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Original research article

Dosimetric impact in the dose–volume histograms of rectal and vesical wall contouring in prostate cancer IMRT treatments

Laura Gómez[a], *Carlos Andrés*[b,*], *Antonio Ruiz*[a]

[a] *Instituto Oncológico, Hospital Recoletas Campo Grande, Valladolid, Spain*
[b] *Servicio de Radiofísica y Protección Radiológica, Hospital Clínico Universitario de Valladolid, Valladolid, Spain*

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ABSTRACT

Aim: The main purpose of this study was to evaluate the differences in dose–volume histograms of IMRT treatments for prostate cancer based on the delineation of the main organs at risk (rectum and bladder) as solid organs or by contouring their wall.

Background: Rectum and bladder have typically been delineated as solid organs, including the waste material, which, in practice, can lead to an erroneous assessment of the risk of adverse effects.

Materials and methods: A retrospective study was made on 25 patients treated with IMRT radiotherapy for prostate adenocarcinoma. 76.32 Gy in 36 fractions was prescribed to the prostate and seminal vesicles. In addition to the delineation of the rectum and bladder as solid organs (including their content), the rectal and bladder wall were also delineated and the resulting dose–volume histograms were analyzed for the two groups of structures.

Results: Data analysis shows statistically significant differences in the main parameters used to assess the risk of toxicity of a prostate radiotherapy treatment. Higher doses were received on the rectal and bladder walls compared to doses received on the corresponding solid organs.

Conclusions: The observed differences in terms of received doses to the rectum and bladder based on the method of contouring could gain greater importance in inverse planning treatments, where the treatment planning system optimizes the dose in these volumes. So, one should take into account the method of delineating of these structures to make a clinical decision regarding dose limitation and risk assessment of chronic toxicity.

* *Corresponding author at*: Servicio de Radiofísica y Protección Radiológica, Hospital Clínico Universitario de Valladolid, Calle Ramón y Cajal, s/n, CP: 47005, Valladolid, Spain.
E-mail addresses: carlosrfk@gmail.com, candresr@saludcastillayleon.es (C. Andrés).
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1. Background

The importance of dose escalation in radiotherapy treatments for prostate cancer has been mainly demonstrated in intermediate and high risk tumours.[1–3] The possibility of dose escalation has been associated with the evolution of the techniques of Intensity Modulated Radiotherapy (IMRT) and Image Guided Radiotherapy (IGRT), allowing us to localize more precisely the target volumes, reducing margins, and minimizing the dose received by the healthy tissue (critical structures). However, dose escalation is limited during prostate cancer treatments owing to the close proximity of the prostate to the bladder and rectum, leading to an associated risk of rectal toxicity and bladder injury.[4] Therefore, the use of intensity-modulated techniques is highly recommended in the treatment of radiotherapy for prostate cancer.[5] Other more complex techniques, such as Volumetric Modulated Arc Therapy (VMAT), non-isocentric frameless advanced robotic system CyberKnife (CK Accuray, Sunnyvale, CA, USA) or helical Tomotherapy (HT Accuray, Sunnyvale, CA, USA), are also used in some centres.[6]

Both the rectum and the bladder are hollow organs. As such, their content (mainly faeces and urine) is irrelevant, so, from a radiobiological point of view, the critical structure is the wall of the organ itself. However, the rectum and the bladder have typically been delineated as solid organs, including the waste material, which, in practice, can lead to an erroneous assessment of the risk of adverse effects. In fact, the International Commission on Radiation Units and Measurements states that, for tubular types of organs, delineation of the wall is preferred to whole-organ delineation, especially for a serial-like organ.[7]

There are also other aspects to consider in the contouring of these critical structures, as the variability of the wall thickness that depends on the distention of the organ (and therefore on its contents). Moreover, the length of the contoured rectum also varies because it is a tubular organ. These variables, however, can be reduced by adjusting the anatomical conditions in the simulation of treatment (by controlling the bladder filling and emptying of the rectum). Fortunately, IGRT techniques allow us to verify these variables during the treatment.

Based on the Quantitative Analysis of Normal Tissue Effect in the Clinic (QUANTEC),[8] analysis and assessment of treatment doses received by critical structures are performed using cumulative dose–volume histograms (DVH), turning them into a very common instrument to evaluate different treatment techniques and to predict the expected risk of toxicity in the patient's treatment.[9,10] The differences in delineation methods may thus lead to an incorrect reading of the dose–volume parameters and modify our clinical decision.

