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Association between EBRT dose volume histograms and quality of life in prostate cancer patients

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ABSTRACT

Aim: To evaluate the association between dose–volume histogram (DVH) values in organs at risk (OAR) and patient-reported HRQoL outcomes.

Background: Data on the association between DVHs and health-related quality of life (HRQoL) in prostate cancer (PCa) patients are limited.

Materials and methods: Five-year follow-up study of 154 patients with organ-confined (stage T1/T2) PCa treated with EBRT between January 2003 and November 2005. HRQoL was evaluated with the Expanded Prostate Cancer Index (EPIC). DVH for OARs (penile bulb, rectum and bladder) were created for all patients for whom data were available (119/154; 77%). The functional data analysis (FDA) statistical method was used. HRQoL data was collected prospectively and data analysis was performed retrospectively.

Results: Worsening of urinary incontinence and obstructive symptoms correlated with higher DVH dose distributions at 24 months. Increased rectal bleeding at months 24 and 60 correlated with higher DVH dose distributions in the 40–70 Gy range. Patients with deterioration in rectal incontinence presented a higher DVH distribution range than patients without rectal incontinence. Penile bulb DVH values and erectile dysfunction were not significantly associated.

Conclusions: DVH parameters and post-radiotherapy HRQoL appear to be closely correlated, underscoring the importance of assessing DVH values prior to initiating EBRT to determine the risk of developing HRQoL related adverse effects. Advanced treatment modalities may be

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appropriate in high risk cases to minimize treatment-related toxicity and to improve treatment outcomes and HRQoL. Future studies are needed to better elucidate the association between pre-treatment DVH parameters in organs at risk and subsequent HRQoL.

1. Background

Three-dimensional conformal radiotherapy (3D-CRT) has long been used to treat early-stage prostate cancer. However, the side effects often have a large negative impact on patient health-related quality of life (HRQoL) due to incidental irradiation to the main organs at risk (OARs)—the bladder, rectum, and penile bulb. High-dose radiotherapy has been shown to improve cancer control, but may further increase the risks of adverse effects. Studies have shown that high doses to the penile bulb and rectum can increase the risk of erectile dysfunction (ED),[1–3] rectal bleeding,[4–8] and urinary toxicity.[4,9]

Radiation-induced toxicity is traditionally measured by physician-assessed clinical parameters.[10] In recent years, patient-reported outcome measures have become increasingly common[11,12,14] due to their greater sensitivity as indicators of HRQoL.[14] Toxicity can also be estimated by examining the dose–volume histogram (DVH) treatment parameters. Numerous studies have compared DVH values to physician-reported toxicity.[4,5,10,15,16] However, to our knowledge only two studies have assessed the association between DVH and HRQoL following external beam radiotherapy (EBRT) in patients with prostate cancer[10,15]; moreover, those two studies only evaluated rectal[15] and gastrointestinal[10] outcomes. No studies have yet assessed the possible association between HRQoL and DVH parameters for the bladder and penile bulb; consequently, relatively little is known about how changes in the DVH values for those organs might impact HRQoL. The availability of such data would help clinicians decide whether it might be beneficial to use a different treatment modality such as volumetric modulated arc therapy (VMAT) to minimize toxicity, thus simultaneously improving both treatment outcomes and patient HRQoL.

2. Aim

Given this context, we retrospectively evaluated the pre-treatment DVH values in a series of 154 patients treated with 3D-CRT to assess correlation between the DVH parameters in the OARs and patient-reported side effects collected prospectively through prostate cancer-specific HRQoL questionnaires.

3. Material and methods

Five-year follow-up study of 154 patients with organ-confined prostate cancer treated with 3D-CRT at a comprehensive cancer-care hospital in Spain.

All HRQoL data were collected prospectively.

Data were obtained from the database of the longitudinal study "Multicentric Study of Clinically Localized Prostate Cancer", which includes clinical and demographic data from a cohort of men treated with radical prostatectomy, 3D-CRT, or brachytherapy. That study has been described in detail elsewhere.[12] Briefly, consecutive outpatients were enrolled from April 2003 to March 2005. Inclusion criteria were stage T1 or T2 prostate cancer and no previous transurethral prostate resection. The study was approved by the ethics review boards of the participating hospitals, including the Ethics Committee of the Catalan Institute of Oncology, and written informed consent was obtained from patients in accordance with the Helsinki Declaration.

