Physica Medica 59 (2019) 127–132

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Assessment of dose to functional sub-structures in the lower urinary tract in locally advanced cervical cancer radiotherapy

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ABSTRACT

Purpose: To provide an analysis of dose distribution in sub-structures that could be responsible for urinary toxicity after Image-Guided Adaptive BrachyTherapy (IGABT) in Locally Advanced Cervical Cancer (LACC).

Methods: 105 LACC patients treated with radiochemotherapy and IGABT were selected. Sub-structures (bladder wall, trigone, bladder neck, urethra) were contoured on IGABT-planning MRIs. D_{2cm3} and $D_{0.1cm3}$, ICRU Bladder-Point (ICRU BP) and Posterior-Inferior Border of Symphysis points (PIBS, PIBS + 2 cm, PIBS − 2 cm) doses were extracted. Internal-Urethral-Ostium (IUO) and PIBS-Urethra (PIBS-U) points were defined as urethral dose surrogates. Finally, the Vaginal Reference Length (VRL) was extracted. Values were converted into total EBRT + BT equivalent dose in 2 Gy fractions using $\alpha/\beta = 3$ and $T_{1/2} = 1.5$ h.

Results: Median D_{2cm3} for bladder and trigone were 71.7[interquartile-range:66.5;74.1]Gy and 57.8[53.3;63.6]Gy, respectively, while median $D_{0.1cm3}$ were 82.2[77.6;89.1]Gy and 70.7[62.0;76.7]Gy, respectively. Median ICRU BP dose was 63.7[56.5;70.5]Gy and correlated with trigone D_{2cm3} and $D_{0.1cm3}$, while bladder and trigone D_{2cm3} had poor correlation ($R^2 = 0.492$), as well as $D_{0.1cm3}$ ($R^2 = 0.356$). Bladder neck $D_{0.1cm3}$ was always lower than trigone $D_{0.1cm3}$ and higher than IUO. Correlation between PIBS + 2 cm and IUO was poor ($R^2 = 0.273$), while PIBS and PIBS-U were almost equal ($R^2 = 0.990$). VRL correlated with dose to bladder base.

Conclusions: The study confirmed that ICRU BP and trigone doses correlate. Bladder D_{2cm3} is not representative of trigone dose because hotspots are often placed in the bladder dome. VRL is a good indicator for bladder base sparing. In addition to D_{2cm3} and $D_{0.1cm3}$ for whole bladder, ICRU BP, trigone D_{2cm3} and $D_{0.1cm3}$, IUO and PIBS are useful for lower urinary tract reporting.

1. Introduction

The gold standard treatment for Locally Advanced Cervical Cancer (LACC) is radiochemotherapy followed by a boost with Image-Guided Adaptive BrachyTherapy (IGABT) to the tumour. This treatment has shown an improved disease control and overall survival compared to two-dimensional Brachytherapy (2DBT) [1,2]. Reduction of urinary toxicity has furthermore been demonstrated by monocentric and multicentric studies [3–7]. Finally, the understanding of dose relationships for several morbidity endpoints such as for rectum and vagina has been improved [8–11].

For bladder dose reporting, the minimal dose to the most exposed 2 cm^3 and 0.1 cm^3 of the bladder (D_{2cm3} and $D_{0.1cm3}$) are key dose parameters as recommended by GEC-ESTRO and ICRU report 89 [12,13]. Furthermore, the International Commission on Radiation Units & Measurements Bladder Point (ICRU BP) [14] is recommended for reporting as it is assumed to represent the dose in a relevant anatomical location of the bladder. The current method for reporting has however several limitations. The D_{2cm3} is not linked with a precise anatomical location in the bladder wall, and the ICRU BP is a point dose estimate not linked to the contours of any normal tissue [10,15–17]. Finally, there is limited clinical evidence that describes any correlation between ICRU BP and D_{2cm3} and bladder morbidity [9,10,18].

