

CLINICAL INVESTIGATION

Prostate

PATIENT-ASSESSED LATE TOXICITY RATES AND PRINCIPAL COMPONENT ANALYSIS AFTER IMAGE-GUIDED RADIATION THERAPY FOR PROSTATE CANCER

MARKETA SKALA, M.D.,\* TARA ROSEWALL, M.Sc.,† LAURA DAWSON, M.D.,\* LORELLA DIVANBEIGI, B.Sc.,† GINA LOCKWOOD, M.A.,‡ CHRISTOPHER THOMAS, Ph.D.,§ JUANITA CROOK, M.D.,\* PETER CHUNG, M.B.,\* PADRAIG WARDE, M.B.,\* AND CHARLES CATTON, M.D.\*

Departments of \*Radiation Oncology, †Radiation Therapy, ‡Biostatistics, and §Medical Physics, Princess Margaret Hospital and the University of Toronto, Toronto, ON, Canada

**Purpose:** The aims of this study were to determine the incidence of patient-assessed late toxicity after high-dose, image-guided radiation therapy in a cohort of men with prostate cancer; and to correlate toxicity with conventional dosimetric parameters and rectal and bladder dose–volume histograms (DVH) reduced using principal component analysis.

**Methods and Materials:** Toxicity questionnaires were sent to 690 men treated for localized prostate cancer to 75.6 Gy or 79.8 Gy using three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) between 1997 and 2003 at the Princess Margaret Hospital. Toxicity was graded according to the modified Radiation Therapy Oncology Group (RTOG)–late effects normal tissue (LENT) scoring system. Late rectal and bladder toxicity scores were dichotomized as < Grade 2 and ≥ Grade 2, and correlated with dosimetric parameters and with the first three principal components of rectal and bladder DVHs.

**Results:** In all, 63% of the patients completed the questionnaire. At a median follow-up of 37 months, the incidence of late rectal toxicity RTOG Grades 1, 2, and 3 was 25.2%, 2.5%, and 0.7% respectively. The incidence of late urinary toxicity RTOG Grade 1, 2, and 3 was 16.5%, 8.8%, and 0.9% respectively. Maintenance of erectile function sufficient for intercourse was reported in 68%. No dosimetric parameter analyzed, including principal component analysis reduction of DVHs, correlated with late toxicity.

**Conclusions:** Postal questionnaire was effective for collection of patient-assessed late toxicity data. The incidence of late toxicity was low, with a lack of correlation to dosimetric parameters. We attribute this to the use of conformal techniques and daily image guidance. © 2007 Elsevier Inc.

Prostate carcinoma, Conformal radiotherapy, Image-guided radiotherapy, Late morbidity, Principal component analysis.

INTRODUCTION

Evidence from prospective randomized trials (1–3) demonstrates a radiation dose–response relationship for prostate cancer, in which biochemical tumor control is improved with higher radiation doses. However, radiation dose escalation is also associated with increased risk of late rectal toxicity (1, 4). The optimal radiation dose and radiation treatment technique for prostate cancer is one that will maximize tumor control and minimize the risk of late treatment-related complications.

Highly conformal treatment techniques such as three-dimensional conformal radiation therapy (3DCRT) and in-

tensity-modulated radiation therapy (IMRT) have been shown to limit the volume of surrounding normal tissues irradiated, and to reduce the rate of radiation-induced toxicity (5). Identification of the optimal radiation treatment technique for prostate cancer has been a topic of empiric research with sequential dose escalation studies (4, 6), and most available data concerning the late radiation effects for prostate cancer are physician-reported. This method of data collection underestimates both the frequency and severity of complications compared with patient-reported outcomes (7, 8).

A pilot study reported by Nichol *et al.* (9) involving the

Reprint requests to: Charles Catton, M.D., Princess Margaret Hospital, 610 University Avenue, Toronto, ON, Canada M5G 2M9; Tel: (416) 946-2121; Fax: (416) 946-2111; E-mail: charles.catton@rmp.uhn.on.ca

Presented in part at the 47th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), Denver, CO, October 16-20, 2005.

Supported by a Canadian Prostate Cancer Research Initiative Idea Grant.

**Acknowledgments**—The authors thank Aaron Dewitt for data entry and Douglas Mosley for advice with principal component analysis.

Conflict of interest: none.

Received Oct 30, and in revised form Dec 27, 2006. Accepted for publication Dec 28, 2006.

first 112 patients treated with escalated dose conformal radiotherapy at Princess Margaret Hospital confirmed the feasibility of collecting patient-reported toxicity data by postal questionnaire. This same technique was used to investigate the larger cohort of patients included in this report.

Although cross-sectional toxicity data collection provides less information than does longitudinal data collection, it is less expensive and less time consuming to collect. It provides a useful “snapshot” of the toxicity rates expected of a particular treatment technique, provided that the sample size is large and the follow-up is sufficient so that most events are likely to have occurred.

Three-dimensional radiotherapy planning systems provide an accurate record of the radiation dose delivered to quantified volumes of normal tissue during a radical course of radiotherapy, as summarized in the dose–volume histogram. This information can be correlated with patient-reported late effects to provide a model that hopefully predicts late radiation toxicity. This model could potentially permit safer radiation dose escalation in the future, and could provide a valuable tool for radiation research by predicting the late toxicity likely to result from novel dose-fractionation schemes for the investigational treatment of prostate cancer with radical radiotherapy.