Previous publications have described the impact of treatment-related side effects on HRQoL at 2,[12] 3,[11] and 5 years[13] of follow-up. For the purpose of the current study, we evaluated a 154 patient subset of this cohort. Patients in this study were all treated with 3D-CRT at the Catalan Institute of Oncology. The D'Amico risk classification system[17] was used to classify patients into low (T1c or T2a, PSA <10 ng/mL and Gleason <6), intermediate (T2b, PSA 11–20 ng/mL or Gleason 7), and high risk (T2c, PSA >20 ng/mL or Gleason >7) groups.

3.1 EBRT procedure

In all cases, a computed tomography (CT) scan was performed with the patient in the supine position with legs and feet immobilized. Slice width was 5 mm and the distant slice was also 5 mm. CT data were exported to the Cadplan treatment planning system (TPS) (Varian Medical Systems). The prostate, bladder, seminal vesicles, and penile bulb were contoured in all patients by the same experienced (>10 years) radiation oncologist. The median dose prescribed to the prostate was 72.8 Gy (range, 72.4–73.2 Gy). Applied margins (5 mm posteriorly and 10 mm in all other directions) were used to obtain the planning target volume (PTV), which included the prostate gland. EBRT was delivered in daily fractions of 2 Gy, 5 days per week.

3.2 Dose volume histograms

All radiotherapy treatments were designed and calculated with the Cadplan TPS, which was in use at our institution until February 2005 when it was replaced with the Eclipse TPS (Varian Medical System).

Using data obtained from the files, we contoured new OARs (penile bulb, bowel, seminal vesicles) and also verified the original outlines for the rectum and bladder. Since the Eclipse contouring tools are more advanced than the older Cadplan tools, specialized software (VODCA, v4.3.4; Medical Software Solutions) was purchased to transfer patient data from Cadplan to Eclipse. The DICOM RT files include CT data (or MRI data), structures, dose matrix and plan data. VODCA can also transfer plan sum data, although no MU units or field data are

supported. After the OAR structures were revised and outlined in Eclipse, a DVH export was done in a tabular form for each patient. This DVH file contained all the dose data for PTVs and OARs. The DVH files were imported in an individual Excel sheet (per patient) for statistical analysis.

3.3 HRQoL assessment

The Expanded Prostate Cancer Index Composite (EPIC)[18] was prospectively administered by telephone interview pre-treatment and at one, three, six, and 12 months post-treatment during the first year, and annually thereafter. The EPIC contains 50 items measuring bother and function of five domains: Urinary Incontinence (4 items); Urinary Irritative-Obstructive (7 items); Bowel (14 items); Sexual (13 items); and Hormonal (11 items). Scores range from 0 to 100.

To measure sexual, bowel, urinary side effects, the five items most closely related to expected toxicity were selected from each EPIC domain. Side-effects were considered to have occurred when there was a worsening on the EPIC item from baseline to the post-treatment assessments.

3.4 Statistical analysis

To check for baseline differences between patients with available DVH data (119 pts) and those for whom DVH data was not available (35 pts), we compared these two groups using the Chi squared or the unpaired *T* test, as appropriate. Patient responses to the 5 EPIC questionnaire items are reported as percentages. Pre- and post-treatment evaluations were compared with Chi-squared tests.

Differences in the DVH values between the groups with and without side-effects were evaluated using the functional data analysis (FDA) statistical approach.[19–21] DVH values were obtained from dosimetries; spline interpolation was performed to transform data to functions. Functional descriptive data (both graphical and numerical) were obtained. The FDA technique was used as it was the most suitable method to assess our working hypothesis: that the variability and the area under the curve (AUC) would determine the side effects perceived by patients. Note that in FDA—as is common with multivariate analytical techniques (e.g., principal component analysis)—no *p* values are obtained to represent data summaries.

4. Results

Due to tape damage during storage, we could not obtain full data for all patients, although we did obtain complete data in most cases (119/154; 77.3%). Importantly, no significant differences (Table 1) in baseline characteristics (age, PSA, Gleason score, T-stage, risk group, prostate volume, co-morbidity, and EPIC scores) were observed between the 119 patients with available DVH and the 35 patients without DVH.

Table 2 shows pre- and post-treatment patient responses to the items selected to measure side effects related to radiation toxicity. Worsening was infrequent and not statistically significant except for urinary obstruction at 5 years ($p < 0.001$).

Table 1 – Patient characteristics.

