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Strategic evaluation of interventions to prevent consequential late proctitis after prostate radiation therapy

New clinical trial designs should be considered

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This review reconsiders evidence and strategies toward the prevention of consequential late rectal toxicity after radiation therapy, with a focus on prostate cancer. Novel clinical trial designs are encouraged, and these insights into the late effects of prostate radiation therapy have additional implications for late toxicity after cancer treatment for other tumors.

Many men with localized prostate cancer receive radiotherapy as part of their definitive treatment course. Median survival for such patients is typically measured in years or decades. However, late effects of RT are a major burden, and risk of late toxicities may be increased when high RT doses are delivered,[1] as is performed for prostate RT. The avoidance of late RT toxicity is therefore critical, so therapeutic strategies that target this need are warranted. Despite numerous improvements in physics-based approaches (e.g., intensity-modulation and image-guidance) that minimize the exposure of normal tissues to RT, there has been little success in identifying biology-based strategies to effectively treat or prevent late RT-induced toxicities. Dosimetric models exist to predict risk of late toxicity and to recommend dose-volume constraints.[2] While these models are valid and helpful from a population standpoint, they perform poorly when it comes to predicting if an individual patient will develop late rectal toxicity.

In this report, we describe an approach to re-evaluation of published evidence, and potential steps forward, concerning understanding and management of consequential late rectal toxicity after RT, with a specific focus on prostate RT. The core principle underlying the hypothesized strategy is the use of candidate therapeutic agents as secondary prophylaxis against late rectal toxicity for use in patients with significant acute toxicity.

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These insights into the late effects of prostate RT have additional implications for late toxicity after cancer treatment for other tumors.

Late gastrointestinal (GI) toxicity after prostate cancer RT is an illustrative example of the need for better preventive medical therapies, since the burden of late effects is high,[3] and yet there are no effective medications available. A wide array of pharmacologic therapies has been evaluated in clinical trials for the prevention and treatment of acute proctitis and the prevention of late rectal toxicity. Prevention strategies studied have primarily included cytoprotective, anti-inflammatory, and anti-oxidant medications, based on the central hypothesis that preventing or ameliorating acute proctitis would reduce the risk of consequential development of late rectal toxicity.[4-6] Unfortunately, despite these clinical trials, there is no clear evidence that any of these therapies are effective in prevention of late toxicity.[7]

One major barrier to the development of medical strategies to prevent late toxicities is that it is difficult to identify patients who are most likely to suffer late toxicities, and events often occur many years after the delivery of RT. Risks of late effects are not uniform among patients, and this likely reflects baseline biological variation in susceptibility among patients.[8] Despite extensive efforts to identify baseline biomarkers that predict which patients are most susceptible to late toxicities after RT, which would allow selective use of preventive interventions, there are no well-validated biomarkers to predict radiation toxicity prior to treatment.[9] Therefore, previous trials of pharmacologic therapies aimed at prevention of acute and late GI effects of prostate cancer RT have included any patient receiving RT, without ability to select based on risk of toxicity, and this reduces the chance of identifying a treatment effect even if a therapy is effective.

In this report, we develop a framework for evaluating published negative trial results of candidate therapies to prevent acute and late rectal toxicity from prostate cancer RT, highlight the data to support the concept of late rectal toxicity as a consequential late effect (CLE) arising from acute RT injury, and propose a novel trial design based on indicators of acute RT response that are currently available to radiation oncologists and clinical

Table 1. Core concepts that provide framework for reconsideration of clinical trial designs and clinical practice for prevention of consequential late effects of RT

1) Mechanisms of CLE development from acute RT injury are substantively understood
2) Clinical data demonstrate that CLEs are a significant component of the burden from late effects of RT.
3) Clinical indicators of acute RT response and injury can be used presently to identify a subgroup of patients at high risk of CLE.
4) There are currently available candidate interventions ("off the shelf") that have a compelling rationale for the prevention of CLE through amelioration of acute RT response.
5) Clinical trials based on indicators of acute RT response offer obvious practical advantages over traditional designs.
6) Clinical trials based on indicators of acute RT response shift the perspective of patients and investigators when considering the range of potential interventions and expand the reasonable options.

trialists. To this end, we will emphasize and expand upon six core concepts (**Table 1**) that we believe should guide clinical trials designed to reduce incidence and burden of CLEs through amelioration of the acute response of normal tissue to RT. Although the current report specifically addresses CLEs of prostate cancer RT, and how clinical observations can guide trial eligibility, these concepts are applicable elsewhere in radiation oncology and can be adapted to biomarker-based selection strategies.