Conformal and IMRT dose distributions are highly complex, and it is not possible to compare treatment plans adequately by visual inspection of isodoses alone. This has led to the widespread use of cumulative DVHs for plan comparison, as these represent the three-dimensional dose distribution as a function of two parameters, *i.e.*, dose and volume.

The risk of late rectal bleeding after prostate radiation has been related to single points on a DVH (10–12). However, potentially critical dose–volume information that might best discriminate between treatment plans at high or low risk for complications is lost in the reduction of the DVH to a single point. Principal component analysis (PCA) is a tool capable of quantifying the variability in a dataset of DVHs and segregating DVHs with similar morphology (*i.e.*, comparable doses to similar relative volumes). This allows comparison between groups of similar DVHs with respect to complication risk, without the loss of information inherent in the simpler methods of analysis. This methodology has been used to reduce DVHs of parallel functioning normal tissues, and to relate the reduced DVHs to the risk of liver toxicity after partial liver irradiation and the risk of xerostomia after parotid gland irradiation (13).

In this study, PCA was chosen as a method to utilize all the information inherent in the DVH of the bladder and the rectum and to relate that information to patient-reported late urinary and rectal toxicity after dose escalated radiotherapy for prostate cancer.

## METHODS AND MATERIALS

The local research ethics board approved the study protocol, and all patients provided written consent before participating in the questionnaire research.

In January 2005 a postal questionnaire, modified from Crook *et al.* (14) (Appendix 1), was sent to 578 low- or intermediate-risk prostate cancer patients treated between 1999 and 2003. No validated quality of life instrument has been designed for administration as a postal questionnaire. It was beyond the scope of this investigation to validate the questionnaire used in this study, although it has been used successfully by others (9, 14). Eligibility criteria included clinical stage T1 to T2, NX, M0 adenocarcinoma of the prostate, and a prescribed dose of 75.6 Gy (years 1999–2000) or 79.8 Gy (years 2000–2003) delivered with 3DCRT (years 1999–2002) or IMRT (years 2001–2003) with on-line image-guided radiotherapy (IGRT). It was not the policy to use adjunctive hormonal therapy for patients with low- or intermediate-risk disease, although 138 (24%) received at least 1 month of neoadjuvant therapy.

A pilot study using the same questionnaire, but excluding the module on erectile function, was conducted in February 2004 with a cohort of 112 patients with intermediate-risk prostate cancer treated from 1997 to 1999 with 3DCRT and image guidance and prescribed a dose of 75.6 Gy (9). This study confirmed the feasibility of collecting toxicity data in this way, and the results from both cohorts have been combined for late bladder and rectal toxicity reporting, dosimetry analysis, and principal component analysis.

Patient responses to the questionnaire were converted to late rectal and urinary toxicity scores according to Storey’s modification of the Radiation Therapy Oncology Group (RTOG)–late effects normal tissue (LENT) late toxicity scoring system (12). Posttreatment erectile function was graded from 0 to 3 based on respondents’ reports of erections that were sufficient for intercourse always (score 0), most of the time (1), some of the time (2), or never (3).

### Radiotherapy planning

All patients had three cylindrical 1 × 5-mm gold markers implanted into the base, posterior aspect of mid-gland and apex of the prostate under transrectal ultrasound guidance before treatment planning. Patients were instructed to present for planning and treatment with an empty rectum and a comfortably full bladder, and were immobilized supine in a rigid immobilization device extending from the waist to mid-thigh. The planning CT was obtained without contrast using 5-mm slice thickness at 3-mm intervals through the prostate. The clinical target volume (CTV) was the prostate alone. The planning target volume (PTV) was defined as an expansion of the CTV by 10 mm, except toward the rectum, where a 7-mm margin was used. Rectal and bladder walls were contoured as hollow structures, limited to the caudal and cranial extent of the irradiated volume.

Dose constraints were used to limit the dose to the contoured organs at risk: femoral heads (100% to receive <50 Gy), rectal wall (50% to receive ≤50 Gy), and bladder wall (50% to receive ≤50 Gy). The PTV was planned to receive at least 95% of the prescription dose. The patients who were prescribed 79.8 Gy were planned so that 50% of the contoured rectal and bladder walls received ≤55 Gy.

The patients were planned using a six-field coplanar conformal technique or a 5-field sliding window IMRT technique using CADplan/Helios, version 6.2 (Varian Medical Systems Inc., Palo Alto, CA). The dose was 75.6 Gy or 79.8 Gy in 42 fractions over 8.5 weeks, prescribed to the ICRU point for the conformal plans or to CTV minimum for the IMRT plans. Five patients received doses between 75.6 Gy and 79.8 Gy.

### Radiotherapy

Setup error and interfraction prostate motion was minimized through daily pretreatment imaging and repositioning to correct the isocenter position relative to intraprostatic fiducial markers, using orthogonal electronic megavoltage portal images, with an action level of 3 mm, as described by Chung *et al.* (15). Between 1997 and 1999, portal films of the fiducial markers were taken 3 times a week and used to correct for organ motion (16).

