Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S123–S129, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.03.078

RADIATION DOSE–VOLUME EFFECTS IN RADIATION-INDUCED RECTAL INJURY

Jeff M. Michalski, M.D.,* Hiram Gay, M.D.,* Andrew Jackson, M.D.,† Susan L. Tucker, Ph.D.,‡ and Joseph O. Deasy, Ph.D.*

*Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO; †Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY; and ‡Department of Bioinformatics and Computational Biology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

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

Reprint requests to: Jeff Michalski, M.D., Department of Radiation Oncology, Washington University School of Medicine, 4921 Parkview Place – Campus Box 8224, St. Louis, MO 63110. Tel: (314) 362-8566; Fax: (314) 747-9557; E-mail: jmichalski@radonc.wustl.edu

Supported by National Institutes of Health Grants NIH RO1 CA85181 and NIH RO1 CA104342.

Conflict of interest: none.

Received Jan 16, 2009, and in revised form Feb 24, 2009. Accepted for publication March 3, 2009.

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).

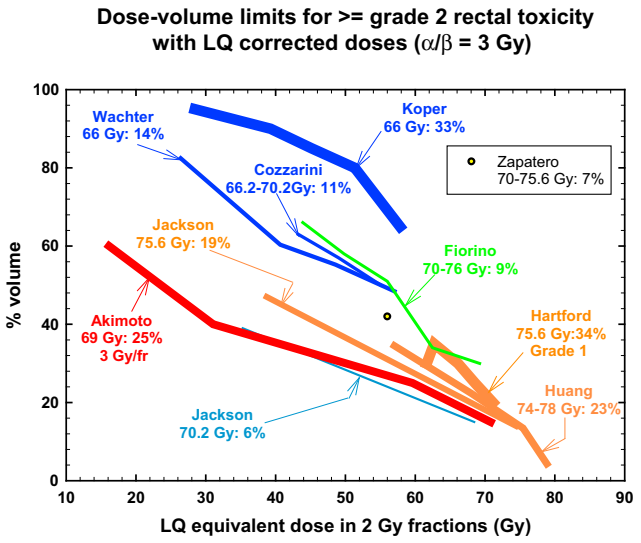

Fig. 1. Dose–volume histogram thresholds found to be significantly associated with Grade ≥ 2 rectal toxicity. Thicker lines indicate higher rates of rates of overall toxicity (percentages are indicated on the graph along with the physical prescription dose). Threshold doses are expressed as linear-quadratic 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.

6. MATHEMATIC/BIOLOGIC MODELS

The published literature includes at least five fits of the Lyman-Kutcher-Burman (LKB) normal tissue complication probability (NTCP) model to rectal toxicity data (7, 10, 23–27) (Table 1). With one exception (10) the published parameter estimates have been remarkably consistent, even though the endpoint has varied somewhat among these studies. The volume parameter, n, has usually, but not always, been found to be quite small (<0.15). Small values of n indicate that high-dose regions play a predominant role in determining the risk of late rectal toxicity (i.e., series architecture), in accordance with the analyses of the DVH cut-points (Fig. 1). An advantage of the LKB model over DVH constraints is that it yields NTCP values for patient-specific treatment plans.

7. SPECIAL SITUATIONS

Given the large numbers of patients included in published studies of rectal toxicity, and the relative consistency of their results for rectal bleeding, existing estimates of toxicity from the LKB model are probably better than for most organs.

In the Dutch randomized trial, bleeding, high stool frequency, and fecal incontinence were scored and modeled separately. Not only were the parameter estimates markedly different for each endpoint, but the organ at risk also differed (27). For rectal bleeding and high stool frequency, modeling based on the DVH of the anorectal wall was best, whereas for fecal incontinence, that of the distal 3 cm of the anal canal wall was most relevant. Furthermore, they estimated the dose-modifying factors for patients with increased risk of rectal injury due to prior abdominal surgery.

Model-based predictions for treatments with prescribed doses >79.2 Gy and diseases other than prostate cancer, for which there is little data, should be viewed as tentative and require validation. Model predictions may not be representative of settings where intensity modulation or image-guided practices are in place. In the prostate cancer dose escalation trial, RTOG 9406, larger planning target volumes (PTVs) were associated with increased toxicity (28). Image guidance should reduce the volume of rectum that overlaps with the high-dose PTV and yield a planned rectal DVH that more closely approximates the volume of rectum irradiated daily.