	Patients with dose–volume histogram (DVH)	Patients without DVH
Number of patients	119	35
Age, mean (SD)	69.1 (5.7)	68.3 (5.8)
<60 years	11 (9.2%)	5 (15.2%)
60–65 years	18 (15.1%)	1 (3.0%)
65–70 years	24 (20.2%)	10 (30.3%)
≥70 years	66 (55.5%)	17 (51.5%)
Missing	0 (0.0%)	2 (5.7%)
PSA (ng/mL), mean (SD)	12.4 (9.6)	8.4 (4.0)
5 or less	15 (12.6%)	9 (25.7%)
6–7	26 (21.8%)	11 (31.4%)
8–10	29 (24.4%)	5 (14.3%)
≥11	49 (41.2%)	10 (28.6%)
Gleason score, mean(SD)	6.4 (1.0)	6.4 (1.0)
≤6	60 (50.4%)	17 (48.6%)
≥7	59 (49.6%)	18 (51.4%)
Clinical T Stage, *n* (%)		
T1	45 (38.1%)	22 (62.9%)
T2	73 (61.9%)	13 (37.1%)
Missing	1 (0.8%)	0 (0.0%)
Risk group, *n* (%)		
Low	28 (23.7%)	11 (31.4%)
Intermediate/high	90 (76.3%)	24 (68.6%)
Missing	1 (0.8%)	0 (0.0%)
Prostate volume	53.0 (27.1)	44.7 (20.7)
Missing	4 (3.4%)	7 (2.0%)
Neoadjuvant hormonal treatment, *n* (%)	31 (37.3%)	8 (25.0%)
Comorbidity (at least 1)	109 (91.6%)	13 (92.9%)
Missing	0 (0.0%)	21 (60.0%)
EPIC scores, mean (SD)		
EPIC urinary incontinence	95.9 (10.7)	90.1 (16.8)
EPIC urinary irritative/obstructive	94.6 (11.2)	93.1 (13.2)
EPIC bowel	96.8 (7.3)	98.0 (4.2)
EPIC sexual	50.3 (24.5)	47.9 (25.5)
EPIC hormonal	93.2 (10.2)	90.4 (16.4)

4.1 Sexual domain outcomes: Penile bulb DVH and HRQoL

The DVH values (Fig. 1) in patients with ED at 24 months were higher in the 30–40 Gy range. In patients with ED at 5 years, the DVH distribution was higher along the entire curve. As Fig. 1 shows, the curves were—contrary to expectations—inverted.

4.2 Bowel domain outcomes: Rectal DVH and HRQoL

Fig. 2 shows the rectal DVH for patients with and without fecal blood and fecal incontinence worsening from pre-treatment.

4.2.1. Bleeding

The DVH distribution in patients with bloody stools (Fig. 2) was higher in the 40–70 Gy range at months 24 and 60.

Table 2 – Pre and post-treatment patient response to the items selected to measure side effects.

	Pre-treatment	1 year post-treatment	5 years post-treatment
Urinary incontinence			
Number of diapers per day			
None	119 (100.0%)	108 (97.3%)	95 (95.0%)
1 pad per day	0 (0.0%)	3 (2.7%)	3 (3.0%)
2 pads per day	0 (0.0%)	0 (0.0%)	1 (1.0%)
3 or more pads per day	0 (0.0%)	0 (0.0%)	1 (1.0%)
p-value		0.11	0.018
Urinary obstructive			
Need to urinate frequently during the day			
No problem	104 (87.4%)	90 (81.1%)	74 (74.0%)
Very small problem	6 (5.0%)	2 (1.8%)	0 (0.0%)
Small problem	5 (4.2%)	10 (9.0%)	6 (6.0%)
Moderate problem	3 (2.5%)	9 (8.1%)	6 (6.0%)
Big problem	1 (0.8%)	0 (0.0%)	14 (14.0%)
p-value		0.061	<0.001
Bowel			
Uncontrolled leakage of stool			
More than once a day	0 (0.0%)	0 (0.0%)	0 (0.0%)
About once a day	0 (0.0%)	0 (0.0%)	0 (0.0%)
More than once a week	0 (0.0%)	0 (0.0%)	4 (4.0%)
About once a week	1 (0.8%)	5 (4.5%)	1 (1.0%)
Rarely or never	118 (99.2%)	106 (95.5%)	95 (95.0%)
p-value		0.109	0.060
Frequency of bloody stools			
Never	106 (89.1%)	88 (79.3%)	84 (84.0%)
Rarely	12 (10.1%)	17 (15.3%)	14 (14.0%)
About half the time	0 (0.0%)	5 (4.5%)	2 (2.0%)
Usually	1 (0.8%)	0 (0.0%)	0 (0.0%)
Always	0 (0.0%)	1 (0.9%)	0 (0.0%)
p-value		0.02	0.24
Sexual			
No problem	77 (64.7%)	71 (64.0%)	72 (72.0%)
Very small problem	2 (1.7%)	1 (0.9%)	
Small problem	5 (4.2%)	6 (5.4%)	5 (5.0%)
Moderate problem	18 (15.1%)	15 (13.5%)	11 (11.0%)
Big problem	17 (14.3%)	18 (16.2%)	12 (12.0%)
p-value		0.96	0.63