There are currently no clear defined constraints on bladder doses to avoid radiation-induced urinary dysfunctions in LACC. Previous studies related to prostate cancer treatment with External Beam Radiation Therapy (EBRT) [19–23] and Low-Dose-Rate (LDR) Brachytherapy [24,25] showed that dose to bladder base, especially to trigone and urethra, is responsible for endpoints such as obstruction, frequency, urgency, dysuria and incontinence. In IGABT of LACC, attempts were made to connect the bladder D_{2cm3} to a location in the bladder wall using the ICRU BP dose ratio [26,27]. More recently, other studies have tried to correlate the dose to the bladder base with urinary morbidity [18,28]. There is an increasing interest in associations between

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https://doi.org/10.1016/j.ejmp.2019.01.017
Received 7 December 2018; Received in revised form 27 January 2019; Accepted 30 January 2019
Available online 13 February 2019

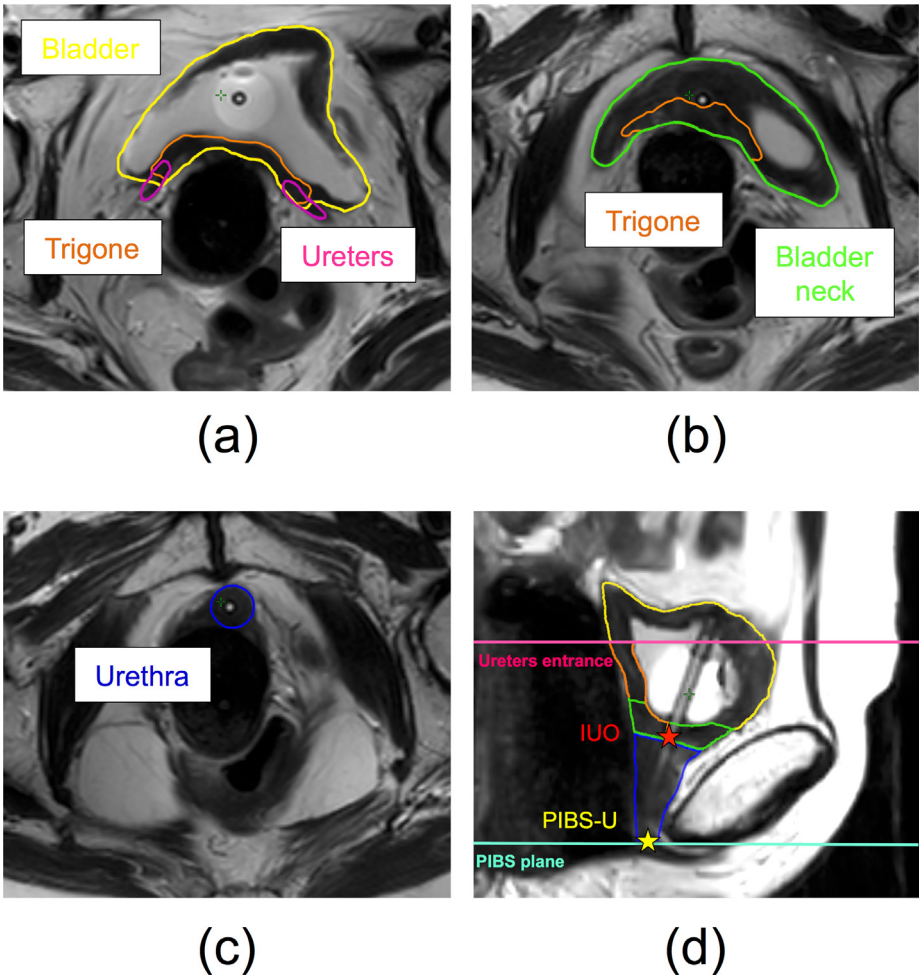

Fig. 1. a–c) Lower urinary tract sub-structures contoured on IGABT planning MRI scans. d) Sagittal MRI scan at the urethra midline where IUO and PIBS-U points are defined.

different regions and sub-structures of the bladder and late radiation-induced urinary toxicity. However, the studies conducted so far are without any systematic assessment of dose distributions in the lower urinary tract.

The aim of the present study was to analyse the dose to distinct anatomical sub-structures of the lower urinary tract that could be responsible for urinary toxicity using a consecutive cohort of patients with LACC included in the *International study on MRI guided brachytherapy* (EMBRACE) study protocol [29]. The prospective, observational and multi-institutional EMBRACE study was initiated to develop, perform and evaluate image guided radiotherapy in cervix cancer with a special focus on improving clinical outcome in terms of tumour control, survival and treatment-related morbidity. The study has enrolled 1416 patients from 2008 to 2015.