The NTCP estimates are population-based: a low risk estimate does not preclude the occurrence of rectal injury, possibly severe, in any individual patient.

8. RECOMMENDED DOSE/VOLUME LIMITS

Organ segmentation

The rectum should be segmented from above the anal verge to the turn into the sigmoid colon, including the rectal contents. Although there can be variation in defining these landmarks, the superior limit is where the bowel moves anteriorly, close to the inferior level of the sacroiliac joints, and the inferior limit is commonly at the bottom of the ischial tuberosities. In prostate cancer therapy, an empty rectum at simulation is advised to avoid introducing a systematic error in PTV coverage. A supine position is associated with less variability in daily organ positioning. These conditions are less critical with image-guided RT.

Dose–volume constraints for conventional fractionation up to 78 Gy

The following dose–volume constraints are provided as a conservative starting point for 3D treatment planning: $V_{50} < 50\%$, $V_{60} < 35\%$, $V_{65} < 25\%$, $V_{70} < 20\%$, and $V_{75} < 15\%$. However, they have yet to be validated as ''relatively-safe.'' For typical DVHs, the NTCP models predict that following these constraints should limit Grade ≥2 late rectal toxicity to <15% and the probability of Grade ≥3 late rectal toxicity to <10% for prescriptions up to 79.2 Gy in standard 1.8- to 2-Gy fractions.

Higher doses in the V_{Dose} parameter have more impact on the complication probability. Clinicians should strive to minimize the V_{70} and V_{75} volumes below the recommended constraints without compromising tumor coverage. Reducing the V_{75} by just 5% from 15% to 10% has a significant impact in the predicted complication probability, whereas reducing the V_{50} from 50% to 45% makes relatively little difference.

Intensity-modulated RT (IMRT) planning yields distinctly different shaped DVH curves than forward-planned 3D conformal RT (3D-CRT), with considerably decreased rectal volume receiving low to intermediate radiation doses. Although the parameters above provide a safe starting point for both 3D-CRT and IMRT, it is likely that because IMRT can achieve better low to intermediate dose–volume constraints, the observed rectal toxicity will be lower (20). The Memorial Sloan-Kettering IMRT experience suggests that doses in the intermediate range of 40–60 Gy may become important in patients who are receiving radiation prescriptions in excess of 78 Gy.

NTCP models

All series from which LKB parameters are reported used 3D-CRT prescribed to doses ≤79.2 Gy for localized prostate cancer. Depending on the patient geometry, dose prescribed, treatment technique, and other clinical variables, the proposed dose–volume constraints might be unachievable (e.g., for doses >79.2 Gy), but every effort should be made to be as close as possible to the constraints especially in the high doses. In situations similar to those from which the model parameters were derived, the LKB model can estimate the complication probability.

A meta-analysis of the results from the four studies (10, 24–26) of Grade ≥2 late toxicity or rectal bleeding gave the overall best estimates of the LKB parameters (95% confidence interval) as n = 0.09 (0.04–0.14); m = 0.13 (0.10–0.17); and TD_{50} = 76.9 (73.7–80.1) Gy. Estimates of TD_{50} were found to be heterogeneous (the null hypothesis that estimates for a model parameter were drawn from the same distribution was rejected, $p < 0.01$; the inconsistency index [I^2] was 79%). Although heterogeneity could not be established for estimates of n ($p > 0.1$), the inconsistency index was substantial

Table 1. Description of endpoints, study details, and Lyman-Kutcher-Burman parameters for published analyses

