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Thomas Lacornerie, Renaud de Crevoisier

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**Achievable dosimetric constraints in stereotactic re-irradiation for recurrent prostate cancer**

M. Baty<sup>1</sup>, D. Pasquier<sup>2</sup>, K. Gnep<sup>1</sup>, J. Castelli<sup>1,3</sup>, Nolwenn Delaby<sup>4</sup>, Thomas Lacornerie<sup>5</sup>, R. de Crevoisier<sup>1,3,6</sup>

<sup>1</sup>Department of Radiotherapy, Center Eugène Marquis, 35000 Rennes, France

<sup>2</sup>Department of Radiation Oncology, Center Oscar Lambret, 59020 Lille University, France

<sup>3</sup>LTSI, Inserm U1099, 35042 Rennes, France

<sup>4</sup>Medical Physics department, Center Eugène Marquis, 35000 Rennes, France

<sup>5</sup>Department of Radiation Oncology, Center Oscar Lambret / Lille / France

<sup>6</sup>LTSI, University of Rennes 1, 35042 Rennes, France

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**Running title:** Dose constraints in stereotactic reirradiation for local recurrence of prostate cancer

**Corresponding author's and statistical analysis author's contact information:** Manon BATY, Department of Radiation Oncology, Centre Eugene Marquis, 3 Avenue de la Bataille Flandres-Dunkerque, 35000 Rennes – France

Email: manon.baty2@gmail.com

Tel: +33 669771924

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**Abstract**

**Background:** Stereotactic body radiation therapy (SBRT) has been proposed as a salvage treatment for recurrent prostate cancer (RPC) after irradiation. One crucial issue is choosing appropriate dose-volume constraints (DVCs) during planning. The objectives of this study were: 1) quantify the proportion of patients respecting the DVCs according to the GETUG-31 trial, testing 36 Gy in six fractions, 2) explain geometrically why the DVCs could not be respected, 3) propose the most suitable DVCs.

**Methods:** This retrospective dosimetric analysis included 141 patients treated for RPC with Cyberknife® (Accuray), according to GETUG-31 DVCs:  $V_{95\%} \geq 95\%$  for the PTV,  $V_{12\text{Gy}} < 20\%$  and  $V_{27\text{Gy}} < 2\text{cc}$  for the rectum,  $V_{12\text{Gy}} < 15\%$  and  $V_{27\text{Gy}} < 5\text{ cc}$  for the bladder. The percentage of patients not respecting the DVCs was quantified. Correlations between the DVCs and anatomical structures were examined. New DVCs were proposed.

**Results:** Only 19% of patients respected all DVCs, with a mean PTV of 18.5 cc (range, 3–48 cc), although the mean PTV was 40.5 cc (range, 3–174 cc) in the whole series. A total of 98% of the patients with a CTV/prostate ratio  $>0.5$  could not respect the DVCs in the organs at risk (OARs). The target coverage and OARs sparing decreased significantly with increase in the values of PTV, CTV, CTV/prostate ratio,  $V_{\text{Overlap PTV/Bladder wall}}$ , and  $V_{\text{Overlap PTV/Rectal wall}}$ . Threshold values of PTV, less than 20 and 40 cc, allowed for the PTV and bladder DVCs, respectively. To improve DVCs respect in case of large target volume, we proposed the following new DVCs:  $V_{12\text{Gy}} < 25\%$  and  $25\%$  and  $V_{27\text{Gy}} < 2\text{ cc}$  and  $5\text{ cc}$  for the rectum and bladder, respectively.

**Conclusion:** GETUG-31 DVCs is achievable only for small target volumes (CTV < half of the prostate). For a larger target volume, new DVCs have been proposed.