Several studies[11–15] have confirmed this hypothesis having observed significant differences in the dose distribution and in the incidence of chronic toxicity depending on the contouring of the rectum. The study of the dose–volume response of the urinary bladder as well as its variations associated with different contouring ways is less well understood compared to the rectum.

In our opinion, these differences could become more important in inverse planning radiotherapy treatments, as IMRT and VMAT, where it is the treatment planning system itself that uses DVHs for optimizing the doses received by the organs at risk (OARs).[16]

2. Aim

The aim of the present study was to evaluate the effects of different delineation methods (organ walls and solid organs) on the rectum and bladder DVHs for prostate cancer IMRT treatments.

3. Materials and methods

Between April 2014 and November 2015, 25 patients diagnosed with intermediate risk prostate adenocarcinoma and treated at Instituto Oncológico of Hospital Recoletas Campo Grande in Valladolid (Spain) were enrolled in this retrospective study. An IMRT treatment over prostate and seminal vesicles was prescribed in all cases.

All patients had undergone radiotherapy treatment planning CT scans performed with a helical CT scanner Siemens Somatom Emotion Duo (Siemens Medical Solutions, Erlangen, Germany) in decubitus supine with a slice thickness of 3 mm. Foam knee wedges and foot blocks were used as immobilization devices in all patients. In order to reduce critical organ volumes variability during treatment, patients were instructed to empty their bladder and rectum (via a fleet enema) 1 h before planning CT, and drink half a litre of water to keep larger parts of the bladder outside the treatment fields. This procedure was repeated previously to every treatment session.

All treatments were delineated, planned and evaluated using ADAC Pinnacle v7.4 (Philips/ADAC, Milpitas, CA, USA) treatment planning system and treated at a Clinac 600 (Varian Medical Systems, Palo Alto, CA, USA) linac, equipped with a multileaf collimator Millenium-120.

With regard to the anatomical structures contouring for clinical dosimetry, the Clinical Target Volume (CTV)[17] encompassed the prostate and the seminal vesicles. Planned Target Volume (PTV) was generated with a 3D margin of 8 mm around the CTV except at the craniocaudal end where a margin of 10 mm was used, and at the anteroposterior end (5 mm margin).

The rectum and the bladder (the OARs analyzed in this study) were contoured as solid organs, i.e., the entire volume of both organs was delimited, including the filling. The upper and lower limits for the rectum were defined, respectively, as the rectosigmoid reflection and the ischial tuberosities. All other OARs (femoral heads and penile bulb) were contoured as usual.

The prescription dose was, for each patient, 76.35 Gy in 36 fractions at 2.12 Gy per fraction for the PTV, obtaining a PTV biological equivalent dose of 78.9 Gy (using the linear quadratic model with $\alpha/\beta = 1.5$ for prostate).[18,19]

IMRT plans consisted of five coplanar Step and Shoot fields. A photon energy of 6 MV was used and the treatment isocentre was put on the geometric centre of the PTV. IMRT optimization parameters were adjusted individually for each patient,

Table 1 – CTV and PTV average and maximum doses. Errors are calculated with a 95% Confidence Interval.

	Average dose (Gy)	Max. Dose (Gy)	V_{70Gy}
CTV	76.73 ± 0.26	80.14 ± 0.52	100%
PTV	76.35 ± 0.24	80.64 ± 0.45	99.5%

trying to cover the target volume with the prescribed dose (at least 99% of PTV covered by 95% of the prescription dose, with a variation of mean doses less than 1% compared to those prescribed) and OAR doses were within tolerances set by the QUANTEC criteria. Target doses obtained after the treatment optimization are summarized in Table 1.

Retrospectively, two new structures, the rectal and bladder walls, were added. In both cases, they were outlined automatically using an inner ring of 3 mm relative to the total volume of the corresponding organ.[20] No change was made in the resulting dose map. New DVH obtained was evaluated through an analysis of the doses received by these new structures as well as those corresponding to the rectum and bladder contoured as solid organs.