2. Material and methods

2.1. Study population

One hundred forty-six consecutive patients with LACC enrolled in the EMBRACE study [29] and treated at Aarhus University Hospital between 2008 and 2015 were considered. Eleven patients with bladder wall involvement were excluded from the study, while twenty-seven patients could not be retrospectively contoured for different technical reasons. The International Federation of Gynecology and Obstetrics (FIGO) stage distribution was: IB (8), IIA (3), IIB (75), IIIA(2), IIIB(8), IVA(1), and IVB(8) in the one hundred and five patients available for the study. Two hundred ten MRI scans have been analysed. Median age was 48 years and interquartile range (IQR) [38;58] years. All patients were treated with EBRT and concomitant chemotherapy followed by two fractions of IGABT. EBRT prescription dose was 45–50 Gy in 23–30 fractions. IGABT included two weekly fractions of MRI-based pulsed dose rate IGABT delivered in 20 + 20 hourly pulses, aiming for a total dose (EBRT + BT) to D90 of CTV_{HR} > 85–90 Gy_{EQD2}. The minimal dose to 0.1 cm^3 and 2 cm^3 of the bladder ($D_{0.1cm3}$, D_{2cm3}) and dose to the ICRU bladder point (ICRU BP) [14] were used to evaluate the dose to the lower urinary structures during treatment planning of IGABT. During the time period where these patients were treated, the dose volume histogram constraint was to keep the total dose (EBRT + BT) to D_{2cm3} below 90 Gy. Each fraction of IGABT, including applicator implantation, scanning, planning and treatment lasted 26–28 h. A tandem-ring applicator with/without interstitial needles was used for IGABT. Prior to each BT procedure, a Foley catheter was inserted in the bladder to allow free flow urine during the complete IGABT procedure.

2.2. Lower urinary tract sub-structures

The pathophysiology of the lower urinary tract is complex and includes numerous anatomical sub-structures and the involuntary and voluntary nervous system. Nevertheless, some main sub-structures that may be associated with radiation induced toxicity can be identified. The elastic smooth muscle that makes up the entire bladder (*detrusor*) expands to allow filling and contracts to empty when a certain urinary volume is reached. The urethra is a tubular structure of about 4 cm

Table 1
Dose parameters extracted from treatment plans. All values are expressed according to the EQD2 formalism for each contribution (EBRT, IGABT and total). For the urethra only the IGABT contribution is reported.

Parameter – Median [IQR]	EBRT dose (Gy)	IGABT dose (Gy)	TOTAL dose (Gy)
Bladder wall D_{2cm3}	43.2 [43.2;49.2]*	25.9 [21.3;29.8]	71.7 [66.5;74.1]
Trigone D_{2cm3}	43.2 [43.2;49.2]*	13.6 [8.8;18.3]	57.8 [53.3;63.6]
Trigone D_{mean}	43.2 [43.2;49.2]*	13.7 [9.1;18.1]	57.6 [53,3;64.3]
Urethra D_{2cm3}	NA	3.3[2.5;5.0]	NA
Bladder wall $D_{0.1cm3}$	43.2 [43.2;49.2]*	37.8 [33.0;43.7]	82.2 [77.9;88.9]
Trigone $D_{0.1cm3}$	43.2 [43.2;49.2]*	25.0 [17.9;31.8]	70.7 [62.3;76.3]
Bladder neck $D_{0.1cm3}$	43.2 [43.2;49.2]*	12.5 [7.0;20.7]	57.6 [52;64.9]
Urethra $D_{0.1cm3}$	NA	5.7 [3.5;8.9]	NA
ICRU BP dose	43.2 [43.2;49.2]*	19.9 [11.7;25.5]	63.7 [56.6;70.3]
PIBS	40.5 [12.8;46.2]	2.6 [1.8;4.3]	42.2 [16.7;49.0]
PIBS + 2 cm	45.9 [44.8;50.3]	6.0 [3.5;11.2]	51.5 [48.1;56.6]
PIBS-2 cm	3.9 [2.4;8.2]	1.4 [1.0;1.9]	4.1 [2.6;7.2]
IUO	43.2 [43.2;49.2]*	6.2 [3.9;9.8]	50.7 [48.3;55.1]
PIBS-U	40.5 [12.8;46.2]	2.6 [1.8;3.8]	43.1 [16.1;49.1]