4.2.2. *Rectal incontinence*

Patients with rectal incontinence (Fig. 2) had a higher DVH distribution from 40 to 70 Gy at 24 months and along the entire curve at 60 months.

4.3 *Urinary domain outcomes: DVH bladder and HRQoL*

4.3.1. *Urinary incontinence*

Fig. 3 shows the bladder DVH for patients with (red line) and without worsening (green line) in urinary incontinence (determined by number of diapers/day pre-treatment versus at 2- and 5-years post-treatment).

Patients with worsening of urinary incontinence (Fig. 3) had a higher DVH distribution versus those without this condition at 24 months, particularly between 0–40 Gy; this difference was not significant at 60 months.

4.3.2. *Urinary obstruction*

Fig. 4 shows the bladder DVH parameters in patients with and without worsening from pre- to post-treatment. Patients with worsening in obstructive symptoms presented differences along nearly the entire DVH curve. These differences were significant at 24 months but not at 60 months.

5. Discussion

Patient-reported outcomes are often considered more sensitive indicators of HRQoL than physician-reported measures.[22] Only two published studies[10,15] have assessed the association between DVH parameters and HRQoL in patients treated with EBRT for PCa. We sought to determine the relationship between pre-treatment DVH values and treatment-related side effects. We found that patient-reported worsening of both urinary incontinence and obstructive symptoms at 24 months was associated with higher DVH values. Higher rates of rectal bleeding at months 24 and 60 were correlated with higher DVH parameters. Patients with worsening rectal incontinence presented a higher DVH distribution between 40 and 70 Gy at 24 months and throughout the curve at 60 months. No association was found between ED and penile bulb DVH parameters. These findings suggest that DVH values and patient-reported side effects are closely correlated, confirming previous reports