The parameters analyzed in the case of the two OARs studied were as follows:

- Rectum and rectal wall: The dose–volume histogram corresponding to the arithmetic mean of the values obtained for the single DVH of each 25 patients analyzed was calculated for both structures. Furthermore, the most common dose parameters used in the analysis of this OAR were studied: V_{50}, V_{60}, V_{65}, V_{70} and V_{75},[21,22] as well as the maximum and average doses in both cases. V_x is defined as the percentage of the volume of the structure receiving at least one dose of "x" Gy. Volume of the rectum receiving 100% of the prescribed radiation dose to PTV was also analyzed.[23]
- Bladder and bladder wall: Arithmetic mean of both structures DVH was calculated and the most common parameters for analyzing doses in the bladder were studied: V_{65}, V_{70} and V_{75},[24] as well as maximum and average doses in both cases.

Dose parameters are shown with an error calculated with a 95% Confidence Interval (95% CI). The Wilcoxon signed-rank test was utilized to test the correlation between pairs of values. Statistical analysis was performed with SPSS v15.0.1 (SPSS Inc, Chicago, IL). Differences were considered significant for $p < 0.05$.

4. Results

After anatomical contouring, the resulting average volume for the 25 patients enrolled in the study is summarized in Table 2.

- Rectum and rectal wall

The arithmetic mean of the DVH for all patients studied can be seen in Fig. 1, with its corresponding statistical analysis (Fig. 2). The average of the maximum doses in both structures was identical, 78.20 ± 0.52 Gy, with 43.43 ± 1.94 Gy being the average dose received by the rectum and 44.06 ± 2.04 Gy being the average dose received by the rectal wall.

Table 2 – Average volume of the structures analyzed. Errors are calculated with a 95% Confidence Interval.

	Average volume (cc)
CTV	98.4 ± 19.3
PTV	222.5 ± 31.2
Rectum	67.2 ± 6.3
Rectal wall	33.3 ± 2.4
Bladder	144.5 ± 27.2
Bladder wall	50.0 ± 5.7

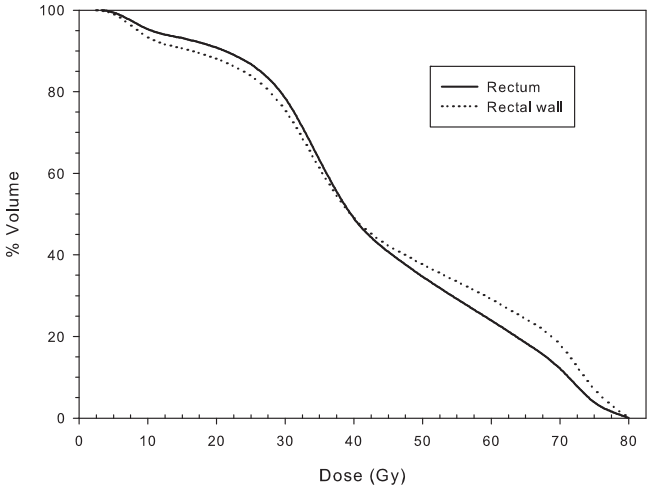

Fig. 1 – Dose–volume histogram for rectal structures.

The comparison of average doses in both volumes for each patient analyzed can be seen in Fig. 3.

The analysis of the relative rectal and rectal wall volumes receiving a particular dose level is summarized in Fig. 4.

The last parameter analyzed in our study is the volume of the rectum and rectal wall receiving 100% of the prescription dose to the PTV. Results (in both relative and absolute volume) are shown in Table 3.

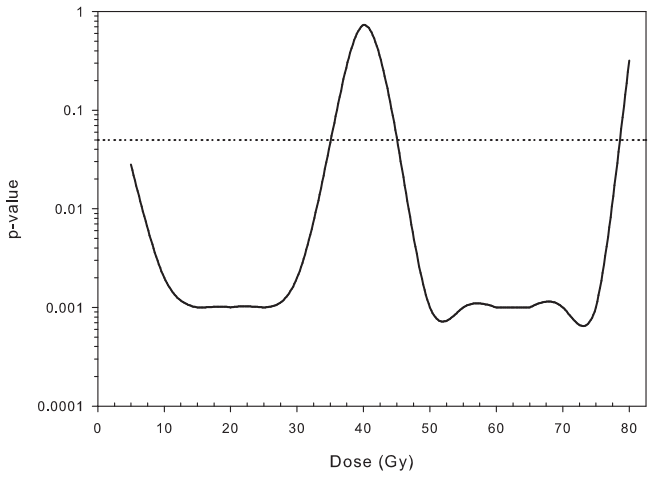

Fig. 2 – The significance of differences at each dose shown in Fig. 1. The dashed horizontal lines show $p = 0.05$ for comparison.