**Keywords:** Recurrent prostate cancer, salvage radiotherapy, stereotactic body radiotherapy, re-irradiation, dose-volume constraints

## Introduction

Despite treatment with external beam radiation therapy (EBRT) or brachytherapy (BT) to cure localized prostate cancer, five-year biochemical relapse rates are 10–15%, 20–25%, and 30–40% for

low-, intermediate-, and high-risk cancers, respectively [1]. The most common first recurrence site after radiotherapy (RT) in the prostate is the site of the dominant primary tumor, particularly in the apex [2–5]. There is no standard treatment for such recurrences owing to the lack of comparative randomized studies and considering the benefits/side effects of the treatments in an asymptomatic recurrent population of patients. Several therapeutic options can be discussed. Palliative attitudes consist of surveillance or androgen deprivation (ADT) amongst most of the elderly population [6]. For younger patients, curative salvage treatments, such as salvage radical prostatectomy (SRP), cryotherapy, high-intensity focused ultrasound (HIFU), re-irradiation using BT [7–13], and stereotactic body radiotherapy (SBRT), can be proposed [14–16].

Re-irradiation with EBRT with conventional fractionation has been abandoned because of its high toxicity and inefficiency [15,17]. However, SBRT, mostly owing to its imaging capabilities allowing target localization, can reduce PTV margins and spare the rectum and bladder. Moreover, the likely low  $\alpha/\beta$  ratio of prostate cancer also favors extreme hypofractionation [18–20]. Finally, based on the good results of the literature in terms of high local control and low toxicity in randomized studies [21–24], SBRT for primary prostate cancer can be considered an option [25,26].

The literature on salvage SBRT consists of a limited number of studies, mostly with less than 20 patients, and a small-sized series with more than 100 patients, without prospective data and follow-up (less than five years) [27–40]. However, the toxicity of SBRT is moderate, and the risk of biochemical recurrence is around 50% and depends mostly on the patient [14,15,41]. Cyberknife® (Accuray) has been used in 70% of patients receiving SBRT [15]. SBRT re-irradiation doses are variable and range from 25 to 38 Gy in 5–6 fractions, as shown in Table 1. Practices are heterogeneous in terms of the prescribed dose and fractionation as well as the definition of the volume of interest (target volume and OARs). Moreover, dose–volume constraints (DVCs) have been empirically defined [42–44] and are highly variable (Table 1). The most common frequency schedule is 36 Gy in six fractions of 6 Gy every other day [30,35,39,40]. Identifying appropriate DVCs for this schedule is crucial in terms of dosimetric feasibility and clinical results.

This study analyzed the dosimetric experience of re-irradiation with Cyberknife®(Accuray) in two experimented French centers using a dose schedule of 36 Gy in six fractions of 6 Gy. The DVCs

presented in Table 1 are currently being used in the ongoing prospective multi-center phase I/II GETUG-31, evaluating the toxicity and efficacy of salvage re-irradiation by SBRT [30,35,39,40]. The DVCs were inspired by a heterogeneous “high-dose-rate-like” dose of 34 Gy delivered in five fractions [38,45]. However, all patients in the GETUG-31 study were required to have a CTV/prostate ratio of less than 0.5. The first objective of our dosimetric study was to effectively quantify the proportion of patients respecting the proposed DVCs. The second objective was to explain geometrically why the DVCs were not respected by a subset of patients. The final objective was to propose the most adapted DVCs for clinical practice.

## Materials and methods

### *Patients and tumor*

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SBRT dosimetric data of 141 patients were retrospectively reviewed. Patients were treated with salvage SBRT with Cyberknife® (Accuray) for local prostate cancer recurrence between 2011 and 2020 at two experimented French Comprehensive Cancer Centers. None of the patients underwent initial radical prostatectomy. The initial T stage was T1 (39%), T2 (42%), or T3 (19%). According to D’Amico classification, the initial disease was defined as low-, intermediate-, and high-risk in 32, 31, and 37% patients, respectively. The first irradiation was EBRT (using 3-dimensional conformal RT (3D-RT) or intensity-modulated RT (IMRT)) in 117 patients and BT in 24 patients. The median EBRT and BT doses were 75 Gy (range, 64–80 Gy) and 144 Gy, respectively.