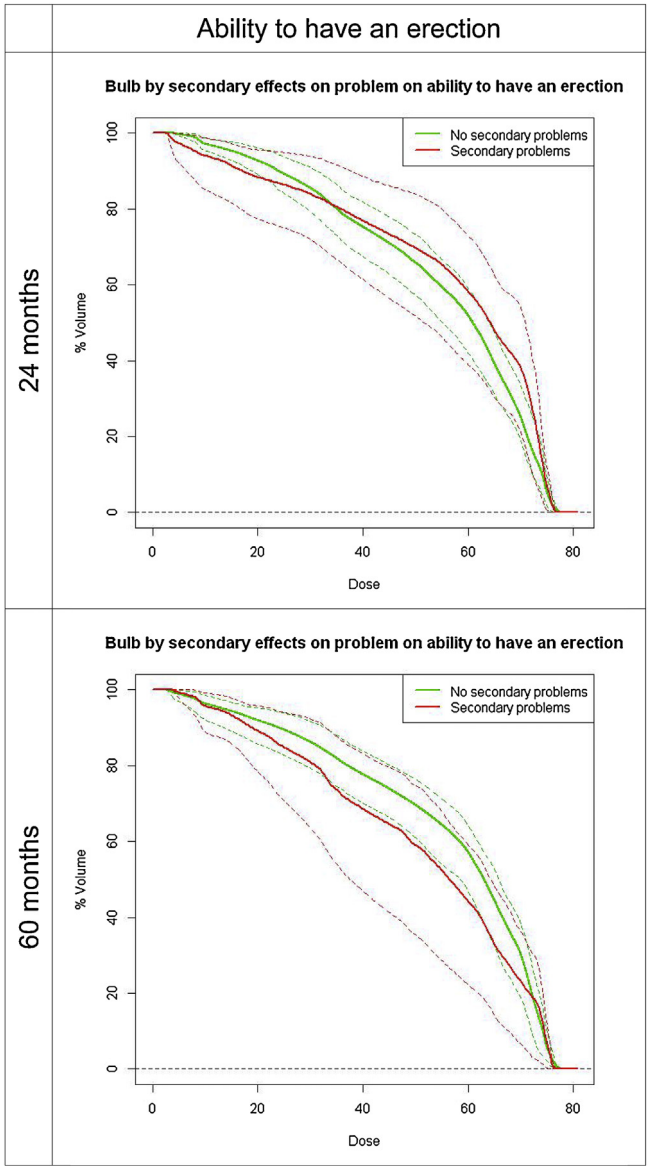

Fig. 1 – Dose volume histograms by sexual function.

on the association between patient- and physician-reported toxicity and HRQoL in PCa.[11–13,23,24]

5.1 *Analytical approach*

The application of FDA—the statistical approach used in this study—to biomedical data is relatively new.[21,25,26]. Indeed, only one study[25] has previously used FDA to assess correlation between toxicity and DVHs. Conventional statistical techniques generally use single points along the DVH curve to assess the relation between DVH values and HRQoL. However, those approaches fail to consider the shape of the curve. By contrast, the FDA technique[19–21] considers all the data along the entire curve, thus overcoming the shortcomings (i.e., single-point analysis) of conventional statistical analyses.

5.2 *Sexual function*

Multiple studies have assessed the association between dose to the penile bulb and toxicity. Roach et al.[27] found that mean doses ≥52.5 Gy to the penile bulb were associated with a higher risk of ED. Mangar et al.[1] found that 83% of patients who developed impotence received ≥50 Gy (D90) to the penile bulb whereas only 29% of patients who maintained erectile function received such a high dose. McDonald et al.[2] evaluated 41 patients treated with hypofractionated radiotherapy, finding that ED decreased by ≥2 in 50% of patients who received a mean penile bulb dose >20 Gy compared to only 9% in patients with a mean dose ≤20 Gy ($p = 0.003$). Importantly, other studies have found no association between penile bulb dose and toxicity.[27–29] These contradictory results are probably attributable to the multifactorial pathophysiology of ED, as several variables—notably age, diabetes, and irradiation of other structures—may be involved. Indeed, the multifactorial nature of ED is evident in our results, as seen in the inverted dose volume curves (Fig. 1), where higher doses were associated with *lower* rates of sexual dysfunction. This unexpected result may simply be a statistical anomaly, but could also indicate that other factors play a more important role in sexual dysfunction.

5.3 *Bowel*

5.3.1. *Rectal bleeding*

Most reported studies have found that high dose irradiation to the rectum is associated with rectal bleeding.[4–7] Nuyttens et al.[4] studied the relation between total dose to the prostate and toxicity in 64 patients who received either 72 Gy or 80 Gy, finding that grade 2 rectal toxicity affected a higher proportion of patients in the high dose group (15% vs. 10%). Fiorino et al.[5] found that patients with larger volumes or higher rectal doses (V50: 70%, V55: 64%, V60: 55%) presented a greater risk of rectal bleeding. Kuban et al.,[6] in a dose escalation study, found that G3 rectal toxicity was significantly associated with 25% of the rectal volume receiving ≥70 Gy. Our data, which show a correlation between DVH and HRQoL (rectal bleeding), are consistent with other published studies. Interestingly, although we adhered to generally-accepted dose constraints, bleeding occurred with a dose volume distribution in the rectum that was higher between 40 and 70 Gy both at 24 and 60 months. This finding raises the question of whether the standard limits are too high, but more data are needed to confirm this.

5.3.2. *Rectal incontinence*

Crevoisier et al.[8] reviewed the literature to assess correlations between exposure (dose/volume) of OARs and rectal, urinary, sexual, and bone toxicity. Based on their findings, the authors recommended the following volume percentage limits: V70 Gy < 25%; V50 Gy < 70%; V55 Gy < 64%; and V60 Gy < 55%. Fiorino et al.[30] found differences in the incidence of rectal incontinence (1.5% vs 7%) with a cut-off point of V40 < 75%. We did not assess the possible association between dose to the anal sphincter and incontinence (very few authors have assessed this association), but it seems likely that incontinence is more closely related to anal sphincter irradiation than to rectal volume, as shown by Buettner et al.[16] Those