Abbreviations: IQR = Inter Quartile Range. D_{2cm3} = minimal dose to most exposed 2 cm^3 of the structure; $D_{0.1cm3}$ = minimal dose to most exposed 0.1 cm^3 of the structure; ICRU BP = International Commission on Radiation Units & Measurements Bladder Point; D_{mean} = mean dose delivered to the structure; PIBS = Posterior-Inferior Border of Symphysis; IUO = Internal Urethral Ostium; PIBS-U = PIBS-Urethra. NA = not available. * = Only 3 values for EBRT contribution: 43.2 Gy (n = 58), 46.7 Gy (n = 46) and 49.2 Gy (n = 1).

composed of several smooth and striated muscle and mucosa layers that contracts during the bladder filling and opens at the moment of emptying by a voluntary nervous reflex. The bladder trigone is a triangular structure enclosed by the ureteral orifices and the opening of the urethra. This structure is highly innervated compared to the rest of the bladder wall. Finally, the bladder base and bladder neck have different stretch-sensitive receptors compared to the bladder dome and are partly responsible for normal urinary continence.

2.3. Sub-structures, dose points and dimensions on treatment plans

Sub-structures were retrospectively contoured for each IGABT plan including bladder wall, trigone, bladder neck and urethra. For the identification of the structures, the planning axial and sagittal T2-weighted (T2W) MRI images were used, as suggested in literature [30].

Contouring of the bladder wall was performed according to the GEC-ESTRO Recommendations [13]. The trigone was defined as a triangular structure enclosed by the entrance of the two ureters into the bladder wall and the internal urethral orifice [18,19], as shown in Fig. 1.a. The bladder neck structure was defined as the region in which the bladder wall is narrower and thicker, as shown in Fig. 1.b. Finally, the urethra was contoured as a tubular structure below the bladder neck (Fig. 1.c and d). The most caudal slice of the urethra was always defined in the reference plane of the posterior inferior border of the pubic symphysis (PIBS), as shown in Fig. 1.d. The choice of this position allows to include in the definition the most functional part of the structure [30].

In addition to the sub-structures mentioned above, a number of dose points was extracted from the treatment plans. First, the dose delivered to ICRU BP was extracted. Furthermore, doses to the PIBS point and the PIBS + 2 cm point, already used in the EMBRACE study for vaginal dose reporting [31], were used as surrogates of the dose to the most proximal and distal part of the urethra. The PIBS-2 cm point was also considered as it could potentially reflect dose to the lower part of the urethra. To obtain more accurate information about the dose in these two different positions of the urethra, two new points were identified: the Internal Urethral Ostium (IUO) and the PIBS-Urethra (PIBS-U). PIBS-U was defined as the intersection of the PIBS plane and the urethra mid-line, as shown in Fig. 1.d. IUO was defined in the intersection between bladder neck and urethra. Finally, the Vaginal Reference Length (VRL), defined as the distance between the PIBS point and the ring centre [31], was also calculated to obtain information about the relative distance between the bladder base and the centre of the BT applicator. The VRL was also compared to the distance between IUO point, related to the position of the bladder base, and the centre of the applicator ring.

2.4. Dose parameters extraction

Dose parameters were extracted from each IGABT plan and converted in equivalent dose into 2 Gy fractions (EQD2) using α/β of 3 and half repair time of 1.5 h.

The minimal doses to most exposed 2 cm^3 (D_{2cm3}) and 0.1 cm^3 ($D_{0.1cm3}$) were extracted for the bladder wall, trigone and urethra, while for the bladder neck only $D_{0.1cm3}$ was considered. Finally, the mean trigone dose (D_{mean}) was extracted.

Dose points (ICRU BP, PIBS, PIBS + 2 cm, PIBS-2 cm, IUO and PIBS-U) were extracted for each fraction and the physical dose was converted to EQD2.

The EBRT prescription dose was considered to represent the EBRT dose contribution in the region of D_{2cm3} and $D_{0.1cm3}$ for bladder and trigone as recommended by ICRU report 89, since these regions were fully irradiated with EBRT. For the PIBS, PIBS + 2 cm and PIBS-2 cm points the EBRT dose contribution was extracted from the EBRT plans. The EBRT prescription dose was considered for IUO, while the EBRT PIBS contribution was considered for PIBS-U. For the urethra, it was considered uncertain to attempt assessment of accumulated dose across EBRT and BT since both modalities present with significant dose gradients across this organ. Therefore, only BT dose was evaluated for the urethra.

