

An evaluation of the robustness of organ-at-risk recommendations made by GEC/ESTRO according to interobserver variability: a single-center experience

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Abstract

Purpose: Groupe Européen de Curiothérapie (GEC) and European Society for Radiotherapy & Oncology (ESTRO) has proposed a rectal dose constraint of the most exposed 2-cc volume (D_{2cc} of ≤ 75 Gy EQD_{2 α/β = 3}) during external-beam plus high-dose-rate brachytherapy (HDR-BT) in localized prostate cancer patients. This study aimed to evaluate D_{2cc} for rectal contouring via interobserver variability.

Material and methods: Four blinded observers contoured rectums of 5 patients. Rectal contouring anatomical limits were determined through previous consensus. Dose-volume histogram (DVH) dosimetric parameters ($D_{0.1cc}$, D_{1cc} , and D_{2cc}) were analyzed according to GEC/ESTRO recommendations and subjected to intra- and interobserver comparisons. Latter comparisons involved coefficients of variation. For each parameter, the mean, standard deviation (SD), and range were evaluated. The effect of interobserver variation on total dose was analyzed by estimating the biologically equivalent rectal dose (EQD_{2 α/β = 3}).

Results: Interobserver coefficients of variation for $D_{0.1cc}$, D_{1cc} , and D_{2cc} were 5.7%, 4.5%, and 4%, respectively. The highest interobserver rectal delineation variation yielded a rectal dose difference up to 5.8 Gy EQD₂. Estimated intraobserver variation for the reported D_{2cc} was 5.5% in the worst-case scenario (non-significant).

Conclusions: We observed acceptable interobserver variability in EQD₂ for D_{2cc} with strong impacts on clinical threshold levels ($D_{2cc} \leq 75$ Gy EQD₂) in some cases. This small, single-center analysis will be extended in a multicenter study.

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Purpose

High-dose-rate brachytherapy (HDR-BT), defined by Morton *et al.* as a method of conformal dose escalation to the prostate [1], involves the placement of sealed sources of radiation in contact with a tumor using after-loading devices. This type of therapy plays an important role in the management of prostate cancer. Notably, dose escalation strategies, which allow the delivery of high radiation doses, have yielded improved local control in patients with prostate cancer. Accordingly, HDR-BT is considered a very acceptable option when used in combination with external beam radiotherapy (EBRT) [2]. A significant number of EBRT and HDR-BT boost studies have reported biochemical relapse-free survival (BRFS) rates of 63-97% in interme-

mediate and high-risk patients [3]. Hoskin *et al.*, in a randomized phase III trial, observed a significant improvement in BRFS with EBRT + HDR-BT versus EBRT alone, along with a 31% reduction in the risk of recurrence [4].

In addition, HDR-BT monotherapy is gaining relevance as a promising treatment for prostate cancer. However, its administration is under protocol and the majority of related studies have involved a relatively short follow-up period [5]. In 2013, Zamboglou *et al.* published a study with the longest follow-up period to date (52.8 months), and reported biochemical control rates exceeding 90% (including intermediate and high-risk groups) [6]. In 2015, Kukielka *et al.* published local control outcomes as high as 96.9% [7]. Similar urinary toxicity has been observed in patients treated with HDR monotherapy [8].

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The primary goal of HDR-BT is the delivery of a high radiation dose to the target tissue; however, this goal is restricted by the presence of the surrounding organs at risk (OAR) such as the rectum, which limit the planned total dose for a definitive treatment [9]. A high dose to the rectum may cause adverse effects such as local inflammation, fibrosis, telangiectasia, ulceration, necrosis, and fistula, which are directly related to the magnitude of the administered dose [10]. Although rare, rectal complications after combined EBRT and HDR-BT have been reported and cannot be completely prevented. The majority of studies have reported grade 2 toxicity with this combination therapy. Proctitis, rectal ulceration, and fistula formation have also been described [11].