All patients experienced biochemical relapse. Local relapse was documented using 18F-choline positron emission tomography (18F-chol-PET), used in France in this indication, or PSMA-positron emission tomography (PSMA-PET) and multiparametric pelvic magnetic resonance imaging (mpMRI). Pathological recurrence was confirmed by prostate biopsy in all patients. The mean PSA level at the time of recurrence was 3.4 ng/mL (range, 0.6-43 ng/mL). The median age of the patients at the time of

SBRT was 74 years (range, 50-93 years). The median time between the two irradiations was 101 months (range, 38–239 months).

### *Image acquisition and dose planning*

Before treatment, three intraprostatic fiducials were implanted, most often at the time of prostate biopsy, to consider translational and rotational movements during SBRT treatment. After at least one week, all patients underwent a simulation computed tomography (CT) scan with contrast media to check for contraindication. Because Cyberknife© (Accuray) does not comprise 3D imaging, patients were asked to have a half-full bladder and an empty rectum at the simulation and at each treatment fraction. In addition, the patient was positioned on a reproducible supine position using a comfort mattress and a knee wedge. One-millimeter-thick slices were acquired from the L5-S1 joint space to the small trochanters. After the CT scan image was transferred into the treatment planning system (TPS), a prostate rigid registration was performed between the mpMRI (performed after fiducial implantation) and CT scan images, based on the fiducials. The gross tumor volume (GTV) and prostatic contours, particularly the apex, could therefore be delineated on the MRI images. The GTV was defined by the recurrent tumor visible on mpMRI and on 18F-chol-PET. The clinical target volume (CTV) was defined as the GTV with an additional margin taken in account the localization of the positive prostate biopsy mapping. In total, the CTV corresponded to the whole prostate, half of the prostate, and only a visible nodule in 38%, 33%, and 26% of patients, respectively. In two cases, the CTV was defined as the whole prostate plus one seminal vesicle. The CTV to PTV margin was mostly 2 mm. The following OARs were contoured on each slice: rectum and rectal wall, bladder and bladder wall, femoral heads, sigmoid, small bowel, penile bulb, and urethra. The rectal wall was generated with a thickness of 5 mm from the external manually delineated rectal contour, extending from 2 cm below the prostatic apex to the rectosigmoid junction. The bladder wall was generated with a thickness of 7 mm from the external manually delineated bladder contour, according to the French GETUG/RECORAD group recommendations [25]. The femoral heads were delineated from their upper limit to the bottom of the small trochanters. The small intestine and sigmoid colon were divided into two separate critical volumes.

The urethra was delineated in the MRI, when it was visible, from the bladder to 2 cm below the prostatic apex. A 3 mm margin was defined around the urethra. For each patient, we retrospectively considered the overlapping volume between the PTV and rectal wall ( $V_{\text{Overlap PTV/Rectal wall}}$ ) and that between the PTV and bladder wall ( $V_{\text{Overlap PTV/Bladder wall}}$ ).

All patients received a total dose of 36 Gy in six fractions, every other day, with Cyberknife® (Accuray). The main dosimetric objective for the target volume was that the PTV receiving 95% of the prescribed dose should be at least 95% ( $V_{95\%} \geq 95\%$ ). The dose-volume histogram (DVH) for the OARs had to respect the DVCs used in the GETUG-31 trial, as presented in Table 1. DVCs were:  $V_{12\text{Gy}} < 20\%$  and  $V_{27\text{Gy}} < 2$  cc for the rectal wall,  $V_{12\text{Gy}} < 15\%$  and  $V_{27\text{Gy}} < 5$  cc for the bladder wall, and  $D_{\text{max}} (35 \text{ mm}^3) < 39$  Gy and  $V_{24\text{Gy}} < 30\%$  for the urethra. In case of dosimetric conflict between the PTV coverage and sparing of the OARs, the radiation oncologist had to compromise, depending on the clinical context and its own experience. The new conformity index (nCI), gradient index (GI), and homogeneity index (HI) have been reported [46–48].