Core Concepts

Mechanisms of development of CLE of the rectum after acute RT injury are substantively understood

Animal models of radiation proctitis have characterized the nature and time course of histopathological events that occur in the acute and late phases of response to radiation injury of the rectum. After exposure to RT, acute inflammatory changes occur, including edema and epithelial atrophy, and these changes progress to confluent hemorrhagic injury and subsequent development of fibrosis and ulceration.[10] Long-term consequential changes of radiation proctitis include angiopathy with thickened walls of vascular epithelium of small arteries within the rectum.[10] In addition to histological evidence that acute rectal mucosa changes progressing to chronic proctitis, additional mechanistic insights come from the correlation of cytokine mRNA expression with development of late rectal injury after RT in mice.[11] Together, these studies provide insights into the mechanisms of consequential late rectal toxicity after RT.

Clinical data demonstrate that CLEs are a significant component of the burden from late effects of RT

Clinical observations in humans suggest that a significant portion of the late effects of RT that develop in the GI tract are attributable to CLE, rather than generic (non-consequential) late effects. Dorr and Hendry have argued this point well, and also point out that dose fractionation and overall treatment time seem to affect both acute toxicity and CLEs similarly, while having the opposite effect on non-consequential late effects.[6] Dorr and Hendry review clinical evidence regarding the influence of overall treatment time on the incidence of late effects after altered-fractionation schedules. They note that higher frequencies of late responses, such as telangiectasias or severe mucosal sequelae of treatment, are observed among patients with severe acute mucositis.[6] These clinical findings are consistent with the radiobiological processes involved in consequential late effects of radiotherapy, which include acute injury to the mucosa and connective tissue, breakdown of mucosal barriers, and subsequent development of ulcerations and obstruction.[6]

Even after adjusting for baseline symptoms and dose-volume considerations, acute toxicity has been shown to be an independent predictor of late GI toxicity after prostate RT, suggesting a strong association between acute tissue injury and progression to late proctitis with a likely consequential relationship.[12] Further, the identification of acute rectal mucosal changes on proctoscopy within 1 wk of prostate RT is associated with an increased risk of late rectal toxicity, especially when accompanied by acute clinical symptoms of proctitis.[13]

Clinical indicators of acute RT response and injury can be used presently to identify a subgroup of patients at high risk of CLE

Although no such validated biospecimen- or imaging-based biomarker of acute RT injury exists, it has been shown convincingly that acute toxicity itself, as measured by physicians, is a readily observable indicator of acute RT response and is strongly associated with risk of CLE. Severe acute GI toxicity during or after pelvic RT is associated with a 2- to 4-fold increase in risk of GI CLE.[6,12,14-16] Futhermore, the additional consideration of early proctoscopic examination can enhance the ability to determine risk of rectal CLEs: Campostrini et al. found that post-RT proctoscopy evidence of acute proctitis, in the presence of clinical symptoms, was associated with 77% risk of late procititis in a prospective study of 130 patients who received prostate RT.[13]

We hypothesize that these clinical indicators of acute RT response can be used to predict risk of CLE in a meaningful way, defining low- vs. high-risk groups, to guide both patient selection for clinical trials and clinical decisions regarding the targeted treatment of acute RT injury with the aim of preventing the development of CLE.

