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Late rectal toxicity after low-dose-rate brachytherapy: Incidence, predictors, and management of side effects

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ABSTRACT As clinical outcomes for patients with clinically localized prostate cancer continue to improve, patients and physicians are increasing making treatment decisions based on concerns regarding long-term morbidity. A primary concern is late radiation proctitis, a clinical entity embodied by various signs and symptoms, ranging from diarrhea to rectal fistulas. Here, we present a comprehensive literature review examining the clinical manifestations and pathophysiology of late radiation proctitis after low-dose-rate brachytherapy (BT), as well as its incidence and predictors. The long-term risks of rectal bleeding after BT are on the order of 5–7%, whereas the risks of severe ulceration or fistula are on the order of 0.6%. The most robust predictor appears to be the volume of rectum receiving the prescription dose. In certain situations (e.g., salvage setting, for patients with increased radiosensitivity, and following aggressive biopsy after BT), the risk of these severe toxicities may be increased by up to 10-fold. A variety of excellent management options exist for rectal bleeding, with endoscopic methods being the most commonly used.

Keywords: Radiation proctitis; Rectal toxicity; Low-dose-rate brachytherapy; Rectal bleeding; Prostate cancer

Introduction

Prostate cancer is the second most common cancer in men worldwide and has a prevalence of at least 2.7 million in the United States alone (1). Management options are defined on the basis of risk stratification and broadly include radical prostatectomy, definitive external beam radiotherapy (EBRT), brachytherapy (BT), and potentially a combination of EBRT and BT, all of which have demonstrated considerable efficacy (2). Because of advancements in screening and treatment, survival after treatment of prostate cancer is excellent. As a result, physicians and patients often jointly make a decision on which treatment modality to use based on concerns of long-term morbidity. Specifically, the three domains of long-term morbidity relevant to the treatment options are sexual function, urinary function, and rectal function, and each treatment modality has a unique toxicity profile (3).

In this review, we summarize the clinical manifestations and pathophysiology of late or chronic radiation proctitis (RP), the pathologic entity describing long-term rectal toxicity after radiation therapy. We then present findings from a comprehensive literature review evaluating the incidence and predictors of RP specifically after low-dose-rate (LDR) BT. Finally, we review the current management options for late RP, with some historical perspective on earlier treatments. Our aim is to provide clinicians with a summary resource to help counsel patients and manage rectal toxicity after BT.

Clinical manifestations and pathophysiology

Classic RP can be divided into acute and late forms, as described in detail in the excellent reviews by Phan *et al.* (4) and Garg *et al.* (4, 5). The acute form generally occurs within 6 weeks of implantation and occurs in approximately 30–35% of patients undergoing BT (4, 6–10). The most frequent symptom is typically diarrhea, and it is characterized on microscopy by superficial mucosal changes and endoscopically by inflamed, edematous, and friable mucosa (11). Other less common symptoms include pain, urgency, constipation, bleeding, and mucous discharge. Typically, acute RP is self-limited and can be

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managed by conservative and supportive care; if significant bleeding or ulceration occurs, more focused treatment may be required, as discussed later. The management of acute RP is beyond the scope of this review.

Late RP, defined as occurring more than 6 weeks after the initial BT, is less common. Symptoms included rectal bleeding, urgency, incontinence, mucous bleeding, and fistula development. Direct anal injury, resulting in stenosis, tenesmus, and pain can also occur. Significant bleeding occurring in approximately 5–7% of patients treated with BT and more severe sequelae, such as significant ulcers or fistulas, occur much less frequently, on the order of 0.5% (see Table 1 and accompanying discussion later) (10, 12).

Unlike with acute RP, the chronic form involves both mucosal and submucosal changes (11), with small vessel vasculitis frequently seen (49). Over time, chronic tissue injury can lead to fibrosis. Late RP can be devastating for patients. In fact, in a series of 13 BT-related medical malpractice cases, 11 were initiated because of a prostatic–rectal fistula (50).