The effects of the doses to the target and normal tissues can be analyzed and calculated by planning systems from dose-volume histograms (DVH). Dose-volume histogram values can be expressed in absolute (cc) or relative volumes (%). The usage of different doses, techniques, and fractionation schedules among departments, however, may present a challenge in the identification of universal quality parameters for the evaluation of brachytherapy treatment plans [12]. In this light, various parameters and indices for OAR documentation (most exposed 0.1-, 1-, 2-, 5-, 10-cc volumes; $D_{0.1cc}$, D_{1cc} , D_{2cc} , D_{5cc} , D_{10cc} respectively) and the target volume (V_{100} , V_{150} , and V_{200} or percentages of the clinical target volume [CTV] receiving 100%, 150%, and 200% of the prescribed dose, respectively; D_{100} and D_{90} , or the doses covering 100% and 90% of the CTV, respectively) have been proposed in the context of Groupe Européen de Curiethérapie (GEC) and European Society for Radiotherapy & Oncology (ESTRO) recommendations for the treatment of cervical cancer [10]. These parameters were subsequently extrapolated, used, and suggested as comparable universal dosimetric parameters in the recommendations by Hoskin *et al.* regarding HDR-BT for prostate cancer [13,14].

Because the use of different EBRT and HDR-BT scheme results in considerable dose heterogeneity, it is difficult to obtain a generalized OAR constraint. The GEC/ESTRO accordingly recommends the use of an absolute dose-volume constraint expressed in $Gy_{\alpha/\beta=3}$ for every fractionation based on an EQD₂ total dose [13]. The $D_{2cc} \leq 75 Gy$ EQD₂ has been indicated for specific cases involving the rectum, and has also been supported by Crook *et al.*, who reported absolute volumes rather than relative doses because the latter are subjective and very sensitive to the number of contoured slides and contoured shape of the wall [15].

Interobserver variation, when contouring clinical target volumes (CTVs), is known as an important source of systematic error in the radiotherapy treatment process. Therefore, several studies have assessed interobserver variability. For example, in gynecological brachytherapy, delimitation of the high-risk CTV has been used to demonstrate acceptable interobserver variability [16,17,18,19]. However, limited data are available on the impacts of contouring errors on doses to the OARs. Given the above issues, this pilot study aimed to determine the degree of interobserver variability with regard to rectal contouring during HDR-BT treatment planning, and to analyze the robustness of D_{2cc} as an acceptable parameter according to the GEC/ESTRO recommendations in our Radiation Oncology Department.

Material and methods

This single-center retrospective study included 5 sets of ultrasound (US) images from prostate cancer patients that were used for HDR-BT planning. Four expert physicians performed rectal contouring.

Study cases

The HDR-BT treatment planning data of 5 patients treated with combined radiotherapy (HDR-BT and EBRT) at La Fe Polytechnic and University Hospital were included. All patients were diagnosed with prostate adenocarcinoma and treated according to the same treatment plan. These patients were selected to provide a range of different prostate sizes for this study (Table 1), as well as for other characteristics.

Treatment planning

HDR-BT treatment planning was performed on an Oncentra Prostate[®] planning device (version 4.2; Nucletron, an Elekta company, Veenendaal, Netherlands). External beam radiotherapy planning was performed on an Eclipse planning device (version 13.0; Varian Medical Systems, Palo Alto, CA, USA).

The treatment was designed such that HDR-BT was performed first, followed by computed tomography (CT) simulation 2 weeks later and EBRT after an additional 2-week interval (i.e., 4 weeks after HDR-BT). In the instance of a complication that would prohibit HDR-BT, this plan would allow a continuous high dose treatment during EBRT.

Table 1. Baseline characteristics of the patient group

Case/Patient	Prostate volume (mm ³)	Age	PSA (ng/ml)	Tumor	Gleason score
1	35.71	63	5.17	T3a	6
2	28.14	72	20.40	T3a	7
3	44.78	78	27.37	T1	7
4	39.47	71	30.00	T2	6
5	53.70	70	9.20	T2	7

PSA – prostate-specific antigen

Brachytherapy was administered in a 15 Gy single fraction, and the intraoperative procedure was based on US imaging findings. The patient was placed in a lithotomy position, and transversal images were captured in 1 mm slices using a trans-rectal ultrasound (TRUS) probe. The CTV was defined as the entire prostate gland, and the planning target volume (PTV) was defined as the CTV plus a 3 mm margin (except in the rectal and vesical directions). The urethra and rectum were contoured as OARs.

Dose distributions were optimized by determining the dwell positions and dwell times for the source within each needle and calculating the D_{90} for the target volume and D_{2cc} for the OARs. The needles were inserted through a transperineal template, using live TRUS images for guidance. Treatment was delivered using a HDR ^{192}Ir source. Needles were removed after treatment, and 4 gold fiducials were implanted for EBRT image guidance.