### Statistical analysis

The frequency and percentage of patients experiencing rectal and urinary late toxicity on a scale of 0 to 4 was calculated. Erectile dysfunction was tabulated and the rates between diabetic and nondiabetic individuals were compared using a Chi-square test. Bladder and rectal toxicity and erectile function were compared between the two dose cohorts using Chi-square tests. The following dosimetric parameters were extracted from the treatment plan DVHs: volume in cubic centimeters of contoured organ at risk; maximum dose delivered to rectal and bladder wall (Dmax); percent volume of rectal and bladder wall receiving  $\geq 50$  Gy (V50); percent volume of rectal and bladder wall receiving  $\geq 60$  Gy (V60); and percent volume of rectal and bladder wall receiving  $\geq 70$  Gy (V70). These dosimetric parameters were compared between the  $<$  Grade 2 toxicity group and  $\geq$  Grade 2 toxicity groups using *t*-tests. The 3DCRT and IMRT patients prescribed 79.8 Gy were compared the same way.

### Principal component analysis

The principal component analysis is described in Appendix 2. The first three components were compared between patients with ( $\geq$  Grade 2) and without rectal and bladder wall toxicity using Mann-Whitney tests.

## RESULTS

In all, 437 replies were received from 690 questionnaires sent, yielding a response rate of 63%. This total included 72 of 112 from the first cohort and 365 of 578 from the second cohort. Patients who responded had similar tumor and treatment characteristics to those of nonresponders. Erectile function information was collected only in the second cohort of patients.

### Toxicity rates

Numbers reporting and rates of toxicity are shown in Table 1. At a median follow-up of 37 months (12–80 months) the incidence of patient-reported late rectal toxicity (445 responses) RTOG Grade 0, 1, 2, and 3 was 71.7%, 25.2%, 2.5%, and 0.7% respectively.

Three patients experienced Grade 3 rectal toxicity. Two patients reported prolonged use of rectal steroids, 1 reported persistent use of incontinence pads, and 1 underwent numerous coagulation procedures for rectal bleeding. One of these patients was found to have radiation proctitis on colonoscopy, as well as colonic polyps and a carcinoma of the cecum.

The incidence of patient-reported late urinary toxicity (443 responses) RTOG Grade 0, 1, 2, and 3 was 73.8%, 16.5%, 8.8%, and 0.9% respectively. Four patients experi-

Table 1. Summary of responses to toxicity questionnaire

| Toxicity score                       | 0           | 1           | 2         | 3        |
|--------------------------------------|-------------|-------------|-----------|----------|
| GI <i>N</i> = 443                    | 319 (73.8%) | 112 (25.2%) | 11 (2.5%) | 3 (0.7%) |
| GU <i>N</i> = 445                    | 327 (73.8%) | 73 (16.5%)  | 39 (8.8%) | 4 (0.9%) |
| Erectile function*<br><i>N</i> = 277 | 118 (43%)   | 13 (5%)     | 58 (21%)  | 88 (32%) |

\* Erectile function scores refer to those who reported pretreatment erectile function adequate for intercourse (277/367, or 76% of total respondents).

enced Grade 3 urinary toxicity. Three reported persistent use of incontinence pads, 1 experienced clinically significant hematuria, and 1 experienced nocturia more frequently than every hour. The patient reporting hematuria also had a previously treated superficial bladder cancer as a co-morbid condition.

In all, 367 patients responded to questions about erectile function. Of these, 89 (24%) indicated that pretreatment function was inadequate for intercourse. Of the remainder, posttreatment function was scored as Grade 0 in 118 (43%), Grade 1 in 13 (5%), Grade 2 in 58 (21%), and Grade 3 in 88 (32%). Overall, 68% of previously potent men reported themselves able to achieve erections sufficient for intercourse at least some of the time, and 48% reported good or excellent function. In contrast, previously potent men with diabetes were less likely to report Grade 0 function (29%, 11/38) and more likely to report Grade 3 function (50%, 19/38) than nondiabetic men, and this difference was statistically significant ( $p = 0.04$ ).

Use of PDE5 inhibitors was reported by 18% of men, and 83% of these found them to be effective.

### Dose

There was no significant difference in potency rates or late rectal/urinary toxicity between the 75.6-Gy and the 79.8-Gy groups; however the median follow-up is shorter for the 79.8-Gy group (24 months vs. 51 months).

### Dosimetry

Archived DVH data were retrieved for 335 of 437 (77%) patients who completed the questionnaire. Corrupted archival tapes prevented data retrieval for the remainder. In all, 146 received 75.6 Gy with the 3DCRT technique, and 189 were prescribed 79.8 Gy. In the 79.8 Gy group, 164 were treated with 3DCRT and 25 with IMRT.