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Cyberknife®(Accuray) treatment plans were optimized using stepwise multicriteria optimization in the Multiplan or Precision TPS (Accuray Incorporated, Sunnyvale, CA, USA, v.1.1.1.1, until January 2020, then v.2.0.1.1). Daily intrafraction IGRT was performed based on the fiducials detected by perpendicular kV/MV imaging. To monitor and track the position of the target during treatment delivery, images were acquired for every three beams with a pre-specified accuracy of less than 1 mm. The InTempo™ Adaptive Imaging System was used, permitting tracking of intra-fraction prostate motion and adapting imaging and treatment delivery, based on how much and how fast the prostate moves.

### ***Endpoints and statistical analysis***

The reported of dosimetric parameters for the target volumes (GTV, CTV, and PTV), OARs (rectum, bladder, femoral heads, sigmoid, small bowel penile bulb, and urethra), and PTV-OARs overlapping volumes are listed in Table 2. The percentage of patients who did not respect the DVCs was quantified for each volume of interest (VOI). The Spearman correlation coefficient ( $\rho$ ) was calculated

to determine the correlations between the recommended dose-volume parameters (for the target and the OARs) and the volumes of the structures (target, OARs, and overlapping structures) or the distance between the PTV and OARs (considering their barycenter). A value of  $p < 0.05$  was considered statistically significant. Only significant correlations with  $\geq 0.2$  (in absolute value) rho were reported. After measuring the strength of the relationship between variables, a linear regression was performed using Pearson's correlation analysis ( $r^2$ ) to measure the statistical relationship between the variables of interest, and information about the magnitude of the correlation was added. We finally proposed DVCs for the OARs, allowing to respect the DVCs in at least 84% of cases.

## Results

The median PTV 36 Gy isodose prescription was 80 % (range: 69–90%).

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### *Dosimetric data and respect of DVCs*

The results of all dosimetric parameters for each VOI are detailed in Table 2 and illustrated by the DVHs in Figure 1. Considering the GETUG-31 DVCs, the mean (range) values were 93% (50–100%) for the PTV  $V_{95\%}$ , 21% (0–90%) and 1.4 cc (0–9 cc) for the rectum wall  $V_{12Gy}$  and  $V_{27Gy}$  respectively, and 17.6% (0–67%) and 4 cc (0–33 cc) for the bladder wall  $V_{12Gy}$  and  $V_{27Gy}$ , respectively.

The percentage of patients respecting all DVCs defined in GETUG-31 trial, was 19%. These patients had a mean PTV of 18.5 cc (range, 3–48 cc), although the mean PTV was 40.5 cc (range, 3–174 cc) in the whole population. These patients had a mean CTV/prostate volume ratio of 0.38 (range, 0.03–1), although the mean ratio was 0.69 (range, 0.03–1.1) in the whole population. At least 98% of the patients with a CTV/prostate ratio more than 0.5 could not respect the DVCs in the OARs.



Table 3 details the percentage of patients not respecting the DVCs, by constraints, in the different VOI and considering the CTV/prostate ratio. This percentage was 52% for the PTV and ranged from 11% to 64%, depending on the OARs.

### *Correlation between dosimetric parameters and anatomical structures*

Table 4.1 shows the correlation between the target volume (PTV and CTV) dose coverage and various VOI (in cc). The target coverage decreased significantly with an increase in the values of the PTV, CTV, CTV/prostate ratio,  $V_{\text{Overlap PTV/Bladder wall}}$ , and  $V_{\text{Overlap PTV/Rectal wall}}$ . Figure 2.1. shows the correlation between the PTV coverage ( $V_{95\%}$ ) and PTV (cc) using a linear regression model. A threshold value of PTV of less than 20 cc allowed respect for the PTV coverage recommendation ( $V_{95\%} \geq 95\%$ ) in all cases. The impact of the PTV on PTV coverage is illustrated in Figure 3 using two examples. In one case, focal re-irradiation was delivered within a PTV of 11 cc, corresponding to a CTV/prostate ratio of 0.15. In the other case, whole gland re-irradiation was delivered within a PTV of 38.6 cc, corresponding to a CTV/prostate ratio of 1. PTV coverages were consequently up to 99% and 81%, respectively. Bladder  $V_{12\text{Gy}}$  was negligible ( $<1\%$ ) in the first case and 20% in the second case.