Authors (reference)	Endpoint	No. of centers/time period studied/RT technique	Incidence, % (*n*)	Total prescribed dose (Gy)/fraction size (Gy)	Parameters (68% CI) [95% CI]	Rectal DVH
Tucker *et al.* (26)	Grade ≥2 RTOG*	42 1994–2000 Mostly 4–7 field 3D-CRT	13.5 (138/1023)	68.4, 73.2, 79.2/1.8 74, 78/2	n = 0.08 [0.04–0.26] m = 0.14 [0.10–0.25] TD_{50} = 78 [72–84] Gy	Rectum plus contents
Söhn *et al.* (25)	Grade ≥2 CTCAE v3.0†	1 1999–2002 4-field 3D-CRT	16 (51/319)	70.2, 72, 73.8, 75.6, 77.4, 79.2/1.8	*a* = 11.9 ± 3.8 n = 1/a = 0.08 m = 0.108 ± 0.027 $TD_{50/not\ reported}$ = 78.4 ± 2.1 Gy Median follow-up: 2.8 y; range, 0.1–6.4 y	Rectum plus contents
Rancati *et al.* (24)	Grade ≥2 bleeding‡	5 1994–2001 3–4-field 3D-CRT	7.0 (38/547) intact and postprostatectomy	64–79.2/1.8–2	n = 0.23 (0.14–0.42) m = 0.19 (0.15–0.25) $TD_{50/1.5}$ = 81.9 (76.8–91.2) Gy	Rectum plus contents
			6.9 (22/321) intact only	70–79.2/1.8–2	n = 0.24 (0.14–0.50) m = 0.14 (0.11–0.19) $TD_{50/1.5}$ = 75.7 (72.1–81.8) Gy	
	Grade ≥3 bleeding§		1.6 (9/547)	64–79.2/1.8–2	n = 0.06 ± 0.01? m = 0.06 ± 0.005? $TD_{50/1.5}$ = 78.6 ± 3.7? Gy	
Peeters *et al.*(27)	Bleeding‖	4 1997–2003 2–4-field 3D-CRT¶	4.9 (23/468)	68 (*n* = 234), 78 (*n* = 234)/2	n = 0.13 (0.04–0.25) m = 0.14 (0.11–0.19) $TD_{50/3}$ = 81 (75–90) Gy	Anorectal wall; method of Meijer *et al.* (35)
	Frequency		6.4 (30/468)		n = 0.39 (0.19–1.11) m = 0.24 (0.18–0.35) $TD_{50/3}$ = 84 (75–103) Gy	Anorectal wall; method of Meijer *et al.* (35)
	Fecal incontinence		6.8 (32/468)		n = 7.48 (0.56–∞) m = 0.46 (0.39–0.52) $TD_{50/3}$ = 105 (88–138) Gy	Anal wall; method of Meijer *et al.* (35)
Cheung *et al.* (10)	Grade ≥2 toxicity, modified scale#	1 1992–1999 3D-CRT 4-field to 46 Gy 6-field to 78 Gy	22.7 (29/128) Without hemorrhoids 16.7 (14/ 84)	78/2	n = 3.91 [0.031–∞] m = 0.156 [0.036–0.271] TD_{50} = 53.6 [50–75.1] Gy n = 0.746 [0.026–∞] m = 0.092 [0.019–0.189] TD_{50} = 56.7 [49.9–75.2] Gy	External rectal wall plus contents

(*Continued*)

Table 1. Description of endpoints, study details, and Lyman-Kutcher-Burman parameters for published analyses (*Continued*)

Authors (reference)	Endpoint	No. of centers/time period studied/RT technique	Incidence, % (*n*)	Total prescribed dose (Gy)/fraction size (Gy)	Parameters (68% CI) [95% CI]	Rectal DVH
Burman *et al.* (23)	Severe proctitis, necrosis, fistula, and stenosis**				n = 0.12 m = 0.15 $TD_{50/5}$ = 80 Gy	

* Grade 2 is defined as "moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding" (2), starting or persisting >120 days after start of therapy.
† Chronic rectal bleeding that excludes Grade 1 bleeding defined as "mild hemorrhage/bleeding; intervention (other than iron supplements) not indicated."
‡ Excludes Grade 1 or "slight" bleeding (≤2 weeks). Late complications were defined as those developing >3 months after the completion of the therapy, or those starting before and persisting for >3 months after the completion of therapy.
§ Grade 3 defined as a single coagulation procedure and/or transfusion. Late complications were defined as those developing >3 months after the completion of the therapy or those starting before and persisting for >3 months after the completion of therapy.
‖ Bleeding requiring laser treatment or transfusion of packed cells and starting >120 days after the start of therapy.
¶ Two patients received intensity-modulated radiotherapy.
# Excludes Grade 1 toxicity defined as excess bowel movements twice baseline and/or slight rectal discharge or blood.
** Based on the Emami *et al.* rectal tolerance estimates in 1991 (36) and provided for historical purposes only.
Abbreviations: RT = radiotherapy; CI = confidence interval; DVH = dose–volume histogram; RTOG = Radiation Therapy Oncology Group; 3D-CRT = three-dimensional conformal radiotherapy; $TD_{50/t}$ = radiation dose that would result in a 50% risk of severe complications within *t* years after irradiation; CTCAE = Common Terminology Criteria for Adverse Events; ? = deduced using a method that yields smaller uncertainties than those of the other studies.
All studies are prospective except Rancati *et al.*