2.5. Statistical analysis

Data analysis to assess differences between IGABT fractions was performed using a paired student *t*-test or a Wilcoxon matched-pairs signed-ranks test. A p-value less than 0.05 was considered statistically significant. The correlation between the dosimetric parameters of the new sub-structures and the current dose reporting for IGABT in LACC (bladder D_{2cm3} and ICRU BP), as well as the urethral dose points (IUO and PIBS-U) with PIBS and PIBS + 2 cm points, was performed with linear regression analysis (Stata v.15, StataCorp LLC, 4905 Lakeway Drive, College Station, TX 77845, USA).

3. Results

Table 1 shows the median values of the dosimetric parameters extracted from the treatment plans. The different contributions (EBRT and IGABT), as well as the total dose, are reported. For the bladder wall, the

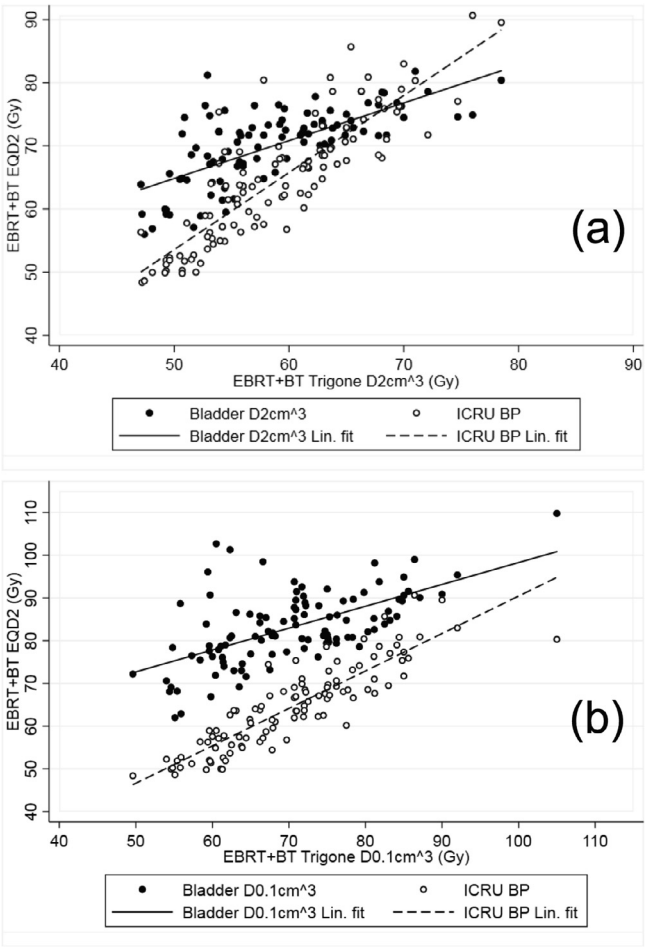

Fig. 2. a) Bladder D_{2cm3} (full circles) and ICRU BP (hollow circles) versus trigone D_{2cm3} and linear fit curves. b) Bladder $D_{0.1cm3}$ (full circles) and ICRU BP (hollow circles) versus trigone $D_{0.1cm3}$ and linear fit curves. Values are expressed in cumulative (EBRT + IGABT) EQD2.

trigone, the bladder neck, the ICRU BP and the IUO point, the prescription dose was considered as EBRT contribution. For PIBS, PIBS + 2 cm and PIBS-2 cm the real EBRT contribution was extracted from the plan. Finally, only the IGABT contribution is reported for the urethra.

The IGABT dose values for bladder base structures (trigone, bladder neck and urethra) were lower than those of the bladder wall. In addition, the bladder neck dose ($D_{0.1cm3}$) was always between the trigone $D_{0.1cm3}$ and the IUO point dose. The EBRT PIBS + 2 cm contribution corresponded to the prescription dose in most cases, while for the EBRT PIBS the range of values was much wider.