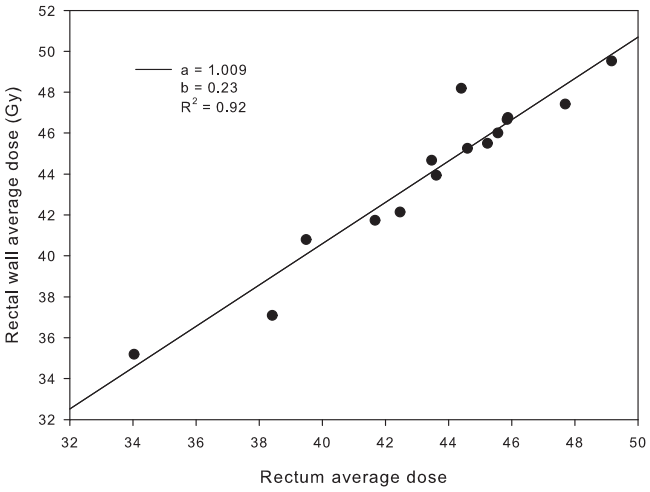

Fig. 3 – Rectal wall average dose vs. rectal average dose. The parameters of the linear regression adjustment ($y = ax + b$) are included.

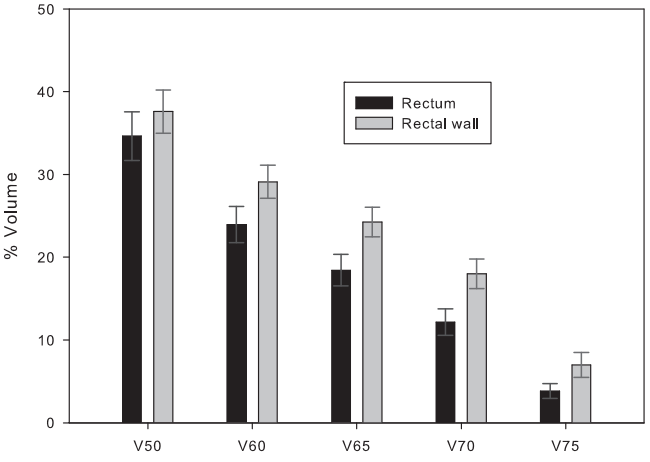

Fig. 4 – Dosimetric parameters analyzed in the rectum and rectal wall: V_{50} ($p = 0.001$), V_{60} ($p = 0.001$), V_{65} ($p = 0.001$), V_{70} ($p = 0.001$), V_{75} ($p = 0.001$). The vertical error bars correspond to the statistical value associated with a confidence interval of 95%.

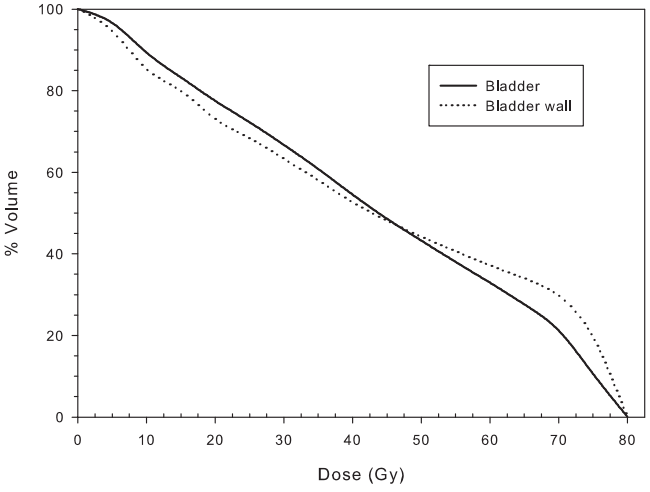

Fig. 5 – Dose–volume histogram for the bladder and bladder wall.