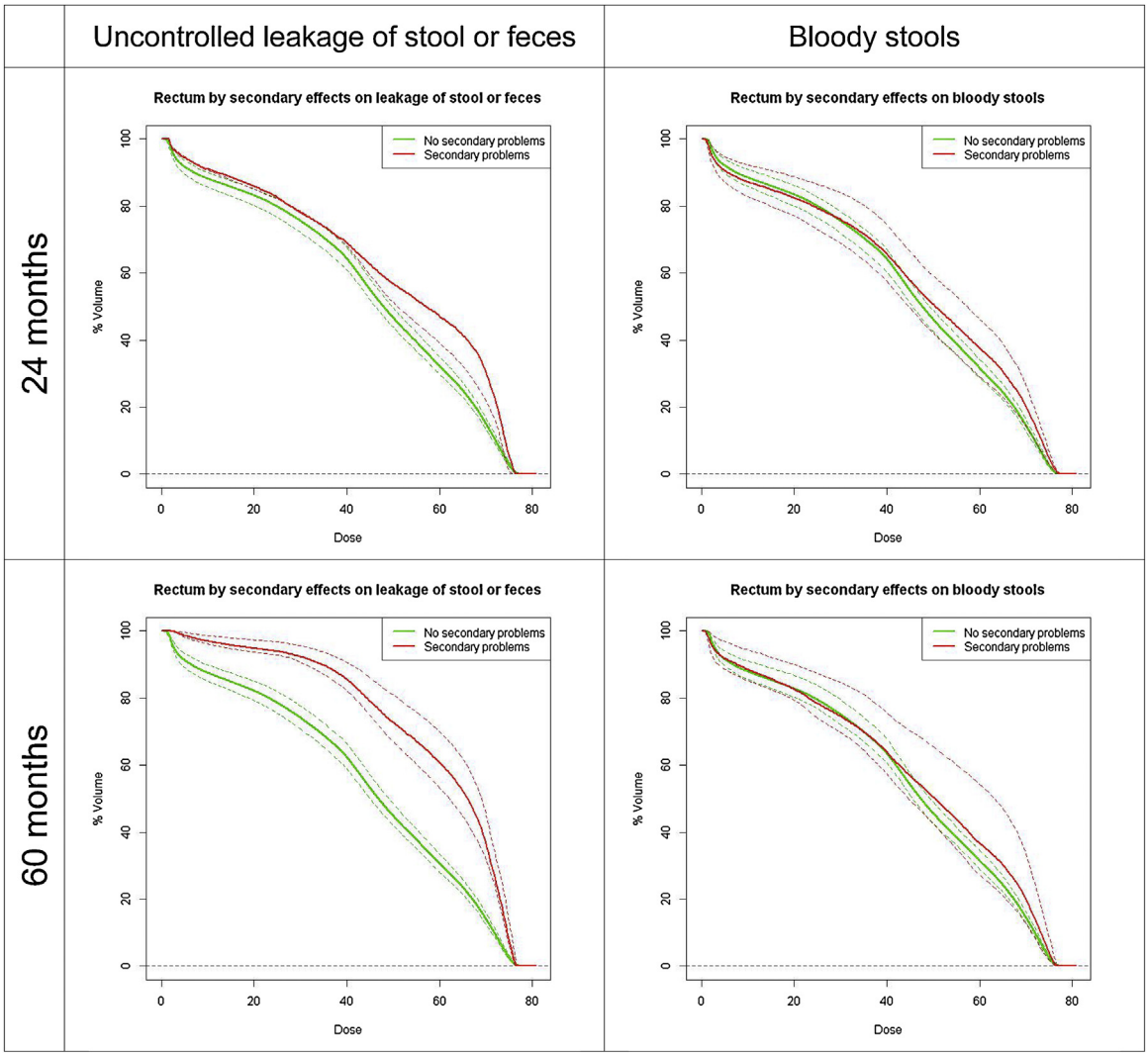

Fig. 2 – Dose volume histograms by bowel side effects.

authors found a significant association between DVH and anal sphincter incontinence (>56% of the volume receiving >53 Gy). Our treatment planning constraints were based on the available literature, as follows: V40 Gy < 60% and V60 Gy < 40%. Thus, in theory, we were limiting the volumes that received high doses. Even so, patients with rectal incontinence had a higher DVH distribution between 40 and 70 Gy at 24 months and also practically along the entire curve at 60 months.

