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RADIATION DOSE–VOLUME EFFECTS IN RADIATION-INDUCED RECTAL INJURY

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The available dose/volume/outcome data for rectal injury were reviewed. The volume of rectum receiving ≥60Gy is consistently associated with the risk of Grade ≥2 rectal toxicity or rectal bleeding. Parameters for the Lyman-Kutcher-Burman normal tissue complication probability model from four clinical series are remarkably consistent, suggesting that high doses are predominant in determining the risk of toxicity. The best overall estimates (95% confidence interval) of the Lyman-Kutcher-Burman model parameters are n = 0.09 (0.04–0.14); m = 0.13 (0.10–0.17); and TD_{50} = 76.9 (73.7–80.1) Gy. Most of the models of late radiation toxicity come from three-dimensional conformal radiotherapy dose-escalation studies of early-stage prostate cancer. It is possible that intensity-modulated radiotherapy or proton beam dose distributions require modification of these models because of the inherent differences in low and intermediate dose distributions. © 2010 Elsevier Inc.

Rectum, Radiation injury, NTCP.

1. CLINICAL SIGNIFICANCE

Approximately 300,000 patients undergo pelvic radiotherapy (RT) worldwide annually (1). Depending on the techniques and doses used, patients may experience a permanent change in their bowel habits.

2. ENDPOINTS

Acute rectal effects occur during or soon after RT and typically include softer or diarrhea-like stools, pain, a sense of rectal distention with cramping, and frequency. Occasionally, superficial ulceration causes bleeding that may require endoscopic cauterization, treatment for anemia, or transfusion. Late injuries are usually clinically manifest within 3 to 4 years after RT and may include stricture, diminished rectal compliance, and decreasing storage capacity with resultant small/frequent bowel movements. Injury to the anal musculature can lead to fecal incontinence or stricture. These morbidities can be severe and markedly affect quality of life (QOL).

Rectal bleeding is usually self–limited, although some patients require medical management with anti–inflammatory suppositories, antibiotics, endoscopic coagulative therapies, or rarely surgical diversion. In patients with endoscopic rectal abnormalities after RT, the most likely diagnosis is RT effect, and biopsy should not be performed because this may lead to chronic infection, poor healing or ulceration.

Radiation Therapy Oncology Group (RTOG) scoring criteria are commonly used to report toxicity (2). The original system was criticized as being vague, nonquantitative, and unvalidated. It emphasizes rectal bleeding and stool frequency but not fecal incontinence or bowel urgency, both of which impact QOL. Because of its objectivity, the presence of any rectal bleeding has been the sole endpoint reported in some series. Interpreting the rate of RT-induced sequelae is complicated because many symptoms are nonspecific and may be related to conditions such as hemorrhoids or irritable bowel disorders.

The Common Terminology Criteria for Adverse Events version 3.0 is being used more often in prospective clinical trials (3). It provides more specific descriptions of common toxicities after cancer therapy and is more quantitative than the RTOG scoring criteria.

3. CHALLENGES DEFINING VOLUMES

Dose–volume studies have used variable definitions for rectum. The superior limit is usually taken to be the rectosigmoid flexure, but there is uncertainty in determining where this occurs. The inferior limit has been variably defined as

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being at the level of the anal verge, the ischial tuberosities (or 2 cm below them), or above the anus (the caudal 3 cm of intestine). Other studies have specified rectal lengths, for example from 1 cm below to 1 cm above the target volume, or from standard treatment fields. Although the rectum is hollow, it is frequently contoured as a solid, including its contents.

The position of the rectum at the time of the treatment-planning CT scan is likely not fully representative of the position during RT because of inter- or intrafraction variations in rectal filling, intestinal gas, and bladder filling. These uncertainties are not considered in the present analysis.

4. REVIEW OF DOSE–VOLUME DATA

The most frequent endpoints considered in the published analyses are either rectal bleeding or RTOG Grade ≥2 late rectal toxicity. Grade 2 RTOG toxicity includes moderate diarrhea and colic, bowel movement more than five times daily, excessive rectal mucus, or intermittent bleeding. Grade 3 consists of obstruction or bleeding requiring surgery. Grade 4 (necrosis/perforation fistula) is rarely encountered in current practice.