Overall, the mean percentage of organ at risk at V<sub>50</sub>, V<sub>60</sub>, V<sub>70</sub> met both institution-specific and published dose constraints. There were no significant relationships between dose delivered to the rectal or bladder wall and patient-reported late rectal or urinary toxicity (Table 2). The V<sub>50</sub>, V<sub>60</sub>, and V<sub>70</sub> for the rectal wall were significantly lower for the IMRT group (Table 3), despite the fact that these pa-

Table 2. Relationship between patient-reported late toxicity and dosimetric parameters

| Toxicity score | <i>n</i> | Dmax (Gy)  | Volume OAR (cc) | V50 (%)    | V60 (%)    | V70 (%)    |
|----------------|----------|------------|-----------------|------------|------------|------------|
| Rectum         |          |            |                 |            |            |            |
| 0–1            | 322      | 77.1 (2.5) | 28.8 (11.)      | 41.9 (9.4) | 33.2 (7.9) | 21.8 (5.8) |
| 2–3            | 13       | 76.6 (2.4) | 32.3 (12.8)     | 43.3 (9.9) | 34.6 (8.4) | 22.2 (5.0) |
| Bladder        |          |            |                 |            |            |            |
| 0–1            | 295      | 77.3 (2.7) | 34.5 (13.2)     | 43.9 (9.0) | 35.5 (8.0) | 24.6 (6.5) |
| 2–3            | 38       | 77.8 (2.8) | 33.8 (12.1)     | 44.2 (8.0) | 36.4 (8.0) | 25.7 (7.0) |

*Abbreviations:* Dmax = maximum dose received; OAR = organ at risk; Volume OAR (cc) = volume of OAR contoured (in centimeters cubed); V50 = percentage of OAR receiving 50 Gy; V60 = percentage of OAR receiving 60 Gy; V70 = percentage of OAR receiving 70 Gy.

Values are mean (SD). *n*: 335 responses for rectal toxicity, 333 responses for bladder toxicity.

tients were preferentially selected for IMRT because of geometrically unfavorable CTV volumes.

#### Principal component analysis

The first three principal components described 95% and 99% of the variance in the rectal and bladder wall DVHs respectively, demonstrating that the majority of the variability in the DVHs could be described with three variables. None of the components were significantly related to late rectal or urinary toxicity.

Figures 1 and 2 plot the first three principal components of the rectal and bladder wall DVH datasets respectively. Figure 1 shows a random distribution of toxicity. There appears to be a cluster of higher toxicity scores in Figure 2; however this trend was not sufficiently robust to allow the development of a late toxicity predictive model.

## DISCUSSION

Our results demonstrate that patients treated with IGRT to doses of 75.6 Gy or higher reported low levels of late rectal and urinary toxicity at a median 37 months of follow-up.

The rate of patient-reported  $\geq$  Grade 2 rectal toxicity was 3.2%. This value is significantly lower than the toxicity reported in the literature for comparable planning techniques and dose regimens (12, 17, 18) which range from

26.5% (3) to 12% (18). This favorable outcome may be a consequence of limiting the dose to the anterior rectal wall with six-field conformal and IMRT and with the use of daily image guidance using implanted fiducial markers. Furthermore, our policy of encouraging patient bowel emptying during planning and treatment may have helped to limit unplanned increases in radiation to the rectum, and resulted in less late toxicity.

Our late patient-reported  $\geq$  Grade 2 urinary toxicity rate of 9.7% was higher than that for rectal toxicity, and comparable to those observed by others (12, 17, 18). This rate of toxicity is despite the use of a full bladder during planning and treatment to move most of the bladder wall away from the irradiated area. This may reflect the difficulty of excluding the base of the bladder from the planning target volume.

The risk of erectile dysfunction (ED) after external beam radiotherapy has not been well characterized, and in a recent review of the literature (19), data compiled from randomized trials showed that ED increased from a baseline of 15% to 47% after prostate radiotherapy. The authors' summary of institution-based series reported that the risk of post-radiotherapy ED ranged from 7% to 63%. In the current series, only 32% of previously potent men reported loss of erectile function sufficient to prevent intercourse, and 48% reported good or excellent function. This favorable result may reflect more recent availability of PDE5 inhibitors. Although penile bulb dosimetric data were not available,

Table 3. Comparison of mean dosimetric parameters by technique

|         | <i>n</i> | Dmax (Gy)   | Volume OAR (cc) | V50 (%)     | V60 (%)     | V70 (%)     |
|---------|----------|-------------|-----------------|-------------|-------------|-------------|
| Rectum  |          |             |                 |             |             |             |
| 3DCRT   | 164      | 78.8 (0.7)  | 23.7 (7.9)      | 40.6 (8.0)  | 32.3 (6.8)  | 23.3 (5.3)  |
| IMRT    | 25       | 81.4 (1.6)  | 27.5 (8.2)      | 33.5 (11.0) | 26.4 (8.0)  | 20.1 (6.1)  |
|         |          | $p < 0.001$ | $p = 0.03$      | $p = 0.004$ | $p < 0.001$ | $p = 0.007$ |
| Bladder |          |             |                 |             |             |             |
| 3DCRT   | 164      | 78.8 (0.8)  | 32.5 (13.1)     | 42.8 (8.4)  | 34.7 (7.3)  | 25.6 (6.1)  |
| IMRT    | 25       | 82.7 (2.1)  | 37.4 (9.1)      | 43.2 (9.8)  | 34.0 (8.2)  | 26.9 (7.0)  |
|         |          | $p < 0.001$ | $p = 0.02$      | $p = 0.85$  | $p = 0.64$  | $p = 0.33$  |

*Abbreviations:* 3DCRT = three-dimensional conformal radiation therapy; Dmax = Maximum dose received; IMRT = intensity-modulated radiation therapy; OAR = organ at risk; Volume OAR (cc) = volume of OAR contoured, in centimeters cubed; V50 = percentage of OAR receiving 50 Gy; V60 = percentage of OAR receiving 60 Gy; V70 = percentage of OAR receiving 70 Gy.