There are currently available candidate interventions ("off the shelf") that have a compelling rationale for the prevention of CLE through amelioration of acute RT response

Potential drugs include anti-inflammatory agents (e.g., 5-aminosalicylic acid), amifostine, and sucralfate, which would be expected to reduce acute response to RT.[7,17] When these drugs have been evaluated as preventive strategies to prevent late rectal toxicity for patients receiving prostate RT, clinical trial results have failed to show that these therapies are effective clinically.[4,7,15]

However, it should be noted that these prior trials applied "all-comers" approaches, meaning that any patient receiving

RT was eligible for the trial—not only those patients with acute GI toxicity, who we have shown are at higher risk of developing CLEs of the rectum. We hypothesize that re-evaluation of these pharmacologic agents using a risk stratification paradigm based upon clinical indicators of acute RT response may yield positive results when such drugs are tested for the prevention of CLEs. On the other hand, it is possible that anti-inflammatory agents may in fact not be effective when administered to patients at high risk of developing CLE. If this is the case, the conducting symptom management trials in an enriched population, as described, would demonstrate the lack of effectiveness of these therapies, and investigative resources could instead be directed to other classes of compounds.

Clinical trials based on indicators of acute RT response offer obvious practical advantages over traditional designs

Benefits of identifying a high-risk group of patients, on the basis of acute effects, to reconsider future trials of interventions to mitigate CLE include: potential for more efficient, fast, and cost-effective trials of candidate therapies; and limiting exposure to risks of candidate interventions to those at highest risk of CLE.

Consider two hypothetical clinical trials designed to evaluate an experimental drug to prevent development of consequential late proctitis after prostate RT, each trial enrolling 100 subjects and randomizing subjects between experimental drug vs. placebo. Suppose that in the first trial, an "all-comers" approach is used, meaning that any patient who receives prostate RT would be eligible to participate. In this scenario, the overall group has a 20% risk of CLE. Based on the number of subjects and the risk of CLE, the trial has 40% power to detect a 50% reduction from 20% to 10% risk of CLE (50 subjects in each group). On the other hand, suppose that in a second trial, the only those patients who are at higher risk of CLE (40%) are eligible to participate—perhaps based upon clinical symptoms and/or endoscopic findings of acute proctitis. This 100-patient trial has a 71% power to detect a 50% reduction from 40% to 20% rate of CLE. This example demonstrates the increased statistical power offered through identifying a high-risk population for clinical trials of symptom management medication, and reflects real opportunities currently available for clinical trial designs of experimental drugs to prevent rectal CLEs after prostate RT.

In this way, previously-reported clinical trials of anti-inflammatory and mucosal-protectant agents may have been predestined to fail, since the study populations were composed of subjects with heterogeneous risk of CLE and low overall rate of late rectal toxicity. Through design of future clinical trials to include only those individuals at high risk of CLEs of the rectum, as defined by clinical indicators of acute response, it is more likely that promising strategies can be more effectively and efficiently evaluated and developed.

Clinical trials based on indicators of acute RT response shift the perspective of patients and investigators when considering the range of potential interventions and expand the reasonable options

Much of the discussion has focused on established drugs with minimal side effects. However, for those patients at very high risk of late proctitis, experimental agents with less supportive data, or with higher risk of side effects, could be considered for evaluation if there was potential for prevention of rectal CLE. For patients with endoscopic and clinical findings of acute proctitis—with 77% risk of late proctitis in the Campostrini et al. report—the risk-benefit ratio may be such that more experimental therapies could be considered. Candidate agents include those that target tumor necrosis factor-α or specific interleukins, such as compounds that have indications currently for autoimmune disorders.[18] Patients at high risk of late proctitis should be considered for clinical trials that evaluate experimental therapies that show promise of reducing risk of CLE, even if accompanied by some risk of adverse effects beyond that observed with traditional anti-inflammatory medications.

Summary

The current science and clinical evidence suggest that the burden of late rectal toxicity after pelvic RT results in large part from CLEs. We have highlighted that mechanisms of consequential toxicity of the GI and genitourinary systems after pelvic RT are substantively understood, and that promising medical therapies are available and ready to be tested. We have argued that previous negative clinical trial results may be explained based upon the lack of selection based upon risk of developing CLEs, and we propose that clinical indicators of acute response (symptoms and endoscopic findings) can be used to identify a group of patients at high risk of late rectal toxicity who should be offered participation in clinical trials of novel preventive medications. Risk-adapted eligibility criteria offer the opportunity for efficient trial design and accelerated drug discovery for prevention of CLEs. The basic rationale is applicable to biomarkers of acute RT response and/or baseline risk of late toxicity identified in future research. We encourage investigators to consider this when evaluating published clinical trial results and planning future clinical trials of novel therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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