Clinical Oncology (2007) **19:** 730–737
doi:10.1016/j.clon.2007.07.007

Overview

Is There a Limit to Dose Escalation for Rectal Cancer?

B. J. Cummings

Princess Margaret Hospital, Toronto, Ontario, Canada

ABSTRACT:
The radiation tolerance of the rectum is not fully understood. Published studies on the radiation treatment of cancers of the prostate, cervix and rectum have been reviewed to determine currently recommended dose–volume guidelines. The need for further studies directed specifically at the treatment of primary rectal cancer and perirectal node metastases is discussed. There seems to be room for escalation of the external beam doses currently given. Cummings, B. J. (2007). *Clinical Oncology* 19, 730–737

Key words: Dose escalation, radiation therapy, radiation tolerance, rectal cancer, rectum

Introduction

Our often fragmentary knowledge of the radiation tolerance of the rectum continues to improve. There is now a considerable volume of empirically derived data related to the tolerance of the rectal wall, although this has not been correlated with detailed pathophysiological studies. Until relatively recently, the conventional concept of rectal tolerance was that presented in 1991 by a National Cancer Institute-funded task force [1]. In their discussion of rectal tolerance, which considered only serious toxicities thought to require intervention (severe proctitis, necrosis, fistula, stenosis), the task force described the data available as limited and 'soft', and in particular did not identify a volume effect for the rectum. The tolerance dose (TD) associated with a probability of a 5% complication rate within 5 years from treatment (TD 5/5) was considered to be 60 Gy (at 2 Gy per fraction) for 100 cm^3, and for a 50% complication rate (TD 50/5) 80 Gy [1]. Additional clinical data compiled since the task force publication clearly indicate that the rectum does exhibit volume effects in response to radiation, and that there is a need to consider thresholds for less severe grades of toxicity.

Surgery remains the established principal treatment for rectal cancer, often coupled with adjuvant radiation and chemotherapy. In considering the potential for greater contributions by radiation we need to understand the radiation tolerance both of small volumes of the rectal wall (to encompass a primary rectal cancer) and of more extended volumes of the perirectal tissues (to encompass the regional lymph nodes). This brief overview draws on information available from animal studies and from clinical studies of cancers of the rectum, prostate and cervix. Much of the clinical data is derived from dose–volume histograms (DVH) or similar constructs. Space does not permit a critical analysis of the many variations in the definition of the rectum, the volumes contoured, set-up errors, organ motion, and all of the many other limitations of data derived from DVHs. Nevertheless, the data do provide useful pointers for future studies. Several investigators have commented on the shortcomings of the most commonly used toxicity scales from the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC), which consolidate different manifestations of toxicity. There is now evidence of different dose–response relationships for different clinical manifestations of rectal damage such as bleeding, rectal urgency, frequency of defecation, and so on [2,3]. Of necessity, this review presents the toxicity scales used by the investigator cited. The follow-up in some studies is brief, and it is known that severe late toxicity may not become apparent for several years and may even improve with time. Most recent studies have provided actuarial rates of toxicity rather than less meaningful crude proportions [4].

Biology and Pathology

The complex nature of the injury to normal tissue and the principles of normal tissue responses during and after radiation therapy were reviewed by Denham and Hauer-Jensen [5]. The morphology of radiation injury to normal tissue was described by Fajardo [6]. The limited information on anorectal physiology after pelvic radiation was collected by Hayne *et al.* [7], who found the results inconsistent; also, these studies did not correlate the results with detailed dose, volume or treatment technique information.

In a discussion of fractionation, Fowler [8] noted that the α/β (Gy) ratio for early reactions for the colon and rectum is about 9–11 and for late reactions 2.5–5. In a more

0936-6555/07/190730+08 $35.00/0

extended discussion of the α/β ratio for late rectal bleeding, Brenner [9,10] concluded from a review of clinical data that the α/β value for RTOG grade ≥ 2 late rectal toxicity is 5.4 ± 1.5 Gy, a value also consistent with most estimates for late rectal damage in rodents. This α/β value, intermediate between classic early and late effect values (8–10 Gy vs 1–3 Gy), is consistent with some 'late' damage being consequential to early rectal damage.