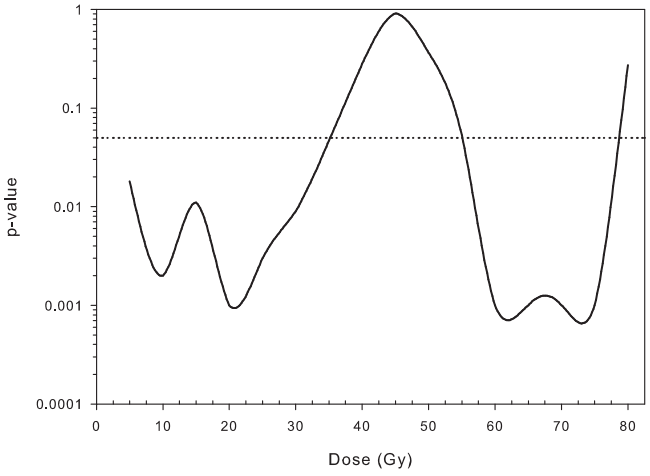

Fig. 6 – The significance of differences at each dose shown in Fig. 5. The dashed horizontal lines show $p = 0.05$ for comparison.

- Bladder and bladder wall

The averaged histogram obtained after the analysis of each clinical dosimetry can be seen in Fig. 5, with its corresponding statistical analysis (Fig. 6). The average of the maximum doses in both structures was almost identical: 79.35 ± 0.59 Gy for the bladder and 79.29 ± 0.57 Gy for the bladder wall, with 43.62 ± 3.90 Gy being the average dose to the bladder and 43.75 ± 3.56 Gy being the average dose received by the bladder wall.

The comparison of the average dose in both volumes for each patient analyzed can be seen in Fig. 7.

The comparison of all of the remaining parameters for these structures is summarized in Fig. 8.

Table 3 – Average volume (relative and absolute) of the rectum and rectal wall receiving 100% of the prescription dose to the PTV. Errors are calculated with a 95% Confidence Interval.

	$V_{100\%}$ (%)	$V_{100\%}$ (cc)
Rectum	2.85 ± 0.67	1.91 ± 0.45
Rectal wall	5.15 ± 1.11	1.71 ± 0.37

5. Discussion

The relationship between chronic toxicity secondary to radiation treatment and critical organ volume receiving a specific dose level, usually assessed by dose–volume histograms, is well documented in the scientific literature. In the special case of prostate adenocarcinoma radiotherapy treatments, the critical organs that limit dose escalation (and therefore the rate of

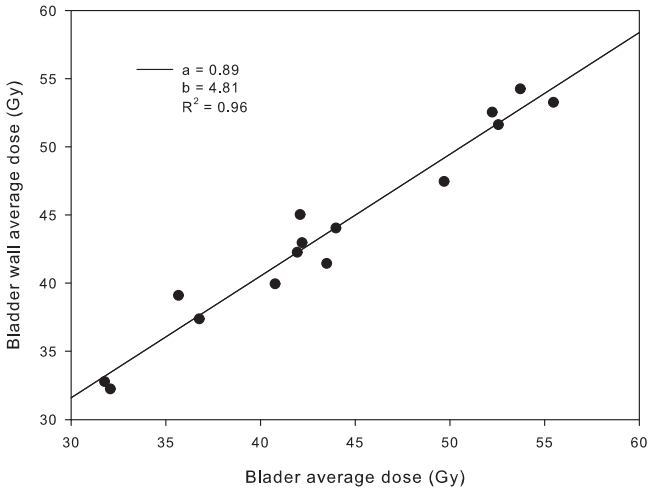

Fig. 7 – Bladder wall average dose vs. bladder average dose. The parameters of the linear regression adjustment ($y = ax + b$) are included.

local disease control) because of the risk of toxicity are mainly the rectum and bladder.

Although the bladder contouring seems relatively simple, the literature does not currently present any standardized method of three-dimensional rectal delineation. Furthermore, the rectum and bladder are moving structures within the pelvis, subject to distention and contraction that will affect their volumes and wall thickness. In IMRT for prostate cancer, dose–volume constraints for critical organs are used in plan optimization. Therefore, it is essential to know the behaviour of the OARs in dose–volume histograms to take therapeutic decisions, because different ways of organ contouring can modify dosimetric results and, therefore, the interpretation of chronic toxicities may vary.