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The PTV to bladder or rectum distances were not significantly associated to PTV coverage.

Table 4.2 shows the correlation between OARs (bladder and rectal wall) dose sparing and various VOI (in cc). The OARs sparing decreased significantly with an increase in the values of PTV, CTV,  $V_{\text{Overlap PTV/Bladder wall}}$ , and  $V_{\text{Overlap PTV/Rectal wall}}$ . Figure 2.2 shows the correlation between the OARs sparing and PTV (cc) using a linear regression model. The coefficients  $r^2 = 0.46$  for the bladder and  $r^2 = 0.29$  for the rectum ( $p < 0.01$ ) mean that these parameters explained 46% and 29% of the correlations, respectively. A threshold value of PTV less than 40 and 180 cc allowed respect for the bladder and rectal wall  $V_{12\text{Gy}}$  constraints in all cases, respectively.

### *Proposal of new DVCs for the bladder and the rectum*

Because less than 20% of patients could respect the DVCs of the GETUG-31 protocol, we proposed new constraints allowing to be respected, at least in more than 84% of cases for the OARs. The new

constraints are listed in Table 5. To improve the respect of the DVCs in case of large target volume, we proposed the following new DVCs for the OARs:  $V_{12\text{Gy}} < 25\%$  and  $V_{27\text{Gy}} < 2\text{ cc}$  for rectum,  $V_{12\text{Gy}} < 25\%$  and  $V_{27\text{Gy}} < 5\text{ cc}$  for bladder.

## Discussion

In this study, we retrospectively analyzed the dosimetric data of 141 patients treated in two experimental centers using SBRT with Cyberknife® (Accuray) at a total dose of 36 Gy in six fractions for local prostate cancer recurrence after first radiation therapy. The goal was not to consider the clinical results of re-irradiation but to quantify the matter such that the GETUG-31 DVCs could be respected depending on the target volume and the OARs. The percentage of patients respecting all DVCs was only 19%, and these DVCs were clearly not adapted to large target volumes (CTV > half of the prostate or PTV > 40 cc) or in cases of a large overlap between the OARs and PTV. We therefore propose new DVCs for the largest local recurrences, that need to be clinically validated. To the best of our knowledge, this study is the first to report detailed dosimetric data in cases of SBRT for recurrent prostate cancer.

Several technical issues remain unresolved in salvage SBRT for intraprostatic relapse after prostate cancer RT. To standardize the practice, the European Society for Radiotherapy and Oncology Advisory Committee on Radiation Oncology Practice (ESTRO ACROP) recently investigated the opinions of 18 international experts on salvage SBRT for intraprostatic relapse using a Delphi consensus that focused on 40 questions [49]. A consensus agreement (>80%) was reached on the minimum time between primary RT and salvage treatment (set at two years) and on the fact that the primary treatment dose should be always considered when deciding the salvage SBRT dose. No consensus could be reached concerning the SBRT dose fractionation schedule and dosimetric constraints. For target volume, a divided opinion (agreement <65%) remained regarding whether a higher, lower, or same dose should be recommended for salvage SBRT compared to the primary treatment. An equivalent prescribed dose >35 Gy in five fractions (considering an  $\alpha/\beta$  of 1.5 Gy) associated with a prescription isodose <80% received major agreement (between 65 and 80%). For OARs, opinion was divided as to whether the

dose should be adjusted by considering the previous dose and time interval between primary and salvage treatment. Significant agreement was observed considering the recommended EQD2 ranges of 2 cc of the rectum (95–105 Gy), 2 cc of the bladder (95–105 Gy), and 2 cc of the penile bulb (no maximum). In a meta-analysis and systematic review by Corkum et al. [15] reporting the outcomes and toxicity in cases of re-irradiation using EBRT or SBRT for prostate cancer recurrence, meta-regression analysis found that increasing the EQD2 was associated with improved biochemical recurrence free survival (BRFS). Regarding dosimetric considerations, the study highlighted that dose constraints for both the CTV and OARs (bladder, rectum, femoral heads, and penile bulb) were still a matter of concern because no agreement was reached regarding a recommendable cumulative dose.