Values are mean (SD). *p*-Values are based on *t*-test.

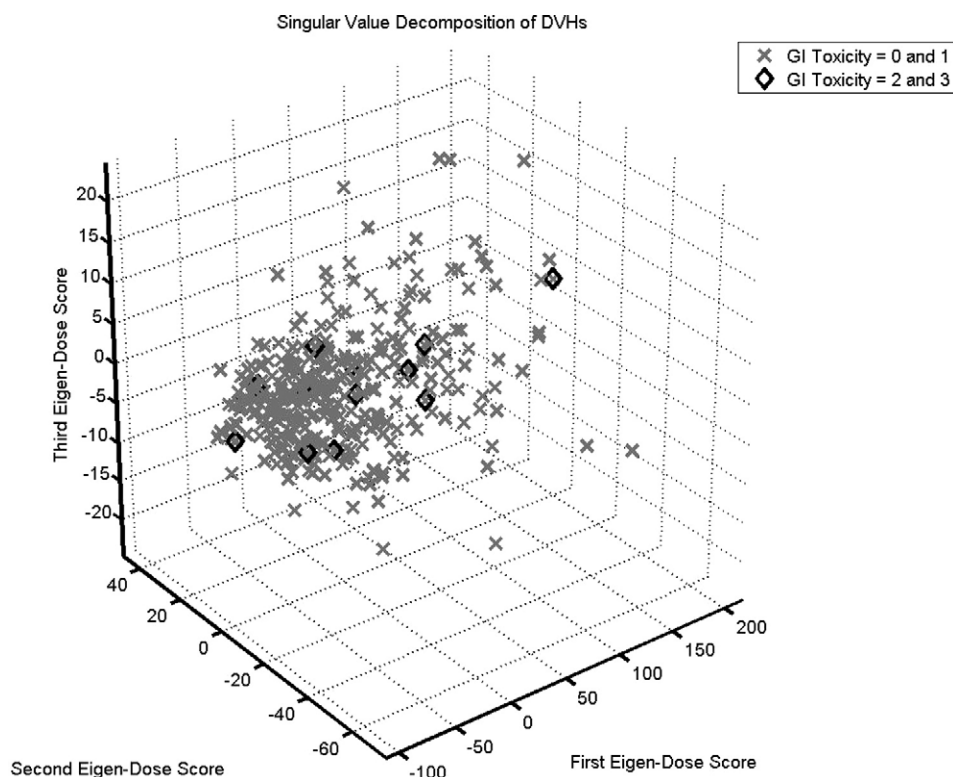


Fig. 1. Scatter plot of the first three eigen-dose scores for the rectal wall. Crosses represent dose–volume histograms (DVHs) corresponding to a late toxicity score of 0 or 1; the diamonds represent DVHs corresponding to a late toxicity score of 2 or 3.

patients included here had a fiducial marker placed at the prostatic apex. This contouring aid kept the inferior extent of the CTV to the minimum required, potentially reducing the overlap with the penile bulb.

We could not correlate dose/volume parameters or PCA to patient-reported late toxicity and were not able to develop a robust model for the prediction of late toxicity based upon PCA with our toxicity rates. Other centers have reported that chronic toxicity may be independent of dose, when normal tissue dose constraints are met (18, 20). However, the lack of association is most likely because of the very low rates of toxicity seen in our cohort of patients. With more toxicity events, Soehn *et al.* (21) successfully used PCA in their analysis of 205 rectal DVHs of patients treated to 70.2 to 79.2 Gy for prostate cancer.

The use of IMRT was not associated with decreased late toxicity, although these patients were preferentially selected for IMRT when the 3DCRT technique could not meet the dose–volume constraints.

Patient-reported toxicity data have been demonstrated to be superior to physician-reported data (7, 8), although collection of patient-reported data are more complex. A postal questionnaire is a relatively simple method of surveying a large number of patients, and the utility of this approach was demonstrated by this and an earlier pilot study (9). The response rate of 63% demonstrates that it was well accepted by those surveyed, although some methodologic limitations are recognized. The questionnaire used has been previously

reported on (9, 14), but has not been validated, and this should be the subject of future investigation. The method of data collection required patients to make a subjective comparison to a state of health before radiotherapy and is subject to recall bias, as patients may not remember problems that predated the radiotherapy, attributing the current level of dysfunction entirely to the treatment. Although it is definitely useful to have reliable information about pretreatment function, this becomes relevant only when ascribing a reported toxicity event to either treatment or a pre-existing condition. Fortunately, the vast majority of patients did not report any serious toxicity at the time that they filled out the questionnaires, so the question generally did not arise. It is likely that some minor pre-existing bowel and bladder toxicity was ascribed to radiotherapy, but this is of less concern than if serious pre-existing dysfunction were to be incorrectly ascribed to treatment.

The issue is more problematic for scoring erectile dysfunction, as functional loss over time is a natural phenomenon as well as a radiation response and as the causes of sexual dysfunction reported by our patients are multifactorial. However, the overall rates of erectile dysfunction at the time that patients filled out the questionnaires remain reliable in our studied population, and our study overestimates the contribution of radiation to erectile dysfunction rather than underestimates it.