Most dose–volume parameters significantly associated with late rectal toxicity consider doses ≥60 Gy. With a few exceptions, V_{Dose} has not been found to be significantly associated with differences in rectal toxicity for doses ≤45 Gy. Results are mixed for intermediate doses. In Fig. 1 we show published dose–volume histogram (DVH) thresholds. Rates of Grade ≥2 rectal toxicity were significantly higher for DVHs passing above these thresholds than for those passing below. Results from each study have been coded by dose spectrum (with red representing the highest biologically equivalent prescription and blue the lowest) and by line thickness (proportional to the overall rate of rectal toxicity in the study). This coding shows that at lower prescription doses, larger volumes must be exposed to intermediate doses before substantial toxicity is seen.

The curves converge at doses >70 Gy and volumes <20%, showing that dose–volume data from multiple centers converge at the high dose range. This implies that these values are more consistently associated with toxicity. To compare clinical DVHs with the thresholds shown in the figure, the DVH and prescription doses were first translated to linear-quadratic equivalent doses delivered in 2-Gy fractions, calculated using α/β = 3 Gy. Thresholds derived from treatments with similar biologically equivalent prescription doses may be found using the color coding specified in the legend. Threshold volumes shown in the graph are for the full length of the anatomic rectum. The reader should bear in mind that, as pointed out in the recommendations below, constraints at intermediate doses need to be validated.

Values of V_{Dose} tend to be highly correlated with one another across a wide range of doses, especially for patients treated at the same institution with similar techniques. Therefore, volumes exposed to intermediate doses may seem to be significant purely through their correlation with more biologically relevant high-dose volumes. Moreover, the volumes exposed to the highest doses are most subject to the discrepancies between the planned and delivered DVH. This too, could lead to an apparent association between toxicity and volumes exposed to intermediate doses. Alternatively, volumes exposed to intermediate and high doses might both have biologic significance if, for example, the volumes exposed to intermediate doses play a role in the recovery of tissue exposed to the highest doses (4).

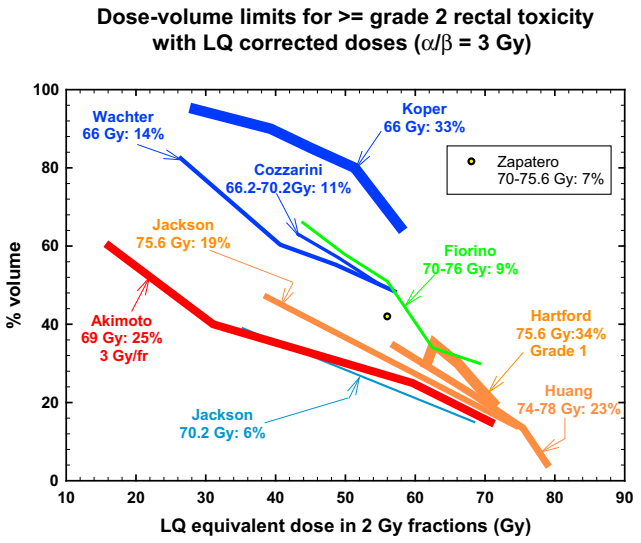

Fig. 1. Dose–volume histogram thresholds found to be significantly associated with Grade ≥ 2 rectal toxicity. Thicker lines indicate higher rates of rates of overall toxicity (percentages are indicated on the graph along with the physical prescription dose). Threshold doses are expressed as linear-quadratic equivalent doses delivered in 2-Gy fractions, calculated using α/β = 3 Gy. The associated linear-quadratic equivalent prescription doses are coded by spectrum from lowest (blue), to highest (red). Volumes shown in the graph are based on the full length of the anatomic rectum. Curves for Huang and Wachter were adjusted downward by 15% and by 50% for Hartford, to account for the different definitions used for rectal volume. Dose–volume data from multiple centers converge at the high dose range, implying that these values are more consistently associated with toxicity. Abbreviations: LQ = linear quadratic

5. FACTORS AFFECTING RISK

Factors reportedly associated with complication risk include diabetes mellitus (5–9), hemorrhoids (10, 11), inflammatory bowel disease (12), advanced age (8), androgen deprivation therapy (13, 14), rectum size (15), prior abdominal surgery (7), and severe acute rectal toxicity (7, 14, 16–20). A high rate of acute rectal toxicity is now recognized as associated with late RT proctopathy (18, 21, 22). In the Dutch randomized dose trial for localized prostate cancer, it was an independent significant predictor for late gastrointestinal (GI) toxicity (20, 22). This raises the question as to whether early interventions that lessen acute toxicity might also reduce the risk of late complications, or whether greater-than-expected acute toxicity might be an early indicator of patient hypersensitivity to RT.