Fig. 2.a shows bladder D_{2cm3} and the ICRU BP dose as a function of the cumulative trigone D_{2cm3} with linear fit curves. Similarly, Fig. 2.b shows bladder $D_{0.1cm3}$ and the ICRU BP dose as a function of trigone $D_{0.1cm3}$ and the linear fit curves. The correlation of the bladder D_{2cm3} with the trigone D_{2cm3} was poorer than for the ICRU BP dose (R^2 = 0.492 versus R^2 = 0.745). Similar observation was found for the correlation between bladder $D_{0.1cm3}$ with trigone compared to the ICRU BP dose (R^2 = 0.356 versus R^2 = 0.782). Moreover, bladder D_{2cm3} was systematically higher than trigone D_{2cm3}. In 53% (n = 56) and 98% (n = 103) of patients the bladder D_{2cm3} was higher than trigone $D_{0.1cm3}$ and D_{2cm3}, respectively.

Median VRL was 5.9 [IQR:4.6;6.8] cm and 5.8 [IQR:4.5;6.5] cm for the first and second fraction respectively, and the difference was not significant (p = 0.07). Furthermore, the VRL showed a linear

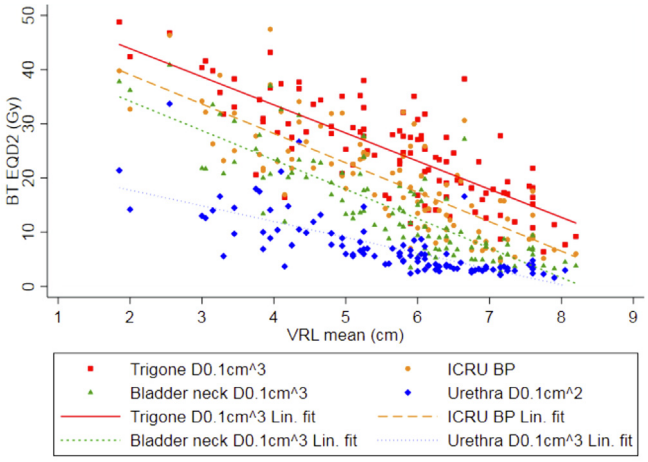

Fig. 3. Trigone $D_{0.1cm3}$ (red squares), Bladder neck $D_{0.1cm3}$ (green triangles), Urethra $D_{0.1cm3}$ (blued diamonds) and ICRU BP (orange circles) as a function of VRL. Only the IGABT contribution in EQD2 is shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

relationship with the distance between IUO and sources (Supplementary Material). This is confirmed by Fig. 3 showing the IGABT contribution in EQD2 for trigone $D_{0.1cm3}$, bladder neck $D_{0.1cm3}$, urethra $D_{0.1cm3}$ and ICRU BP as a function of the VRL (mean of the two fractions) and the linear fits. All parameters were inversely related to the distance from the applicator.

Regarding the urethral dose surrogates, the median values of the total contribution (EBRT + IGABT) for PIBS and PIBS-U points, as well as for PIBS + 2 cm and IUO points, were similar. However, the difference between IUO and PIBS + 2 cm was borderline significant (p = 0.06), while for PIBS and PIBS-U it was not (p = 0.52). This is confirmed by Fig. 4 which shows the cumulative contribution in EQD2 for IUO dose as a function of PIBS + 2 cm dose (a) and for PIBS-U dose as a function of PIBS dose (b). Four PIBS + 2 cm point doses higher than 90 Gy were removed to improve the readability of the plot. Especially with regard to IUO point dose, the correlation with PIBS + 2 cm was poor in high dose ranges (R^2 = 0.273). On the other hand, the correlation between PIBS-U point dose and PIBS was good (R^2 = 0.990).

4. Discussion

Despite the awareness regarding limitations in current bladder dose reporting for LACC IGABT in relation to radiation-induced urinary toxicity, no study has yet performed a thorough analysis of the dose distribution in the lower urinary tract with a systematic comparison to the parameters currently in use. This study aimed to give an overview of the sub-structures potentially related to urinary adverse effects and to provide new information regarding dose and volume that could be useful for the determination of new dose-effect curves. The results were compared with the current bladder dose reporting, to determine which parameters could be used or if new definitions need to be introduced.