The pre-treatment potential doubling time of human rectal tumours has a median value of about 5 days (range 3–18) [8]. Suwinski *et al*. [11] analysed the reduction in incidence of pelvic relapses of rectal cancer after pre-operative adjuvant radiation as a function of radiation dose and overall treatment time. They concluded that, for a given overall treatment duration, the dose–response curve is relatively steep. They presented graphs that suggested that a linear-quadratic equivalent dose for 50 Gy in 2 Gy fractions ($LQED_{2Gy}$) would reduce the incidence of pelvic recurrence by about 80%. Although it is hazardous to extrapolate beyond the limits of the clinical data available (and the investigators acknowledged the many assumptions in their analysis), their graph suggests that 60 Gy ($LQED_{2Gy}$) should reduce the incidence of pelvic recurrence by about 90%. The clinical studies reviewed by Suwinski *et al*. [11] were from before the current era of extended surgical resection, such as total mesorectal excision, and from a time when presumably the tumour burden to be controlled by radiation may have been greater than in current practice. This may provide some reassurance when the treatment of subclinical lymph node metastases by radiation is considered (discussed below).

Animal Studies

Kummermehr and Trott [12] described the essence of animal experiments on late normal tissue damage by radiation as the clarification of pathogenesis and the quantification of the influence of treatment parameters. In a rat model, van der Kogel *et al*. [13] described two waves of injury in the rectum, one of acute ulceration and the other of slowly progressive submucosal fibrosis, vascular sclerosis and colitis cystica profunda. Increasing the overall treatment time resulted in a significant rise in isoeffective doses for chronic injury, suggesting that the early mucosal response contributed significantly to more delayed reactions. Trott *et al*. [14] concluded that different mechanisms may be at play in the development of functional (obstruction) vs structural (ulceration) damage. The larger the volume or the longer the section of the rectum irradiated, the earlier functional damage was seen. Ulceration of atrophic mucosa seems to be a consequence of secondary damage, such as by the passage of faeces over the mucosa. Annular ulceration and stenosis were seen only if the volume of chronic damage exceeded a threshold length and segment of the circumference. Dubray and Thames [15] reanalysed data generated by Kummermehr and Trott and their colleagues according to a mathematical model that assumed a hierarchical architecture of the rectum, with independent functional units. They suggested that the parameters for late rectal stenosis derived from their model were consistent with damage to a mixture of early and late responding tissues, with high or intermediate fractionation sensitivity, early and fast repopulation, and possibly slow repair kinetics. Kummermehr and Trott [12] observed that this model of a presumed target cell (or unit) in the rectal wall failed to account for many other factors within the data, such as the large range of isoeffective total doses found for different treatment schedules.

Other animal studies have addressed the issue of healing of surgical incisions in the irradiated rectum from the perspective of the integrity of colorectal anastomosis, although not for lesser injuries such as those of local excision of a rectal tumour. The general conclusion has been that tolerance is fairly high if only one segment of the anastomosis has been irradiated [16]. However, the animal models do not provide dose correlations that can be translated to humans.

Human Studies

The systematic dose escalation studies for the treatment of prostate cancer and the introduction of high dose rate brachytherapy for uterine cervical cancer have provided useful information on the radiation tolerance of the rectum. The end point usually reported has been intermittent frequent bleeding from the rectal wall (usually RTOG/EORTC grade 2) on the basis that the greater frequency of low-grade complications allows better analysis of dose–volume–risk statistics. There are many differences between the details of different studies, such as treatment techniques, radiation prescription factors, morbidity scales and analysis of results that are not addressed here. These differences probably account for the range of dose-tolerance estimates from different studies. In the treatment of both prostrate and cervix cancer, the highest doses have been concentrated in the anterior wall of the rectum. Also, the studies discussed are generally from before the introduction of highly conformal techniques such as intensity modulated radiotherapy.

Prostate Cancer

Skwarchuk *et al*. [17,18] reviewed 743 patients with clinically localised prostate cancer treated by three-dimensional conformal radiation therapy (3D-CRT). The 5-year actuarial incidence of grade 2 or greater late rectal toxicity was $3.4 \pm 2.9\%$ at 64.8 Gy (3/96 patients), $7.8 \pm 4.3\%$ at 70.2 Gy (18/266 patients) and $15.9 \pm 6.6\%$ at 75.6 Gy (45/320 patients). The incidence of grade 3 or greater late toxicity was less than 2% at each dose level. Patients were treated at 1.8 Gy per fraction by six individually shaped coplanar fields. The treatment volume extended 1.5 cm above and 1.5 cm below the prostate and seminal vesicles. In constructing the DVH, the rectal wall was contoured from just below the sigmoid flexure to just above the anal verge. The likelihood of bleeding increased significantly for patients with smaller overall rectal wall