External beam radiotherapy was planned using CT images. The CTV was defined as the prostate gland, and the PTV was defined as the CTV with a 5 mm margin in all directions except posteriorly, where the margin was 4 mm. Volumetric modulated arc therapy (RapidArc, Varian Medical Systems) and image-guided radiation therapy were used, and daily cone beam CT or orthogonal kV images were combined. The prescribed dose was defined such that 95% of the PTV should receive at least 95% of the prescribed dose (46 Gy).

Contouring

An expert group comprising 2 radiation oncologists, 1 radiologist, and 1 urologist usually involved in prostate brachytherapy and prostate US was established. This group had previously determined rectal delineation criteria in consensus.

Two identical US image sets were generated from the original HDR-BT contouring plan. Image assembly was anonymized to avoid bias. Ultrasound image sets were obtained with a Primus 6.5 MHz ultrasound device (Hitachi, Ltd., Tokyo, Japan). Axial images of the prostate were captured from the base through the apex. Rectums were contoured on 5 image sets by 4 blinded observers.

Each observer contoured the rectal wall on the axial slides in 5 mm slide increments according to the previously established consensus criteria. All observers were blinded to the other physicians' contours and were only provided the urethra contour as a reference for longitudinal rectum delineation.

In our study, the radiologic anatomic boundaries of the rectum, according to the previous consensus, were: 1) 10 mm upward of the CTV volume in the cranial direction; 2) 10 mm below of the CTV volume in the caudal direction; 3) the posterior layer of Denonvillier's fascia in the anterior direction; and 4) the rectal wall visible on the US screen in the posterior direction (see Figures 1 and 2).

Study design

Four observers delineated the rectum on 5 US image sets from 5 prostate cancer patients. The observers repeated the delineation procedure twice at a 1-week interval.

Forty rectal contours (4 observers \times 5 patients \times 2 records for each case) were created and made available for analysis. Only the main investigator, who supervised the delineations performed by the 4 observers but did not actively participate in the delineation process, controlled the data registry and adequate identification of the patients and data. Figure 3 presents the scheme of the study.

Dose volume histogram analyses

Dose-volume histograms were used to evaluate plans according to the GEC/ESTRO recommendations on HDR-BT for prostate cancer [13]. For each patient, the plan from a single HDR-BT fraction selected for contouring was used to calculate the DVH parameters. Using the source configuration from the optimized plans, the $D_{0.1cc}$, D_{1cc} , and D_{2cc} for the rectum were calculated for the observed contour set for each case.

For each DVH parameter, the mean value and standard deviation (SD) were calculated for each observer. To

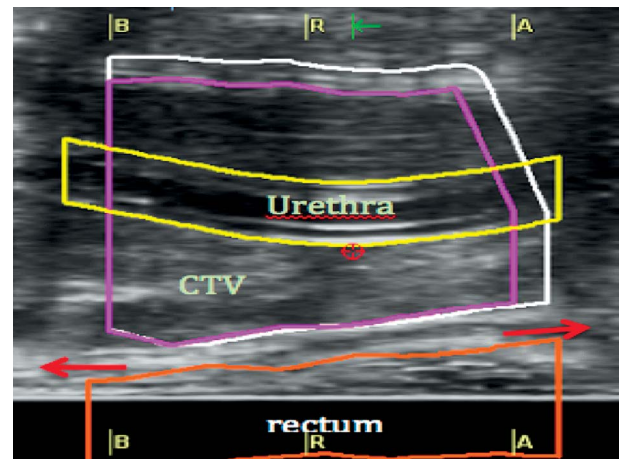


Fig. 1. Sagittal ultrasound (US) image showing the prostate and different rectal contours. The rectal structure includes a 10 mm margin that is craniocaudal with respect to the clinical target volume (CTV; red arrow). The shaded region (orange) indicates the rectal contour delineated by each observer

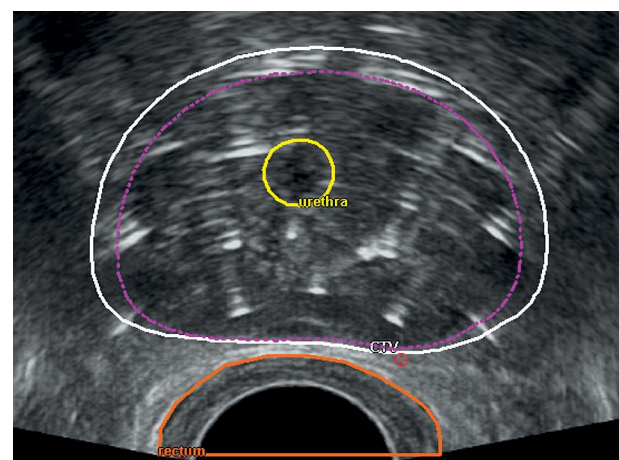


Fig. 2. Transverse ultrasound image showing an example of a rectal contour (orange line)