The volumetric parameter bladder D_{2cm3} indicates the maximal hotspot of the bladder, but does not identify the location of the hotspot in the bladder. The ICRU BP, on the other hand, is located close to the bladder base but often underestimates the hotspots especially in patients where this is placed more cranial compared to ICRU BP position [15–17,32]. Furthermore, a single point dose cannot be representative of the dose distribution in functional structures such as the trigone or the bladder neck. Attempts have been made to correlate the position of the dose hotspot to the bladder base, through the ratio between bladder D_{2cm3} and ICRU BP dose [26,27], which in turn would allow to identify patients who received high doses to the bladder base. This statement is in line with the results of the present study, as the ICRU BP point had a

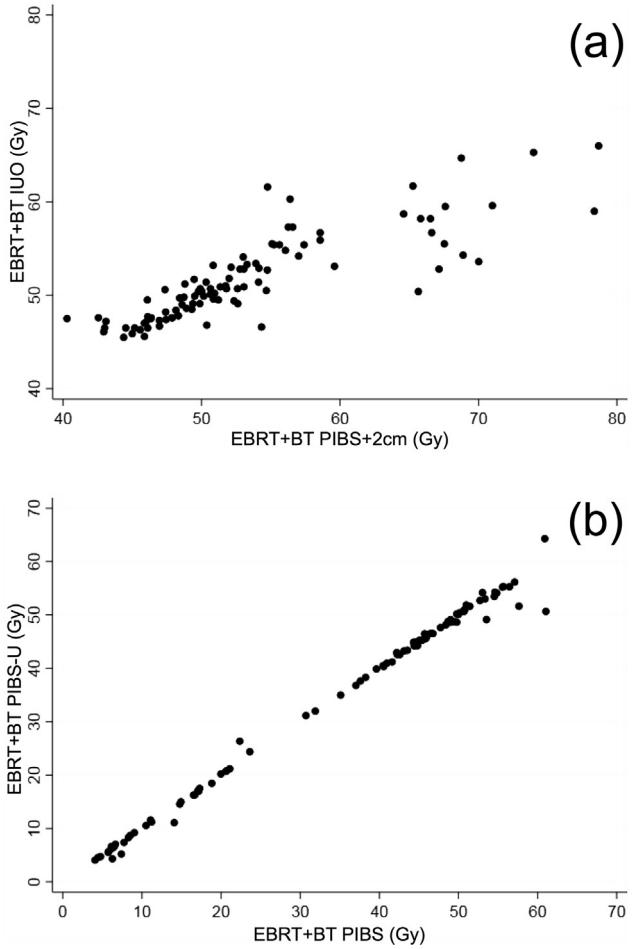

Fig. 4. a) IUO point doses versus PIBS + 2 cm point (cumulative contribution). b) PIBS-U point doses versus PIBS point (cumulative contribution).

good correlation with the dose hotspots in the trigone area (both D_{2cm3} and $D_{0.1cm3}$).

Georg et al. [9] concluded that D_{2cm3} is the strongest predictor of overall urinary morbidity and suggested 100 Gy as a dose-volume constraint. However, the clinical feasibility of this constraint in relation to predict morbidity may be limited. First, the incidence, the temporal pattern and the severity of the different endpoints are not the same. Urinary frequency and incontinence, for example, are fluctuating endpoints which may show only once during follow-up, making the determination of dose-effect relationship more difficult [33]. Furthermore, assuming that all endpoints have the same cause contradicts that toxicity may result from either global injury of the whole bladder, or focal injury to a small portion of the bladder [34]. Viswanathan et al. reiterated the same concept [35], also stating that all regions of the bladder may not be equally important, and studies to estimate the functional effect of doses to different regions of the bladder are needed.

Underlining the need to analyse individual urinary endpoints to assess dose-effect relationships, Zakariaee et al. focused on the dose to the bladder base for LACC treatment with HDR IGABT [28]. Although the study only included 30 patients and no functional sub-structure was identified, some evidence suggested a correlation between dose to small volumes (0.5–2 cm^3) in the region of the bladder neck and urinary incontinence. Similarly, Manea et al. focused on the correlation between late urinary toxicity and trigonal dose-volume parameters using information from 300 patients treated with PDR IGABT [18]. The correlation between trigone dose and late urinary morbidity was confirmed, but all urinary endpoints were pooled in the analysis. A modern insight to the historical recommendation of keeping ICRU BP dose less than 70–75 Gy [36] was provided, although only in univariate analysis.