Prolonged use of steroid enemas has not been shown to be effective in the treatment of chronic proctitis, and toxic-

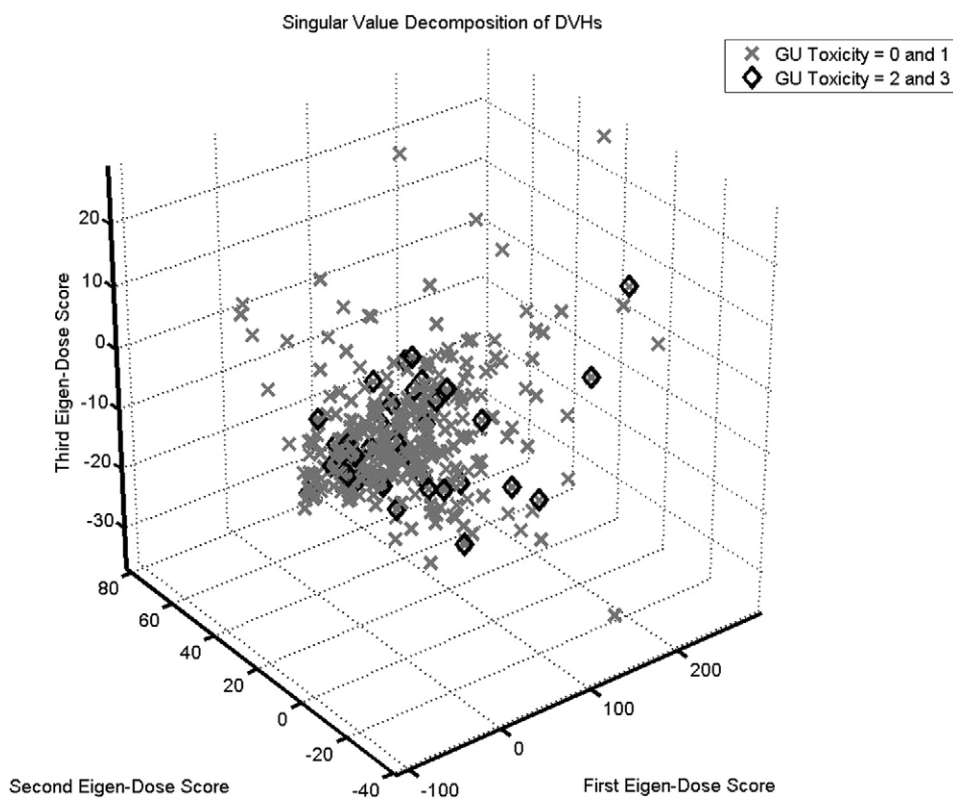


Fig. 2. Scatter plot of first three eigen-dose scores for the bladder wall.

ity should probably not be scored as Grade 3 based on this criterion alone (22). In addition, the number of coagulation procedures performed for bleeding are taken into account, and this may reflect the treatment modality used (laser or formalin) as well as patterns of care and physician expertise, rather than symptom severity.

Also, comorbidities that exacerbate or mimic the signs and symptoms of late radiation effects such as bleeding or lower urinary tract symptomatology are more prevalent in the elderly and may confound the evaluation of radiation toxicity. Two of our patients scored with Grade 3 toxicity had significant comorbidities that may have contributed to their reported bleeding episodes.

The quantification aspects of toxicity scoring in the modified RTOG LENT system used are particularly suitable for adaptation into a postal questionnaire, but may not have been sensitive enough to pick up subtle events related to dose–volume effects. Furthermore, the dosimetric parameters that are related to serious toxicity (Grades 3, 4) may not be the same as those that contribute to less serious (Grades 1, 2) toxicity. There were insufficient Grade 3 or 4 events to evaluate this.

The Expanded Prostate Cancer Index Composite (EPIC) (23) is a widely used, validated instrument for assessing treatment related toxicity in the urinary, bowel, and sexual domains; however it was not intended to be administered as an unsupervised postal questionnaire. The urinary and rectal domains of EPIC evaluate patient bother, rather than simply quantifying frequency and incontinence. The use of bother-

sensitive, patient-reported toxicity may become more important as a significant toxicity event in the future.

## CONCLUSION

The incidence of patient-reported late toxicity is an important factor in the evaluation of high-dose radiation therapy. Postal questionnaires provide an effective method of surveying large numbers of treated patients and data were successfully collected on late effects with a questionnaire based upon the RTOG LENT toxicity scoring system.

The low rates of reported rectal and urinary toxicity are attributed to the use of bowel preparation and conformal IGRT. The normal tissue dose constraints appear to be very safe and could be increased to allow further dose escalation with acceptable rates of toxicity.

Toxicity evaluation instruments that reflect the impact of high-precision radiotherapy on quality of life may better describe the more subtle symptoms of dysfunction. More sensitive scales are required to compare differences in outcome as major toxicity becomes less prevalent with improved treatment methods.

Novel methods of DVH analysis such as PCA remain an important area of study to extract maximum information from the treatment plan and to develop predictive models of late-reacting normal tissues. However, late toxicity could not be linked to PCA in this study because of the very low incidence of toxicity reported by the patients.