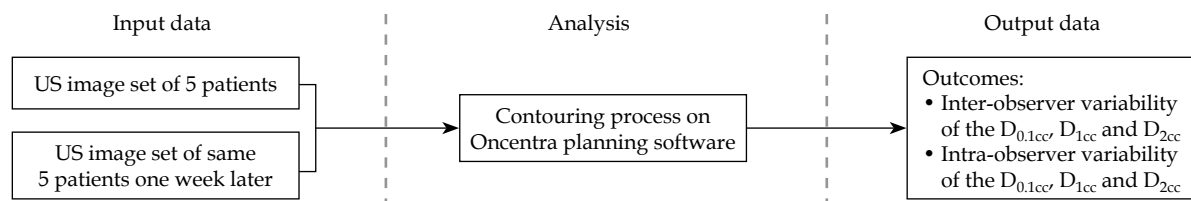


Fig. 3. Scheme of the study design. US - ultrasound; $D_{0.1cc}$, D_{1cc} , and D_{2cc} , most exposed 0.1-, 1-, and 2-cc volumes of the rectum

compare variability in the different DVH parameters according to Duane *et al.*, the coefficient of variation (COV) was used to provide a measure of the data dispersion as a proportion of the mean [19].

The 4 observers determined the means and SDs of the 2 measurements recorded for the matched US image sets for each parameter. The overall mean of these 4 measurements was then calculated for each patient. The interobserver COV was obtained by calculating the ratio of the SD to the mean for each patient. In the end, the overall COV for the 5 patients was calculated to provide a measure of interobserver variation across the entire group [19]. For the 5 patients, the differences in dose values between duplicated US image sets were analyzed using the non-parametric Friedman test. Statistical analyses were conducted using XLSTAT software (version 2014.6.01; Addinsoft, Paris, France).

The impact of contouring uncertainties on the total dose delivered to the rectum was evaluated by estimating the total dose (EBRT + HDR-BT), assuming that the rectum received the prescribed EBRT dose (46 Gy) as described above. All dose values were biologically normalized to an EQD₂ expressed in units of Gy _{$\alpha/\beta=3$} .

The intraobserver COV was calculated to determine intraobserver variability. This value was defined as 2 SDs of the value resulting from the following equation: absolute value [first measurement - second measurement]/mean measurement, where the absolute value is the absolute difference between the 2 measurements made by the same observer [19]. For the 5 patients, the differences in dose values between duplicated US image sets were analyzed using the Wilcoxon signed-rank test. Statistical analyses were conducted using XLSTAT software (version 2014.6.01; Addinsoft, Paris, France). The test revealed no statistically significant differences in the $D_{0.1cc}$, D_{1cc} and D_{2cc} dose parameters ($p = 0.059$, 0.418 , and 0.281 , respectively).

Results

Interobserver variation: impact on reported dose volume histogram

The mean reported $D_{0.1cc}$, D_{1cc} , and D_{2cc} values for the rectum from 2 sessions of contouring are summarized for each patient in Table 2.

The overall mean of the interobserver COV for all patients and all observers is presented in Table 3. Greater interobserver variation was observed for $D_{0.1cc}$. However, the larger SD of 2.62 for case 5, relative to the SDs of 0.28-0.5 for the other cases, might be explained by interobserver variation. The global test revealed significant differences

in the $D_{0.1cc}$, D_{1cc} , and D_{2cc} for the rectum among the observers ($p < 0.05$) using the Friedman test.

Interobserver variation: impact on evaluated total rectum dose

The greatest interobserver variation in the $D_{0.1cc}$ group was 16.8% greatest for case 5, with $D_{0.1cc}$ values ranging from 1.47-18.42 Gy, indicating that the potential total reported rectum $D_{0.1cc}$ ranged from 82.55-98.22 Gy. Similar magnitudes of interobserver variation were observed for D_{1cc} and D_{2cc} . The greatest interobserver variations for D_{1cc} and D_{2cc} were also observed in case 5, with values of 6.4% and 4.5%, respectively. The reported range of variability in D_{2cc} was 0.61-2.53 Gy, indicating that the potential total reported rectal D_{2cc} ranged from 71.10-77.25 Gy. The higher interobserver variability described above for D_{2cc} corresponds to a worst-case scenario of a rectal contouring variation that might result in a recorded dose difference of up to 5.8 Gy, as shown in Table 4.