($I^2 = 40\%$). Estimates of m showed no indications of heterogeneity ($p > 0.1, I^2 = 0$). The source of heterogeneity in both n and TD_{50} was the study from the M. D. Anderson Cancer Center (10). If that data set was excluded, the best estimate of TD_{50} became 78.5 (75.2–81.8) Gy. Other parameters remained the same to 10% in the confidence intervals; however, all indications of heterogeneity disappeared ($p > 0.1, I^2 = 0$ for all parameters). Excluding prostatectomy patients (24) from the analysis resulted in essentially no change in the overall best estimates of parameter values or in measure of heterogeneity.

It is notable that the LKB parameters from studies of Grade ≥3 late rectal bleeding (24, 27) (Table 1) are broadly similar to those above. It might be expected that the dose response for Grade 3 complications should be shifted to higher doses, but this was not seen. However, Rancati *et al.* (24) showed a decrease in n (to 0.06) for Grade ≥3 complications, indicating an increased dependence on the highest doses. Daily deviations of rectal position probably result in some patients receiving higher cumulative rectal DVHs than planned. Such patients may skew the corresponding NTCP modeling analysis, making the resulting parameters overestimate the complication risk. For this reason, the model predictions have some uncertainty regarding their applicability depending on the immobilization, treatment, and localization techniques used. In the presence of daily localization and IMRT, these models may tend to overestimate the risk of toxicity because the model parameters were based on patients treated mostly without IMRT or daily localization. Patients treated with IMRT have been reported to have lower complication rates than those treated with standard 3D-CRT (20).

Hypofractionation

Until more clinical data are available for the various hypofractionated schedules, DVH dose bins should be adjusted to conventional 1.8- or 2-Gy fractions using the linear-quadratic model with an α/β ratio of 3 for the rectum. Whereas some have proposed a rectal α/β ratio of 5.4 Gy, the choice of α/β ratio of 3 is a reasonably conservative estimate (29). The LKB model could then be used on a linear-quadratic–adjusted DVH to estimate the rectal complication probability. An interim report of a prospective robotic radiosurgery Phase II trial of 36.25 Gy in 5 fractions observed a reduced rate of severe rectal toxicities with an every-other-day vs. consecutive-day treatment schedule (30). This observation warrants further exploration.

3D-CRT vs. IMRT

Most of the mature published clinical data on dose-related rectal toxicity come from 3D-CRT. Increasingly, IMRT is being used to treat pelvic malignancies, especially localized prostate cancer, often leading to a much lower volume of rectal tissue receiving intermediate to high doses. Modeling derived from 3D-CRT treatments may need to be modified to predict complications from IMRT treatments. As discussed in "Review of Dose–Volume Data," intermediate dose levels are often correlated to the specific 3D treatment techniques used, and rectal volumes exposed to these doses

are often correlated to biologically relevant high-dose volumes. This may explain why intermediate doses have inconsistently been associated with rectal toxicity. However, if volumes exposed to intermediate and high doses both have biological significance, then the reduction of rectal volumes exposed to doses in the 45-60 Gy range by IMRT may become more important.

9. FUTURE TOXICITY STUDIES

Improvements in modeling of late rectal toxicity will likely come from DVHs that more accurately reflect the actual distribution of the doses delivered to the rectum, and the separate scoring and modeling of different aspects of rectal toxicity (bleeding, stool frequency, and fecal incontinence). Determination of the relevant anatomic structures for the different rectal endpoints (7, 31) will improve our ability to predict them. Reporting absolute and relative rectal volumes receiving or exceeding dose thresholds is encouraged.