## REFERENCES

- Pollack A, Zagars G, Starkschall G, *et al.* Prostate cancer radiation dose response: Results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097–1105.
- Zietman A, DeSilvio M, Slater J, *et al.* Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. *JAMA* 2005;294:1233–1239.
- Peeters S, Heemsbergen W, van Putten W, *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.
- Hanks G, Hanlon A, Pinover W, *et al.* Dose selection for prostate cancer patients based on dose comparison and dose response studies. *Int J Radiat Oncol Biol Phys* 2000;46:823–832.
- Dearnaley D, Khoo V, Norman A, *et al.* Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: A randomised trial. *Lancet* 1999;353:267–272.
- Zelevsky M, Liebel S, Gaudin P, *et al.* Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Rad Onc Biol Phys* 1998;41:491–500.
- Litwin M, Hays R, Fink A, *et al.* Quality-of-life outcomes in men treated for localized prostate cancer. *JAMA* 1995;273:129–135.
- Talcott J, Rieker P, Propert K, *et al.* Patient-reported impotence and incontinence after nerve-sparing radical prostatectomy. *J Natl Cancer Inst* 1997;89:1117–1123.
- Nichol A, Chung P, Lockwood G, *et al.* A phase II study of localized prostate cancer treated to 75.6 Gy with 3D conformal radiotherapy. *Radiother Oncol* 2005;76:11–17.
- Benk V, Adams J, Shipley W. Late rectal bleeding following combined X-ray and proton high dose irradiation for patients with stages T3-T4 prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1993;26:551–557.
- Boersma L, van den Brink M, Bruce A, *et al.* Estimations of the incidence of late bladder and rectum complications after high dose (70–78 Gy) conformal radiotherapy for prostate cancer, using dose–volume histograms. *Int J Rad Onc Biol Phys* 1998;41:83–92.
- Storey M, Pollack A, Zagars G, *et al.* Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomised trial. *Int J Radiat Oncol Biol Phys* 2000;48:635–642.
- Dawson L, Biersack M, Lockwood G, *et al.* Use of principal component analysis to evaluate the partial organ tolerance of normal tissues to radiation. *Int J Radiat Oncol Biol Phys* 2005;62:829–837.
- Crook J, Esche B, Futter N. Effect of pelvic radiotherapy for prostate cancer on bowel, bladder, and sexual function: The patient's perspective. *Urology* 1996;47:317–394.
- Chung P, Haycocks T, Brown T, *et al.* On-line aSI portal imaging of implanted fiducial markers for the reduction of interfraction error during conformal radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2004;60:329–334.
- Wu J, Haycocks T, Alasti H, *et al.* Portal film analysis of an escalated dose conformal prostatic irradiation protocol using fiducial markers and portal images to confirm target organ and isocentre position. *Radiother Oncol* 2001;61:127–135.
- Michalski J, Purdy J, Winter K, *et al.* Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. *Int J Radiat Oncol Biol Phys* 2000;46:391–402.
- Zelevsky M, Fuks Z, Hunt M, *et al.* High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol* 2001;166:876–881.
- Bhatnagar V, Stewart S, Huynh V, *et al.* Estimating the risk of long-term erectile, urinary and bowel symptoms resulting from prostate cancer treatment. *Prostate Cancer Prostatic Dis* 2006;9:136–146.
- Vargas C, Yan D, Kestin L, *et al.* Phase II dose escalation study of image-guided adaptive radiotherapy for prostate cancer: Use of dose–volume constraints to achieve rectal isotoxicity. *Int J Radiat Oncol Biol Phys* 2005;63:141–149.
- Soehn M, Yan D, Liang J, *et al.* Influence of dose volume histogram (DVH) pattern on rectal toxicity [Abstract]. *Int J Radiat Oncol Biol Phys* 2005;63:S58.
- O'Brien P, Hamilton C, Denham J, *et al.* Spontaneous improvement in late rectal mucosal changes after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:75–80.
- Wei J, Dunn R, Litwin M, *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.
- Wall M, Rechtsteiner A, Rocha L. Singular value decomposition and principal component analysis. In: Berrar D, Dubitzky W, Granzow M, editors. A practical approach to microarray data analysis. Norwell, MA: Kluwer; 2003.
- Jackson J. A user's guide to principal components. Hoboken, NJ: John Wiley & Sons; 1991.

## APPENDIX 1

*Prostate cancer radiotherapy late side effects evaluation*

For each question, please circle the response which best describes your symptoms.

*Questions regarding bowel function*

1. How frequently would you open your bowels BEFORE starting the radiotherapy?

Once\_\_\_ Twice\_\_\_ Three times\_\_\_ Four times or more per day\_\_\_

2. How frequently do you open your bowels now?

Once\_\_\_ Twice\_\_\_ Three times\_\_\_ Four times or more per day\_\_\_

3. Are you concerned because your bowel movements are more urgent?

Yes\_\_\_ No\_\_\_

4. In the past 6 months have you ever lost control of your bowels?

Yes\_\_\_ No\_\_\_

5. Do you take anti-diarrheal pills such as Lomotil or Imodium?

Never\_\_\_ Occasionally\_\_\_ Every week\_\_\_ Daily\_\_\_

6. Are there some foods that you have to avoid because they will cause diarrhea?

Yes\_\_\_ No\_\_\_

7. Had you ever noticed any blood associated with your bowel movements (e.g., in stool) *before* radiation therapy treatment?