Intraobserver variation: impact on reported dose volume histogram parameters

The intraobserver variation for the reported D_{2cc} ranged from 2.5% to 6.3%. Variations in rectal delineation were consistent for each patient. Given that the $D_{0.1cc}$, D_{1cc} , and D_{2cc} values for observer 1 were similar in both US image sets, we tested for differences in dose values between duplicate US image sets for this observer using the Wilcoxon signed-rank test.

Discussion

To date, advances in technology and clinical experience have led to major progress in HDR-BT for prostate cancer. However, the delineation of target volumes and OARs remains dependent on the observer. Variability in the delineation of these elements can limit the brachytherapy dose distribution, representing a main source of uncertainty that can impact clinical and treatment outcomes [20,21,22,23]. Hence, quantification of the dosimetric impact of this delineation variability is necessary.

Studies of variability in contouring of target volumes and OARs are well represented in the literature [24]. Many such studies (e.g., a study by Wong *et al.* [25]) indicate that delineation guidelines could improve interobserver homogeneity. Furthermore, in other studies (such as that Buch *et al.* [26]) the use of high-resolution image as contrast enhanced magnetic resonance imaging could improve the dosimetry to OARs. Although the GEC/ESTRO recommendations for HDR-BT of prostate cancer

Table 2. Values of the most exposed 0.1, 1, and 2-cc volumes ($D_{0.1cc}$, D_{1cc} , and D_{2cc} , respectively) of the rectum for each patient and observer based on a single 15 Gy high dose rate brachytherapy plan. Data are shown as the means of values obtained at 2 different time points. Interobserver mean, range, and standard deviation for each patient are represented in the right side $D_{0.1cc}$ (Gy)

Patient	Observer A	Observer B	Observer C	Observer D	Mean	Range	SD
$D_{0.1cc}$ (Gy)							
1	12.41	11.98	12.30	11.79	12.12	11.79-12.41	0.28
2	12.48	12.16	12.63	11.79	12.27	11.79-12.63	0.37
3	12.45	12.45	12.68	11.96	12.39	11.96-12.68	0.30
4	13.62	12.43	13.22	12.91	13.04	12.43-13.62	0.50
5	13.56	15.65	19.16	13.65	15.51	13.56-19.16	2.62
D_{1cc} (Gy)							
1	10.35	11.47	10.50	10.13	10.61	10.13-11.47	0.59
2	10.43	11.13	10.54	9.84	10.49	9.84-11.13	0.53
3	10.89	11.52	10.82	10.50	10.93	10.50-11.52	0.43
4	11.40	11.60	11.51	11.23	11.44	11.23-11.60	0.16
5	11.61	13.15	12.98	11.79	12.38	11.61-13.15	0.79
D_{2cc} (Gy)							
1	9.69	9.37	9.58	9.24	9.47	9.24-9.69	0.21
2	9.36	9.12	9.48	8.72	9.17	8.72-9.48	0.34
3	9.82	9.92	9.86	9.61	9.80	9.61-9.92	0.13
4	10.32	9.71	10.49	10.22	10.19	9.71-10.49	0.34
5	10.62	11.13	11.76	10.81	11.08	10.62-11.76	0.50

Table 3. Overall interobserver coefficients of variation (%) for the recorded most exposed 0.1, 1, and 2 cc volumes ($D_{0.1cc}$, D_{1cc} , and D_{2cc} , respectively) of the rectum based on the single 15 Gy high-dose-rate brachytherapy plan

	Dosimetric parameters		
	$D_{0.1cc}$	D_{1cc}	D_{2cc}
Coefficient of variation (COV)	5.71	4.46	4.06

have been published and updated in 2013 with the inclusion of D_{2cc} and $D_{0.1cc}$ doses for the rectum [13], to our knowledge, we are the first group to report the effects of interobserver and intraobserver variability on rectal delineation in the context of HDR-BT treatment for prostate cancer.