An interesting and important finding in this study is that some parts of the curve show an effect (e.g., on urinary obstruction and rectal bleeding) at low doses but high volumes. This suggests that, over time, rectal incontinence could develop, even at low doses, if the volume is large enough (see Fig. 3). Nevertheless, no definitive conclusions can be made because we did not assess anal sphincter irradiation.

In general, our findings indicate that rectal incontinence and bleeding increase as the DVH increases, suggesting that the dose should be lowered to avoid this adverse effect. If the likelihood of poor tumour control precludes this option, then the alternative would be to switch (if possible) to more advanced treatment modalities such as VMAT.

5.4 *Urinary domain outcomes*

Several studies have found an association between total dose and urinary toxicity.[4,9] However, it is difficult to identify a clear association between DVH and toxicity because other factors—including urinary symptomatology prior to irradiation and prior transurethral resection—may affect the results. It also seems likely that the pathogenesis of urinary toxicity may be related to the urethra and/or to the bladder, thus making the specific cause more difficult to identify. Anatomic variability during the course of irradiation can also play a role.

5.5 *Urinary incontinence*

Our planning constraints for the bladder were V40 Gy < 60% and V60 Gy < 40%. Fiorino et al.[30] showed that the likelihood of urinary incontinence was higher in patients whose bladder volume received ≥40 Gy and in patients who underwent surgery prior to radiotherapy. Other studies have reported higher rates of grade 2 toxicity among patients irradiated with doses >76 Gy,[4] higher late urinary toxicity in patients treated

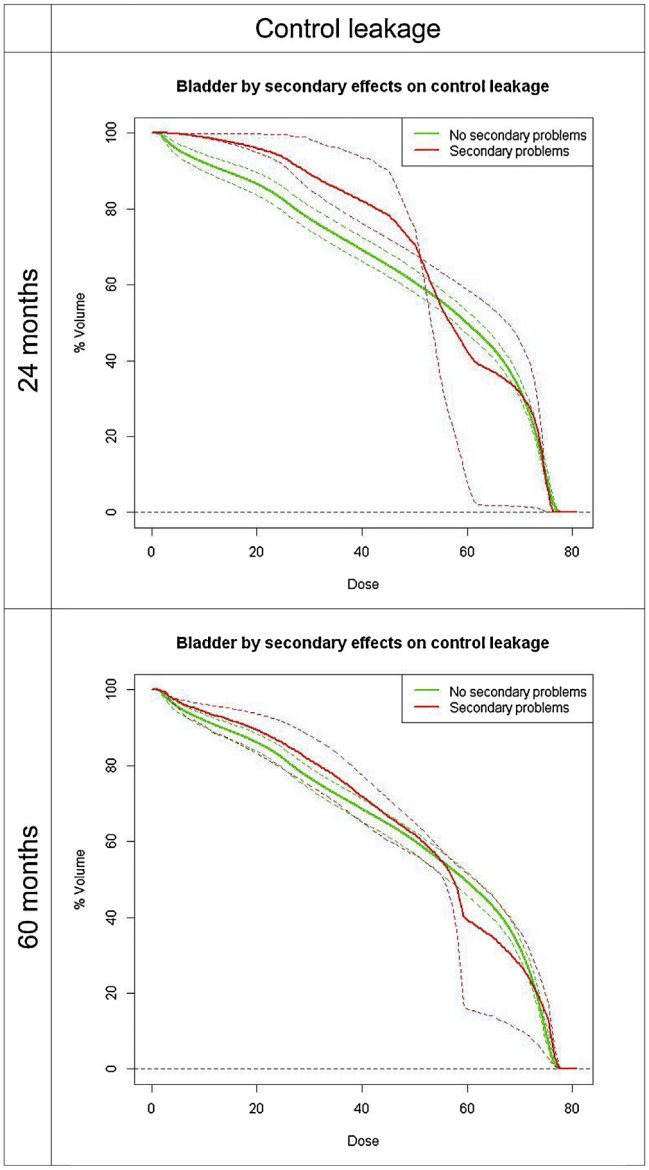

Fig. 3 – Dose volume histograms by the presence of urinary incontinence.