In our study, we used a schedule of 36 Gy in six fractions, which is one of the most used schedules in the literature and corresponds to four studies that included 23 to 100 patients [30,35,39,40]. The DVCs were heterogeneous between studies (Table 1) and similar to ours in two studies [30,35]. Our median PTV (36 cc) was within the range of the PTV reported in the literature (13–48 cc) [30,35,39,40]. The delivered mean dose in the PTV in our series was slightly higher (40 Gy) than that in others (30–37 Gy), except for one study reporting a median PTV volume of only 13 cc [40], and the dose received by the rectum was relatively similar between all studies, including ours. The bladder doses between studies were relatively similar, except for a small maximal dose in one study [35].

The main explanation for not respecting the DVCs in our series is related to the large target and overlapping volumes between the PTV and OARs (Tables 3, 4.1, and 4.2; Figures 2.1 and 2.2). The overlap between the PTV and rectum can be decreased using a rectal spacer. Using a spacer in prostate irradiation (79.2 Gy in 1.8-Gy fraction) has been shown in a phase III trial to dramatically decrease the dose to the rectum and consequently to slightly decrease the rectal grade  $\geq 1$  and grade  $\geq 2$  toxicities [50]. In a re-irradiation case, Scher et al. showed the benefit of rectal spacing in reducing the rectal dose without decreasing rectal toxicities in a subset of 23 patients [39]. Finally, rectal toxicity is relatively low in re-irradiation cases (grade  $\leq 2$  <5%) [41]. Table 3 and Figure 2.2 suggest that the most critical organ from a dosimetric point of view is the bladder. Clinical studies on re-irradiation show that the most frequent and limiting toxicity is urinary toxicity [15,41,51], which is related to both bladder and

urethra irradiation. The simplest way to decrease a bladder dose is to increase the bladder filling at the time of simulation and treatment. The issue of urethral sparing is particularly complex owing to its lack of visibility on MRI (without a urinary probe) [52,53] and the delicate geometrical balance between the urethral dose sparing and surrounding tumor treatment.

Minimizing the dose to OARs can be achieved by minimizing the CTV, and it raises the issue of the appropriate CTV definition for recurrent prostate cancers. In our bicentric cohort, a relatively large number of patients were treated in the whole prostate (38%), whereas all the patients in the GETUG-31 had a CTV/prostate of  $<0.5$ . Despite not meeting the inclusion criteria of GETUG-31, patients in our study may still be safely treated, acknowledging the trade-off between tumor coverage and OAR sparing. Patient selection and target volume (GTV/CTV/PTV) definition play crucial roles in the target volume. The literature does not show a clear consensus on the definition of intraprostatic recurrence of CTV. In a survey by the Italian Association of Radiotherapy and Clinical Oncology (AIRO), only 16% of radiation oncologists declared that they always preferred partial prostate re-irradiation, while almost two-thirds relied on clinical considerations in the choice of partial or whole gland irradiation [54]. In the ESTRO-ACROP Delphi Consensus, the experts' pool reached a consensus that the GTV identified on an mp-MRI with an "adaptive" margin should be considered as CTV [49]. Some studies have reported CTV expansion of up to 5 mm around the GTV partial prostate radiation, while PTV expansion ranges from 0 to 5 mm. Our GTV definition was based on the recurrent tumor visible on mpMRI and mostly 18F-chol-PET. PSMA-PET is more sensitive and specific than 18F-chol-PET to detect relapse in case of rising PSA after local treatment [55–57] and could be used to optimize the definition of the GTV. In a small series of 25 patients, the GTV was defined by the union volume of the tumor visible on MRI and 68Ga- PSMA-PET [40]. The CTV was defined as a 3 mm circumferential expansion around the GTV (not considering therefore biopsy results). These definitions lead to reduce dramatically the PTV to a median value of 13 cc (versus 36 cc in our series) and therefore the dose at OARs. However, the clinical impact of the target volume has been further investigated in the literature, and no significant difference has been found in terms of BRFS or toxicities between whole and partial prostate re-irradiation when focusing on studies utilizing only SBRT [15]. Only one recent study retrospectively