In the present study, despite the use of contouring consensus-based rectal delineation criteria, significant interobserver differences were detected in the dose parameters; specifically, the average interobserver COVs for $D_{0.1cc}$, D_{1cc} , and D_{2cc} were 5.71%, 4.46%, and 4.06%, respectively. Although rectal contouring was consistent among the observers, caudal limit contouring was difficult because of the varied interpretations of the rectal border and delimitation of the sphincter muscle. This difficulty was

Table 4. Range (standard deviation) of the biologically equivalent dose (EQD_2) of the most exposed 2 cc volume (D_{2cc}) of the rectum for each patient, based on the single 15 Gy high-dose-rate brachytherapy plan plus 46 Gy external beam radiotherapy

Case/Patient	D_{2cc} (Gy)	Dose difference (Gy)
1	68.60-70.62 (0.91)	2.0
2	66.45-69.67 (1.41)	3.2
3	70.25-71.66 (0.61)	1.4
4	70.70-74.30 (1.54)	3.6
5	74.95-80.71 (2.53)	5.8

clearly observed in the analysis of case 5, wherein a COV of 16.8% was calculated for $D_{0.1cc}$. This variability is reasonable because $D_{0.1cc}$ represents the smallest dose point of the largest dose near the rectum wall and is therefore highly sensitive to inaccuracies in contouring. No statically significant intraobserver differences in the dose parameters were reported.

Evidence for variations in the delineation of OARs has been primarily reported from gynecological studies using the GEC/ESTRO recommendations. Hellebust *et al.* reported interobserver delineation variability of 5-8% for

the D_{2cc} of the rectum in a study of the dosimetric impact of magnetic resonance imaging-based cervical cancer brachytherapy [27]. Saarnak *et al.* [28] reported a higher variability rate (approximately 11%). In our study, we obtained an interobserver COV < 5% for D_{2cc} , although random dosimetric variations were observed in individual cases. The low dose variability observed in our study might be associated with proper training of the physicians and implementation of the consensus contouring guidelines. However, no previously published data regarding HDRBT for prostate cancer were available for comparison.

The impact on the total received dose (HDR-BT + EBRT) corresponded with an EQD₂ range of 1.4-5.8 Gy. This difference in doses was similar to the range published by Hellebust (2-3 Gy_{α/β=3}) [27]. Nesvacil *et al.* [29] reported a slightly higher inter-fractional dose difference range of 4-8 Gy EQD₂ for OARs in a multicenter study.

Regarding rectum delineation, the observers emphasized the quality of the US images but also noted difficulty with correctly contouring the final area of the rectum proximal to the anus in some cases. In one particular case, the large prostate volume led to uncertainty when contouring the anterior limit of the rectum proximal to the prostate, although this difficulty might have been limited to this particular case or to inherent uncertainties of the observers. This incident was relevant to the dosimetric analysis because the upper limit of the EQD₂ (5.8 Gy) represents the total dose received by the rectum at a dose range of 74.95-80.71 Gy, which exceeds the recommended dose according to the GEC/ESTRO.

The impact of dosimetric variability is more significant in high dose regions near the target volume than in low dose regions. However, whereas the OARs are associated with low doses, factors such as interobserver variability in delineation could lead to severe toxicity of the OARs. George *et al.* [30] referred to side effects after radiotherapy (EBRT and brachytherapy) for cervical carcinoma; specifically, the presence of telangiectasias correlated with the 2-cm³ high dose rectal volume, and ulcerations were limited to the small 0.1-cm³ high dose volume. In our study, we observed dose uncertainties up to 5.8 Gy, which was higher than the range of 2-3 Gy published by Georg *et al.* [30] (no correspondence with critical consequences). Nevertheless, dosimetric uncertainties become important with respect to interobserver variability when the OAR doses approach the maximum limit in an attempt to optimize the brachytherapy treatment.

The sample size is a limitation in this study. It is relatively small and a larger or multicenter study should be made before extrapolation to population. However, we believe that the results obtained will establish a starting point of the robustness of D_{2cc} as an acceptable parameter according to the GEC/ESTRO recommendations in our experienced Radiation Oncology Department.

Conclusions

In general, we obtained acceptable interobserver variability in the EQD₂ for the reported D_{2cc} , although a high impact on clinical threshold levels ($D_{2cc} \leq 75$ Gy EQD₂) was present in some cases. Interobserver variability was lowest

for D_{2cc} (< 5%), in agreement with previously published studies on brachytherapy for gynecological cancers. In our study, the impact of interobserver variation on the EQD₂ for the reported D_{2cc} had the potential to yield a worst-case scenario dose difference of up to 5.8 Gy_{α/β=3}. Although the GEC/ESTRO recommendations provide a common language for reporting dose information, future studies are needed to identify correlations of interobserver delineation variability with adverse effects and clinical outcomes.

The outcomes obtained in this pilot study should be validated. In addition, a multicenter study is needed as a follow-up to this small, single-center study.

Disclosure

Authors report no conflict of interest.

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