Finally, there is growing recognition that individual factors, such as genetic predisposition, comorbidities, and lifestyle choices (e.g., diet and smoking habits), can affect normal-tissue complication risk. Identification of the relevant factors for each endpoint, and incorporation of these factors into the dose–volume-based models, will undoubtedly improve the prediction of sequelae.

The dose constraint parameters provided here will provide clinicians with guidance for RT treatment planning, but they should not replace clinical judgment. These parameters, especially those at the intermediate dose range (45–60 Gy), require prospective validation.

10. TOXICITY SCORING

Current methods of scoring rectal toxicity need to be examined. The inclusion of patient-reported outcomes complements objective physician-scored criteria. Tools to score both acute and late effects need to be efficient and validated. Toxicity assessments should measure clinically relevant events that matter to patients. Several QOL scales have been developed and validated that measure the impact of therapy after the treatment of prostate cancer (32, 33). The Expanded Prostate Cancer Index Composite includes a validated bowel domain that is potentially applicable to any patient receiving pelvic RT (33). Although the original RTOG/European Organization for Research and Treatment of Cancer late toxicity scales have been criticized for their lack of specificity and objectivity, quantifiable modifications to the criteria have been proposed (34). In the Dutch randomized trial five GI indicators were used to characterize the origin and clinical course of toxicity. Using both physician notes and patient self-assessments, Peeters *et al*. (27) characterized GI toxicity according to these five indicators that were correlated to specific anatomic and dose–volume parameters. Development and validation of a rectal toxicity scoring system that incorporates physician assessments and patient-reported outcomes is a priority.

REFERENCES

1. Andreyev HJ. Gastrointestinal problems after pelvic radiotherapy: The past, the present and the future. *Clin Oncol (R Coll Radiol)* 2007;19:790–799.
2. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
3. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, version 3.0. Washington, DC: Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Department of Health and Human Services; 2006.
4. Jackson A, Skwarchuk MW, Zelefsky MJ, *et al*. Late rectal bleeding after conformal radiotherapy of prostate cancer. II. Volume effects and dose-volume histograms. *Int J Radiat Oncol Biol Phys* 2001;49:685–698.
5. Akimoto T, Muramatsu H, Takahashi M, *et al*. Rectal bleeding after hypofractionated radiotherapy for prostate cancer: Correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding. *Int J Radiat Oncol Biol Phys* 2004;60:1033–1039.
6. Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: A predictor for late radiation morbidity. *Int J Radiat Oncol Biol Phys* 1999;43:475–479.
7. Peeters ST, Lebesque JV, Heemsbergen WD, *et al*. Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;64:1151–1161.
8. Skwarchuk MW, Jackson A, Zelefsky MJ, *et al*. Late rectal toxicity after conformal radiotherapy of prostate cancer (I): Multivariate analysis and dose-response. *Int J Radiat Oncol Biol Phys* 2000;47:103–113.
9. Vavassori V, Fiorino C, Rancati T, *et al*. Predictors for rectal and intestinal acute toxicities during prostate cancer high-dose 3D-CRT: Results of a prospective multicenter study. *Int J Radiat Oncol Biol Phys* 2007;67:1401–1410.
10. Cheung R, Tucker SL, Ye JS, *et al*. Characterization of rectal normal tissue complication probability after high-dose external beam radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1513–1519.
11. Huang EH, Pollack A, Levy L, *et al*. Late rectal toxicity: Dose-volume effects of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;54:1314–1321.
12. Willett CG, Ooi CJ, Zietman AL, *et al*. Acute and late toxicity of patients with inflammatory bowel disease undergoing irradiation for abdominal and pelvic neoplasms. *Int J Radiat Oncol Biol Phys* 2000;46:995–998.
13. Liu M, Pickles T, Agranovich A, *et al*. Impact of neoadjuvant androgen ablation and other factors on late toxicity after external beam prostate radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;58:59–67.
14. Schultheiss TE, Lee WR, Hunt MA, *et al*. Late GI and GU complications in the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;37:3–11.
15. Wachter S, Gerstner N, Goldner G, *et al*. Rectal sequelae after conformal radiotherapy of prostate cancer: Dose-volume histograms as predictive factors. *Radiother Oncol* 2001;59:65–70.
16. Cozzarini C, Fiorino C, Ceresoli GL, *et al*. Significant correlation between rectal DVH and late bleeding in patients treated