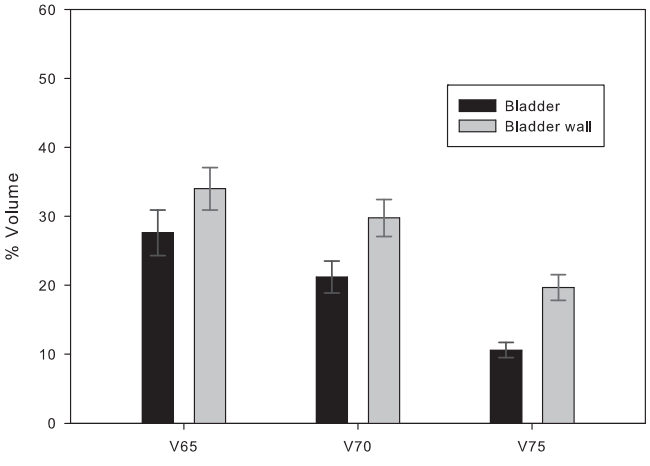

Fig. 8 – Comparison of dosimetric parameters analyzed in the bladder and bladder wall: V_{65} ($p = 0.001$), V_{70} ($p = 0.001$), V_{75} ($p = 0.001$). Vertical error bars correspond to the statistical value associated with a confidence interval of 95%.

The available literature mainly focuses on chronic rectal toxicity evaluation using dose–volume histograms.[13,25] Several studies have shown a closer relationship between chronic toxicity and various dose–volume parameters with the rectal wall volume than with the rectum volume.[26] Furthermore, chronic toxicity was more closely related to the percent volumes of the organ than to their absolute volumes.

While doses to the rectal wall in 3D Conformal Radiotherapy have been studied, our study extends to IMRT treatments in the rectum and the bladder as well. The bladder is an organ with similar characteristics to the rectum, because it is a container organ and it can also restrict the dose that a patient can receive. Furthermore, the bladder is intentionally filled as much as possible to keep larger parts of it outside the treatment fields. This fact leads us to consider that the difference in volume between the bladder wall and the solid organ may be more relevant than in the case of the rectum, which is desired to be as empty as possible. Thereby, the bladder volume contoured as a solid organ is approximately three times the volume of the bladder wall, reduced to a factor of 2 in the case of the rectum, as can be seen in Table 1.

The results of our study show a dependency of the mode of delineation of OAR in the subsequent analyzes of the dose that received, not only for the rectum, but also for the bladder. This difference is more relevant in inverse planning treatments where is the treatment planning system itself which optimizes the dose in these organs using the dose–volume histograms, so the optimization and segmentation of treatment beams will lead to different results, depending on the mode of contouring of critical structures.

In our patient series we found that from medium levels of dose (around 40 Gy at the rectum and 45 Gy in the bladder), the percentage of volume of the organ that receives a determinate dose is significantly higher in the case of the rectal and bladder walls (Fig. 9). Therefore, care has to be taken when designing dose–volume constraints on wall structures since most of the literature is based on solid structures.

In this way, the increase of the relative volume irradiated with 60 Gy is 22% ($p = 0.001$) to the rectal wall and 13%

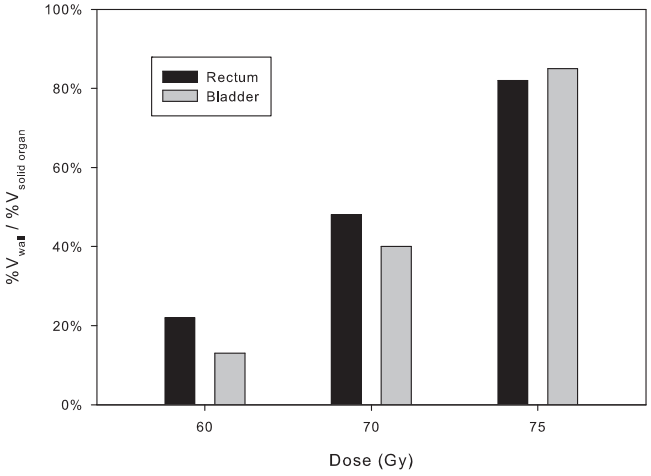

Fig. 9 – Relative increase of the volume of rectal and bladder walls irradiated compared to the total volume of the solid organ, for three representative dose values.