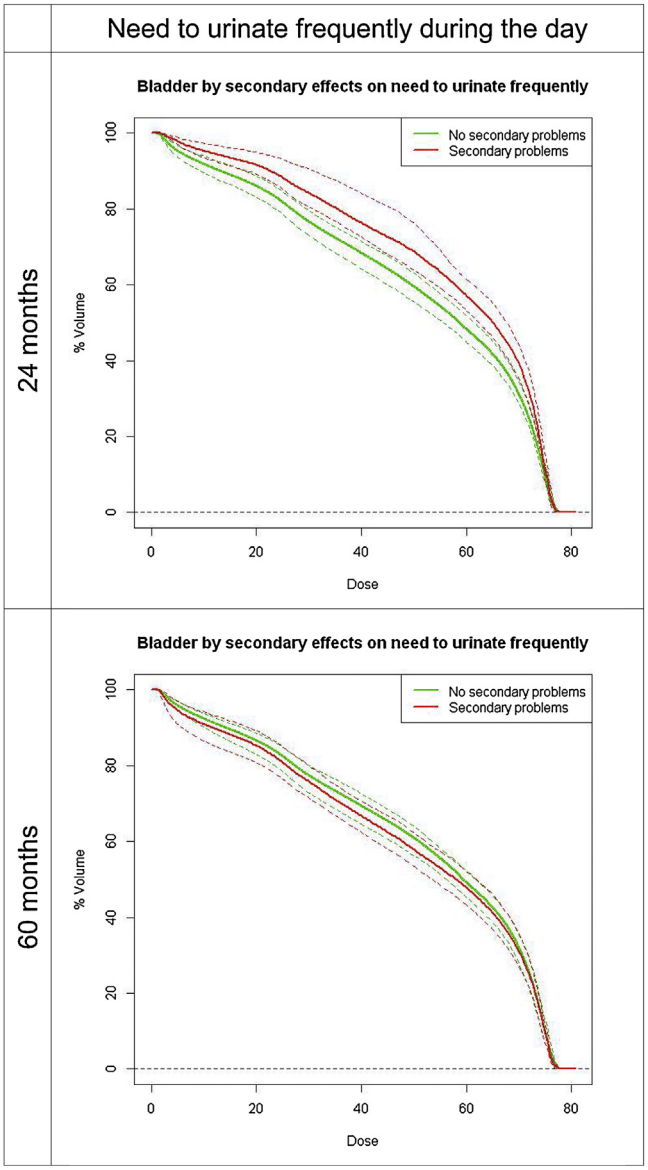

Fig. 4 – Dose volume histograms by urinary obstructive side effects.

with 80 Gy,[9] and obstructive symptoms for doses at the trigone level.[31] At 24 months, we observed that AUC V40 is where patients with incontinence received the highest percentage of bladder volume. However, this difference was not maintained at 60 months.

5.6 *Urinary obstructive symptoms*

Nuyttens et al.[4] found that only 33% of patients who received lower doses (≤72 Gy) developed grade 2 urinary toxicity versus 47% of those who received higher doses (>76 Gy). In a dose escalation study, Beckendorf et al.[9] observed that 80 Gy led to a significantly higher incidence of late urinary toxicity. It seems probable that obstructive symptoms are closely related to urethral irradiation, which is why it is more difficult to detect an association between bladder DVH parameters and toxicity. Heemsbergen et al.[31] found that dose differences to the trigome were highly significant predictors of obstructive symptoms at two years. These data suggest that obstructive symptoms and bladder DVH values are unlikely to be associated. In our series, we found differences at 24 months along nearly the entire curve (item: "*need to urinate frequently during the day*") but these differences were not evident at 60 months. Although obstructive symptoms may be more closely associated with total dose to the urethra, we did not assess this variable.

5.7 *Strengths and limitations*

Assessing patient perspectives about treatment-related morbidity is challenging and numerous factors can influence the results, including radiation dose, target margins, DVH characteristics, data collection methods, and perhaps even treatment modality. Nevertheless, numerous studies have

demonstrated the patient-reported outcomes provide a more reliable indicator of the patient's true status.

6. Conclusions

The results reported here confirm previous reports showing that DVH parameters and post-radiotherapy HRQoL are closely correlated, thus allowing us to identify before treatment starts those patients who are most likely to develop treatment-related toxicity. In such cases, clinicians should consider alternatives, such as adding a boost with brachytherapy or switching to a more advanced techniques (such as VMAT or IMRT) when feasible. Future studies, preferably using the FDA analytical technique, are needed to better elucidate the association between DVH parameters in OARs and HRQoL.

Conflict of interest

None declared.

Financial disclosure

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