Due to the lack of a comprehensive description of the dose to functional areas of the lower urinary tract, this study was addressed to analyse in detail the dose distributions to sub-structures that might be involved in radiation-induced urinary toxicity, such as, in addition to the trigone, the bladder neck and the urethra. Based on the analysis, the results confirmed that the dose hotspots are often placed in the bladder dome during IGABT. On the other hand, ICRU BP dose, although some patient-to-patient scattering is still present, has a good correlation with trigone D_{2cm3} and $D_{0.1cm3}$. In particular, the median value of ICRU BP dose is halfway between the trigone $D_{0.1cm3}$ and D_{2cm3} or D_{mean}. These results were also found by Manea et al. [18], who verified a correlation between ICRU BP dose and trigone median dose.

The trigone and the bladder wall receive considerable BT dose, and total EBRT + BT D_{2cm3} EQD2 dose for these two structures were 53.3 Gy and 66.5 Gy, respectively, for the majority (75%) of patients in our cohort. The bladder neck, involved in the internal urethral sphincter closure process, generally receives lower BT doses when compared to the trigone. The present study therefore suggests that contouring of the bladder neck does not add further information because the dose parameter is always between the trigone dose, placed in the posterior part of the bladder wall that is most irradiated during treatment, and the dose to the most proximal part of the urethra, represented by the IUO point. The IUO and PIBS-U points, representing the dose to the proximal and distal urethra, respectively, had low BT dose contribution (< 9.8 Gy and < 3.8 Gy in 75% of the patients, respectively). The dosimetric variation across patients for PIBS-U was mainly driven by different EBRT dose contribution, and in particular, the lower border of the EBRT target is influencing the dose to PIBS-U. Only in a few patients a considerable BT dose (> 15 Gy) was delivered to the IUO (n = 5) and PIBS-U (n = 1), this being due to the treatment of residual disease. Nevertheless, the cumulative PIBS + 2 cm reached values > 90 Gy for four patients where it was particularly close to the sources during brachytherapy, while the respective cumulative IUO doses were in the range of 56–66 Gy.

The PIBS and PIBS + 2 cm points, already used for vaginal dose reporting [31], were compared with the PIBS-U and IUO points to test their possible use as surrogates for urethral dose. The PIBS + 2 cm point did not have a good correlation with the IUO point, especially for higher doses. The PIBS-U and PIBS dose values were generally very similar; although scattering was still seen in the higher dose range.

Finally, the VRL was on average a good indicator for dose sparing of bladder base structures. This result suggests that optimal positioning of the applicator during IGABT treatment is of high importance for dose sparing of the lower urinary tract. However, pushing the applicator more cranially could increase the dose to the bowel, so a compromise to minimize the dose to both organs must be found.

Although new information on dose to the lower urinary tract sub-structures is provided, the study had some limitations. First, it was descriptive, therefore no association between dose and late toxicity was performed. Furthermore, the study used data from a single centre and therefore there was limited variability in the applied technique. In fact, the use of different techniques, applicators and vaginal packing may affect the dose to lower urinary tract sub-structures. Finally, all patients in the study were treated with PDR BT. The total EQD2 bladder doses in a patient cohort boosted with HDR BT would be expected to be higher due to the radiobiological effect of the more hypo-fractionated HDR.

As a next step, the results of this study will be applied to a broader cohort, using information from the EMBRACE study to integrate the new dosimetric parameters with clinical factors and follow-up information (both physician assessed and patient reported outcome). The integration of the new dosimetric parameters with clinical factors, may have potential to improve the understanding of late radiation-induced urinary toxicity.

5. Conclusion

Current dose reporting in IGABT for LACC is not sufficient to describe actual dose distribution responsible for radiation-induced urinary toxicity. Bladder D_{2cm3} does not represent the trigone dose, and dose hotspots are often placed in the bladder dome. Instead the ICRU BP dose was shown to be important for dose reporting as a good correlation with the trigone dose was found. We propose that D_{2cm3} and $D_{0.1cm3}$ should be used for reporting of trigone, while IUO and PIBS are proposals for new dose reporting points for the urethra. EBRT dose was the main contribution for PIBS-U, therefore particular care must be given to treatment planning. VRL is a good indicator for bladder base dose sparing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2019.01.017.

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