Clearly, not all rectal mucosal damage leads to clinical sequelae. Wachter *et al.* (51) performed endoscopies on 44 patients treated with EBRT for prostate cancer, developing a Vienna Rectoscopy Score that included points for the degrees of mucosal congestion, telangiectasia, ulceration, stricture, and necrosis. Seven of 9 patients with intermittent rectal bleeding had Vienna Rectoscopy Scores of 2–3, compared with 7 of 35 asymptomatic patients. Endoscopies were subsequently performed in 164 volunteers 12 and 24 months after EBRT for prostate cancer (52). The most frequent pathologic findings were telangiectasias (58% and 57% at 12 and 24 months after EBRT) and congested mucosa (39% and 40% at 12 and 24 months after EBRT).

In addition to mucosal changes detected on endoscopy, changes in anorectal function can also be observed. In the largest study examining anorectal metrics after EBRT, Yeoh *et al.* (53) followed 34 patients after EBRT in the context of a Phase III trial of hypofractionation vs. standard fractionation and reported 5-year outcomes. The investigators measured anorectal motility and sensory function as well as anal sphincteric morphology. They found that all measures of anorectal motility (e.g., basal pressure and squeeze pressure) were lower than at baseline, as were measures of anorectal sensory function (e.g., volume at first perception of rectal distention and rectal compliance). On the other hand, sphincter morphology was not changed. Patients with urgency had significant reduction in rectal compliance.

Scoring systems

Most modern series have used the combined European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) toxicity grading scale or a modification thereof, in assessing the incidence and severity of RP (see Table 2, adapted from Lund *et al.* (54)). Most investigators have included rectal ulceration as Grade 3 toxicity as well. Other scoring systems include the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE), which stratifies rectal toxicity into 10 different subsets (proctitis, fistula, hemorrhage, mucositis, necrosis, obstruction, pain, perforation, stenosis, and ulcer) (55). Some argue that the CTCAE may capture a more comprehensive profile of symptomatology, although overall rates of patient-specific CTCAE maximal toxicity and RTOG toxicity appear similar (7, 10). The Late Effects Normal Tissue/Subjective Objective Management Analytic (LENT/SOMA) scoring system categorizes toxicities on the basis of being subjective, objective, or related to management (56). Unfortunately, the correlation between both the RTOG and LENT/SOMA scales with quality-of-life questionnaires is poor (54).

More recently, the expanded prostate cancer index composite for clinical practice (EPIC-CP) has emerged as a validated tool for scoring rectal toxicity based on patient questionnaires (57, 58). Although this scoring system has not been commonly used to track rectal morbidity after BT (only two of the 42 studies in our comprehensive literature review used the EPIC scoring system, see Table 1) (3, 48), we believe that in future work, scoring systems based on patient-reported quality of life should be used. This is particularly important because end points such as rectal bleeding are clearly clinically significant, whereas more clinically minor issues, such as chronic diarrhea, may actually be seen as quite burdensome by patients. Additionally, as suggested by Yeoh *et al.* (53), effective treatments exist for rectal bleeding, whereas anorectal dysfunction causing chronic diarrhea and urgency are more difficult to manage.

Incidence and predictors of late toxicity

Incidence: a comprehensive literature review

At least 42 published investigations have included reports of the incidence of rectal toxicity in patients receiving LDR BT, either alone, in combination with EBRT, or in the salvage setting. Their results are summarized in Table 1. Notably, the end points and definitions of rectal toxicity vary, making direct comparisons between studies difficult. However, although it is likely that some patients' end points are represented in multiple studies (simply captured at various time points), the total number of patients across these studies is 13,812, with a median followup of 3.4 years. Therefore, robust conclusions can be drawn.

First, from studies that have rigorously scored late toxicity on the RTOG scale, the incidence of ≥2 toxicity is typically on the order of 5–7%, with most of these toxicities being Grade 2 (typically rectal bleeding). In most cases, these appear to resolve spontaneously within a time frame of 18–36 months, and the median duration of toxicity (when reported) appears to be closer to 6 months. Second, the