoperineal resection) or (2) abdominalperineal resection alone. The results of this trial will help guide the utility of radiation for the management of rectal cancer [6].

New Horizons of Radiation Omission

MRI Directed Therapy

While the standard of care in the USA is that any patient with T3 or greater or node-positive disease is recommended for neoadjuvant chemoradiation based primarily on the German Rectal Cancer Trial, it is important to note that in Europe, these criteria are not absolute [42]. In the most recent European Society of Medical Oncology (ESMO), neoadjuvant RT is only recommended for "intermediate risk rectal cancer", defined as cT3a/b (very low, levator ani clear, MRF clear) or cT3a/b (mid- or high rectum, cN1-2 (non extranodal), no EMVI), and a high quality, margin negative TME cannot be achieved [43]. The surgeon, therefore, determines which patients will receive neoadjuvant therapy.

Preoperative high-quality MRI can accurately assess lymph node involvement and surgical margins—the factors that are used to justify the need for radiation—and justify the omission of neoadjuvant radiation. The potential omission of radiation based on pre-operative MRI results was recently demonstrated in a large series out of the UK [44]. In 2020, the British National Health Service (NHS) issued criteria to standardize the treatment of rectal cancers which advocated for neoadjuvant radiation for all rectal cancer except for T1-2 N0. This study looked at patients that had high-quality MRI prior to the NHS recommendations and did not receive neoadjuvant radiation. High-risk MRI criteria were defined as MRI-detected extramural venous invasion, MRI-detected tumor deposits, and MRI-detected circumferential resection. These features were compared to standard high-risk features being T3 or greater and/or MRI node positive. MRI-based criteria were able to stratify for DFS and OS better than standard criteria. Most striking, 139 patients, classically defined as high-risk by standard criteria but low-risk based on MRI criteria, had similar disease-free survival as 118 low-risk patients suggesting up to 37% of patients in this study cohort would have been possibly overtreated using the standard criteria to justify preoperative radiation [45•]. While these data are compelling, it is important to note that the series is retrospective, and it is unclear that other centers can replicate the high-quality MRI studies that this British group has been performing for years.

A prospective study evaluating the use of pre-therapeutic MRI to determine the need for neoadjuvant chemoradiation further underlined that imaging may be a useful tool to guide treatment [46]. In this trial, patients with tumors with at least 1 mm between the mesorectal fascia and tumor received immediate surgery without neoadjuvant treatment. However, patients with tumors in the middle and lower third of the rectum that were less than 1 mm from the mesorectal fascia received neoadjuvant chemoradiation. However, while the trial has completed accrual, the primary endpoint, or 5-year locoregional control rate, has not yet been evaluated. Still, the 3-year rate of local recurrence was 3.3% for the entire cohort and for those patients that did not receive neoadjuvant chemoradiation, the local recurrence rate was 2.2% compared to 4.3% for those that received neoadjuvant chemoradiotherapy followed by surgery. Of note, those that received neoadjuvant treatment had more advanced disease. Still, while final trial analyses are pending, these results illustrate that neoadjuvant chemotherapy may not be necessary for all patients. Thus, when discussing these cases in the tumor board, it should be recognized that some T3 or N + patients will be potentially overtreated with radiation.

Chemotherapy Alone

Another approach for possible radiation omission stems from the results of trials investigating chemotherapy alone in a subset of rectal cancer patients. Historically, patients with some of the contra-indications to radiation discussed above or who refused radiation were treated with success with chemotherapy alone prior to surgery. Based on this experience, Memorial Sloan Kettering Cancer Center enrolled 32 patients in a pilot trial selectively omitting radiation for rectal cancer patients. Patients received six cycles of FOLFOX, with bevacizumab in the first four cycles, and nonresponsive patients with stable or progressive disease subsequently received radiation and then TME, whereas responders underwent immediate TME bypassing preoperative radiation. The primary endpoint was the R0 resection rate. All study participants had an R0 resection and 25% had a pathological complete response. The 4-year local recurrence rate was 0%, and DFS was an impressive 84%[47].

The encouraging results of the pilot trial led to the PROSPECT trial, an NCI-sponsored multi-institutional randomized Phase III trial. This trial is exploring neoadjuvant FOLFOX without radiation in patients who achieve a pathological response to chemotherapy against the standard neoadjuvant chemoradiation followed by resection and adjuvant FOLFOX [48]. It is important to remember that the trial excludes N2 or greater disease, T4 disease, and lesions that are distally requiring an APR. The trial completed accrual, and we eagerly anticipate the results. This trial might demonstrate that select patients can forgo radiation prior to surgical resection. This will be especially important for those patients who have an absolute or relative contraindication to radiation.

Immunotherapy

Generally, immunotherapy, in the form of check-point inhibitors, has not had great success in the treatment of colorectal adenocarcinomas and, in particular, rectal adenocarcinomas. However, carcinomas with micro-satellite instability (MSI) have been shown to respond well to immunotherapy [49•]. Only 5–10% of rectal adenocarcinomas have MSI [50]. A recent small prospective trial investigated the role of single-agent dostarlimab for the treatment of rectal cancers with MSI as part of the neoadjuvant regimen for rectal cancer. Twelve patients completed at least 6 months of immunotherapy, and of those patients, 100% had a complete response without the need for additional radiation or surgery [51•]. While the results are premature without long-term follow-up, this trial might reveal a potential revolutionary therapy for patients with MSI rectal cancers. Moreover, the trial illustrates the importance and impact of personalized medicine and how it might spare patients of over treatment. Further studies are desperately needed to verify these premature data before this becomes the standard of care.

Conclusion

Radiation continues to be an important component in the management of rectal cancers. In fact, at this time, in many of the contexts discussed, if radiation is omitted, it is important to educate patients that not giving radiation represents a deviation from the standard of care. Still, the use of radiation in the management of rectal cancers remains an area of debate and ongoing investigation. There are subsets of patients where radiation is absolutely contraindicated and relatively contraindicated. Moreover, novel interventions are illustrating that there might be other emerging cohorts of patients, such as those with MSI rectal cancers, where radiation might be inconsequential in the management of rectal cancers. In the rapidly evolving field of rectal cancer management, we might see more developments and changes in the treatment paradigm for rectal cancers and the use of radiation.

Data Availability All data generated or analysed during this study are included in this published article.

Declarations

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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•• Of major importance

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