Never\_\_\_ Once only\_\_\_ Occasionally\_\_\_ At least once a week\_\_\_ Daily\_\_\_

8. Have you noticed any blood associated with bowel movements at any time 6 months after radiation therapy?

Never\_\_\_ Once only\_\_\_ Occasionally\_\_\_ At least once a week\_\_\_ Daily\_\_\_

9. If the answer to #8 was yes, have you had:

\_\_\_ Tests to investigate the bleeding?

\_\_\_ Prescription medications to treat it (other than Metamucil or hemorrhoidal suppositories)?

\_\_\_ Transfusions because of heavy bleeding?

\_\_\_ Rectal surgery because of bleeding?

#### *Questions regarding bladder function*

10. Since radiotherapy, have you had a problem with dripping or leaking urine?

Yes\_\_\_ No\_\_\_

11. If the answer to #10 is yes:

a) When you drip urine, about how much usually comes out?

A few drops\_\_\_ Less than a tablespoon\_\_\_ More than a tablespoon\_\_\_

b) How often do you drip or leak urine?

More than once a day\_\_\_ About once a day\_\_\_ Less than once a day\_\_\_

c) Some men wear pads, rubber pants, adult diapers, or a clamp to help with wetness. Do you use anything like that now?

Yes\_\_\_ No\_\_\_

d) If you use pads, how often do you wear them?

Sometimes\_\_\_ Always\_\_\_

12. Since your radiotherapy, do you feel that your urinary stream is:

Slower than before\_\_\_ The same\_\_\_ Improved\_\_\_

13. Before your radiotherapy, did you have to get up at night to urinate?

Never\_\_\_ Rarely\_\_\_ Once a night\_\_\_ 2 to 3 times per night\_\_\_ 4 to 5 times per night\_\_\_

14. Since your radiotherapy, do you have to get up at night to urinate?

Never\_\_\_ Rarely\_\_\_ Once a night\_\_\_ 2 to 3 times per night\_\_\_ 4 to 5 times per night\_\_\_

15. Since your radiotherapy, have you noticed blood in your urine?

Never\_\_\_ Occasionally\_\_\_ Frequently\_\_\_

16. Since your radiotherapy, do you have pain or burning on urination?

Never\_\_\_ Occasionally\_\_\_ Frequently\_\_\_

17. If you have pain on urination, have you needed to take painkillers?

Never\_\_\_ Occasionally\_\_\_ Daily\_\_\_

#### *Questions regarding sexual function*

18. Before you had radiotherapy, could you have erections when you were stimulated?

Yes\_\_\_ No\_\_\_

19. Since your radiotherapy, have you had any full erections?

Yes\_\_\_ No\_\_\_

If the answer to #19 is “no,” have you been able to have any partial erections?

Yes\_\_\_ No\_\_\_

20. How often were they firm enough to have intercourse?

Never\_\_\_ Some of the time\_\_\_ Most of the time\_\_\_ Always\_\_\_

21. Since your radiotherapy, have you tried treatments of any kind to help your sexual function?

Yes\_\_\_ No\_\_\_

22. If yes, have these been effective?

Never\_\_\_ Some of the time\_\_\_ Most of the time\_\_\_ Always\_\_\_

#### *Question regarding diabetes*

23. Do you have diabetes mellitus (“sugar diabetes”)?

Yes\_\_\_ No\_\_\_

## APPENDIX 2

### *Principal component analysis*

Principal components for rectal and bladder wall dose–volume histograms (DVHs) were calculated, independent of toxicity assessment. Principal component analysis (PCA) is a multivariate statistical technique that uses linear transformation to convert a number of related variables into a smaller set of uncorrelated variables. The PCA of a dataset yields a number of vectors referred to as *principal components* that describe the variance within that dataset. The first principal component describes the greatest amount of variance in the dataset, the second describes the greatest amount of remaining variance in the dataset, and so on. All components are orthogonal to each other and measure different

dimensions of the data (see Ref. 13). The first three components for each organ at risk were analyzed with respect to toxicity.

The bladder and rectal wall DVHs were divided into 87 × 1 Gy dose bins. The PCA was carried out twice on each dataset: once with the DVHs in cubic centimeters and once with the DVHs normalized to percent volume of the organ at risk.

The PCA was performed using singular value decomposition. The equation for the singular value decomposition is as follows:  $X = USV^T$ , where  $X$  = matrix of DVHs,  $U$  = matrix in which the columns are the left singular vectors (eigensubjects),  $S$  = matrix in which the nonzero diagonal

elements are the singular values, and  $V^T =$  matrix in which the rows are the right singular vectors (eigendoses), and is the transpose of matrix  $V$ .

Because the data had been column-centered before calculation, the right singular vectors are the principal components. The square of the singular values is proportional to the variance described by each principal component. The matrix multiplication of  $US$  (alternatively  $XV$ ) are known as the principal component scores and are the

coordinates of the subjects in the space of principal components. This can also be thought of as a projection of the DVHs onto the principal component space, the purpose of which is to aid in the visualization of structure in the data if 1 projection is plotted against another. Clustering of DVHs in these projection scatter plots was analyzed to determine which DVHs contribute strongly to the variance explained by that principal component (see Refs. 24, 25).