($p = 0.001$) to the bladder wall compared to the corresponding solid organs, increasing to 48% (rectum, $p = 0.001$) and 40% (bladder, $p = 0.001$) in the case of 70 Gy and 82% (rectum, $p = 0.001$) and 85% (bladder, $p = 0.001$) when we reach doses of 75 Gy. These data are essential in the treatment analysis, because the percentage of rectal and bladder volumes receiving doses between 50 and 80 Gy is a significant predictor of chronic toxicity.[27,28] Based on the study of Marzi et al.,[26] late rectal toxicity is mostly influenced by the amount of volumes receiving doses $\geq$70 Gy, suggesting a major importance of the dose–volume constraint V_{70} in comparison with the others at intermediate doses. In this dose level, the difference between the rectum and rectal wall DVHs was 48% in our study, reinforcing the idea of standardizing the contouring method. Our results are consistent with those obtained by Guckenberger et al. for the rectum.[11] Statistical analysis of the results also shows that these differences are statistically significant at the dose range used to predict bladder and rectal toxicity in the literature, as can be seen in Figs. 2 and 6. It is thus evident that the parameters of DVHs greatly depend on the delineation methods. This is because the percentage of rectal and bladder volume receiving a specific dose becomes smaller when a larger total volume is contoured.

We found, however, that the differences are no longer significant in the analysis of the maximum dose received in both sets of contouring, giving a dosimetrically identical results for both groups. This is due to the fact that, in a conformal dose distribution, the largest doses are close to the PTV so the maximum value in the OAR lies on the wall.

In the low doses area (below 35 Gy), it seems that solid organs tend to overestimate the received dose by the real tissue ($p < 0.05$ in both cases), although the differences are not clinically relevant. Furthermore, in the central area of the histogram (between 35 and 50 Gy) the differences between the two studied groups are no longer statistically significant. This low dose region is not considered to be of major relevance for acute and late toxicity. In the available literature, no correlation between rectal toxicity and exposure with doses of less than 40 Gy was observed.[29,30]

We extended the analysis to compare the volume of the rectum that receives 100% of the prescription dose, according to studies of Carlson et al.[23] No significant differences ($p = 0.08$) were found in the total volume of organ that receives the prescribed 76.32 Gy (on average, slightly less than 2 cc in both cases); however, these differences become statistically significant ($p = 0.007$) when we study the relative volume (in %) of the organ receiving 100% of the prescription dose, because the total volume appreciably oscillates (by a factor of 2) if we evaluate the entire rectum or the rectal wall. This result coincides well with Kusumoto et al.[31] because they demonstrated that the absolute volume DVHs can be used for evaluating rectal toxicity because it depends less than that of relative DVHs on the contouring methods used for high dose levels.

Regarding the rectum length, Kusumoto et al.[31] also demonstrated that uniformity in delineation length is also important. Longer rectum length resulted in smaller DVHs values than did shorter length because the percentage of rectal volume receiving a specific dose becomes smaller when the larger total volume is contoured. In our study, some anatomical structures (rectosigmoid reflection and ischial tuberosities) were taken as reference for rectum delineation, so rectum length was not a parameter influencing our results.

Although it seems that, when we refer to hollow organ, dose-wall histograms seem more suited to predict toxicity than dose–volume histograms, it could not be a real representation of the dose distribution to rectal and bladder walls during the treatment, taking into account that considerable variations may occur in the shape and position of internal organs during the course of radiotherapy for prostate cancer.

Moreover, patient size reduction during prostate radiotherapy leads to an increase of delivered dose to the clinical target volume, rectum, bladder and femoral heads.[32] With guided imaging techniques it is easier to check and ensure the anatomy of these structures during the treatment. With guided imaging techniques it is easier to check and ensure the anatomy of these structures during the treatment and, therefore, to evaluate possible differences compared to the images obtained in the CT simulation, so the dose distribution will be more similar to that shown on histograms. It seems, therefore, that the delineation of the wall of hollow organs can bring more clarity and reliability to the treatment parameters analysis when using IGRT techniques. Furthermore, it has been shown that VMAT techniques would be preferred to IMRT regarding the dosimetric changes in the target and critical organs under a patient size variation.[33]

In all cases analyzed, OAR doses were below the tolerances established by the QUANTEC criteria for both sets of structures: solid organs and their corresponding walls. However, special care must be taken when the patient quality of life could be compromised according to the expected toxicities through the analysis of the treatment DVH. In view of these results, it seems more conservative to use rectal and bladder wall DVHs.

In our radiotherapy department, in order to work in the most conservative way possible, and taking into account the results presented in this study, we have decided to make treatment optimization considering both sets of structures (solid organs and its respective walls) when planning prostate IMRT treatments to ensure that both structures are below reasonable limits, thus minimizing the risk of rectal toxicity and bladder injury. A more specific interpretation would require further investigation of this issue.

Conflict of interest

None declared.

Financial disclosure

None declared.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the

institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

This article does not contain any studies with animals performed by any of the authors.

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