after radical prostatectomy with conformal or conventional radiotherapy (66.6-70.2 Gy). *Int J Radiat Oncol Biol Phys* 2003;55:688–694.
17. Fiorino C, Sanguineti G, Cozzarini C, *et al*. Rectal dose-volume constraints in high-dose radiotherapy of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2003;57:953–962.
18. O'Brien PC, Franklin CI, Poulsen MG, *et al*. Acute symptoms, not rectally administered sucralfate, predict for late radiation proctitis: longer term follow-up of a phase III trial—Trans-Tasman Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 2002;54:442–449.
19. Vargas C, Martinez A, Kestin LL, *et al*. Dose-volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;62:1297–1308.
20. Zelefsky MJ, Levin EJ, Hunt M, *et al*. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:1124–1129.
21. Denham JW, O'Brien PC, Dunstan RH, *et al*. Is there more than one late radiation proctitis syndrome? *Radiother Oncol* 1999; 51:43–53.
22. Heemsbergen WD, Peeters ST, Koper PC, *et al*. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: Consequential late damage. *Int J Radiat Oncol Biol Phys* 2006;66:3–10.
23. Burman C, Kutcher GJ, Emami B, *et al*. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys* 1991;21:123–135.
24. Rancati T, Fiorino C, Gagliardi G, *et al*. Fitting late rectal bleeding data using different NTCP models: Results from an Italian multi-centric study (AIROPROS0101). *Radiother Oncol* 2004;73:21–32.
25. Sohn M, Yan D, Liang J, *et al*. Incidence of late rectal bleeding in high-dose conformal radiotherapy of prostate cancer using equivalent uniform dose-based and dose-volume-based normal tissue complication probability models. *Int J Radiat Oncol Biol Phys* 2007;67:1066–1073.
26. Tucker SL, Dong L, Bosch W. Fit of a generalized Lyman normal-tissue complication probability (NTCP) model to Grade ≥ 2 late rectal toxicity data from patients treated on protocol RTOG 94-06. *Int J Radiat Oncol Biol Phys* 2007;69:S8–S9.
27. Peeters ST, Hoogeman MS, Heemsbergen WD, *et al*. Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: Normal tissue complication probability modeling. *Int J Radiat Oncol Biol Phys* 2006; 66:11–19.
28. Michalski JM, Bae K, Roach M, *et al*. Long-Term Toxicity Following 3D Conformal Radiation Therapy for Prostate Cancer from the RTOG 9406 Phase I/II Dose Escalation Study. *Int J Radiat Oncol Biol Phys* 2009.
29. Brenner DJ. Fractionation and late rectal toxicity. *Int J Radiat Oncol Biol Phys* 2004;60:1013–1015.
30. King CR, Brooks JD, Gill H, *et al*. Stereotactic body radiotherapy for localized prostate cancer: Interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys* 2009;73: 1043–1048.
31. al-Abany M, Helgason AR, Cronqvist AK, *et al*. Toward a definition of a threshold for harmless doses to the anal-sphincter region and the rectum. *Int J Radiat Oncol Biol Phys* 2005;61: 1035–1044.
32. Litwin MS, Hays RD, Fink A, *et al*. The UCLA Prostate Cancer Index: Development, reliability, and validity of a health-related quality of life measure. *Med Care* 1998;36:1002–1012.
33. Wei JT, Dunn RL, Litwin MS, *et al*. Development and validation of the Expanded Prostate Cancer Index Composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 2000;56: 899–905.
34. Peeters ST, Heemsbergen WD, van Putten WL, *et al*. Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 2005;61:1019–1034.
35. Meijer GJ, van den Brink M, Hoogeman MS, *et al*. Dose-wall histograms and normalized dose-surface histograms for the rectum: A new method to analyze the dose distribution over the rectum in conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;45:1073–1080.
36. Emami B, Lyman J, Brown A, *et al*. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21: 109–122.