correlated DVCs to toxicities in a small series of 26 patients re-irradiated with a total dose range of 20–30 Gy in 2–5 fractions. A dose/volume effect was reported for late GU toxicity considering a bladder D25% [58]. Otherwise, cumulative re-irradiation constraints (calculated by converting the dose–volume limits into equivalent uniform dose (EQD2) using  $\alpha/\beta = 3$  Gy) appeared to be safe for  $D_{30\%} < 57.9$  Gy for the bladder and  $D_{30\%} < 66.0$  Gy,  $D_{60\%} < 38.0$  Gy, and  $V_{122.1\text{ Gy}} < 5\%$  for the rectum.

The choice of DVCs is likely to impact the local control and toxicity. In the GETUG-31 study comprising 100 patients with a median follow-up of 29 months, the BRFS rate at three years was relatively low (55%), although toxicity was remarkably moderate because no patient had a grade of acute GI toxicity of  $>1$ , and the rates of grades 2 and 3 acute GU toxicity were 8 and 1%, respectively [35]. The three-year grade GU and GI toxicities of  $\geq 2$  were 21 and 1%, respectively. Considering this good tolerance and the difficulty in respecting the DVCs in the vast majority of patients, as observed in our study, the question arises as to whether other doses of DVCs should be proposed. The main issue to test our proposed less-restrictive DVCs in OARs was to improve biochemical control by considering the risk of increasing toxicity. Our study showed that smaller target volumes ( $PTV < 40$  cc and/or  $CTV/\text{prostate ratio} \leq 0.5$ ) were easier to treat with respect to DVCs than larger target volumes. One practical option could be to calculate these parameters at the delineation step before initiating dosimetry, in view of re-irradiating only the small recurrences using the proposed DVCs as in the phase I/II GETUG-31 study where only patients with a small prostate cancer recurrence were selected ( $CTV/\text{prostate ratio} < 0.5$ ).

In daily practice, the  $CTV/\text{prostate ratio}$  is often much higher than 0.5, and the GETUG-31 DVCs cannot be respected. For these cases, several therapeutic options are possible. The first option is to propose salvage SBRT in a dosimetric compromise where OAR sparing is privileged and accepted for underdosing the tumor and exposing the patient to a higher risk of recurrence while limiting toxicities (chosen by the majority of physicians). The option proposed in this study is to use less restrictive DVCs for the OARs, presenting the advantage of increasing the dose to the tumor and the disadvantage of increasing potential toxicities. By slightly modifying only two DVCs (rectal wall DVCs modified from  $V_{12\text{Gy}} < 20\%$  to  $< 25\%$  and bladder wall DVCs from  $V_{12\text{Gy}} < 15\%$  to  $< 25\%$ ), the percentage of patients respecting the DVCs increased by 64%. Another promising approach to improve the respect

toward the DVCs is the use of MR-Linac. The better soft-tissue contrast provided by MRI and the advent of functional MR sequences may improve the definition of the prostate boundaries and OARs as well as the precise location of intraprostatic lesions and thus the accuracy and safety of ablative high-precision radiation treatments [59,60]. In a small series of 20 patients, a salvage MR-Linac-based SBRT was performed (30 Gy in 5 fr) with a GTV corresponding to the visible lesion on an mpMRI without any additional margins for the CTV, leading to a small PTV (median value of 14 cc, versus 36 cc in our study) [61]. Another strategy to improve the respect of DVCs may be the use of a simultaneous integrating high focal boost on the smaller intraprostatic lesion visible on MRI, while taking the prostate PTV to a lower dose. A recent FLAME phase III study on primary prostate cancer showed that a focal boost on a macroscopic visible tumor (up to 95 Gy in 2.7 Gy), compared with a 77 Gy in 2.2 Gy of an entire prostate without boost, increased biochemical bDFS without significant impact on toxicity and quality of life [62]. Moreover, this approach of focal dose escalation up to an equivalent of 90 Gy can be performed using proton radiation therapy, as shown in a series of 36 patients, without violating the OAR constraints and therefore suggesting a potential clinical benefit to improve tumor control while limiting toxicity [63]. This approach has however never been reported in case of re-irradiation.

Another option for large intraprostatic recurrences is to move toward other salvage treatments. A recent systematic review and meta-analysis of local salvage therapies after RT for prostate cancer (MASTER) compared the efficacy and toxicity of SRP, HIFU, cryotherapy, SBRT, low-dose-rate BT (LDR-BT), and high-dose-rate BT (HDR-BT) [16]. However, re-irradiation with SBRT or BT results in less severe GU toxicity than that of SRP with comparable oncologic results. The phase 2 RTOG-0526 trial included a series of 92 patients re-irradiated between 2007 and 2014 with LDR-BT ( $I^{125}$  for 92%) [64,65]. With a median follow-up of seven years, the occurrence of late grade 3 GU/GI adverse events was 14%, with no grade 4 events. Local and distant failures at 10 years were 5 and 19%, respectively. More recently, encouraging preliminary clinical results have been reported using MR-guided adaptive SBRT in a small series of patients [66–68]. This technique provided better tumor volume delineation and daily adaptation of the dosimetric plan to variations in anatomy and the possibility of continuous tracking by cine-MRI acquisitions.

The main limitation of our study was that only dosimetric data were analyzed without reporting clinical results. The goal of this study was to thoroughly investigate the issue of DVCs for a given salvage SBRT protocol, demonstrate the impossibility of respecting these DVCs for the majority of patients, explain the reason for this impossibility, and finally propose DVC alternatives. We did not report the toxicity outcome and were therefore unable to compare the toxicities in patients respecting the GETUG-31 nor our proposed DVCs. These new DVCs need to be clinically validated.

**Conclusion:** The DVCs of the GETUG-31 protocol proposing 36 Gy in six fractions as salvage SBRT for recurrent prostate cancer after the first irradiation can be respected only for small target volumes (CTV < half of the prostate) because of the small OAR–PTV overlap. With larger target volumes, by moderately modifying two DVCs (V12Gy of the rectum and bladder walls), the percentage of patients respecting the DVCs increased by more than 60%.

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**Ethics approval and consent to participate:** Institutional ethics approval was given the 26<sup>th</sup> may 2020 to perform this dosimetric analysis.

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**Table 1. Fractionation schedule and dose-volume constraints in case of prostate reirradiation in the literature**

All OAR constraints are given for the entire organ, except for \*, which considers the wall of the organ.

Fr: fractions;  $V_{x\% \geq y\%}$ : the volume (in %) of the considered VOI receiving x% of the prescribed dose should be more than y%. PI: prescription isodose; NR: not reported.

In bold: dose constraints used in the study, according to the GETUG-31 phase I/II trial.

**Table 2. Dosimetric values in our series in case of prostate reirradiation at a total dose of 36 Gy in six fractions**

$V_x$ : volume (in % or cc) of a considered VOI receiving  $x$  (in % or Gy) of dose;  $D_x$ : dose (in Gy) received in  $x\%$  of the considered volume; GTV<sup>#</sup>, defined on MRI  $\pm$  PET imaging; nCI, new conformity index; GI, gradient index; HI, homogeneity index.

All constraints are given for the entire organ, except for \*, which considers the organ wall.

In bold: dose constraints used in the study, according to the GETUG-31 phase I/II trial.

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**Table 3. Description of patients not respecting volume-dose constraints defined in the GETUG-31 trial, when prescribing a total dose of 36 Gy in 6 fractions**

DVCs: dose-volume constraints. Values are presented as mean  $\pm$  standard deviation (range).  $V_x$ : volume (in % or cc) of a considered VOI receiving x (in % or Gy) dose

**Table 4.1 Correlation between target volume coverage (dose) and volumes of interest (rho values)**

The Spearman correlation coefficient (rho) was calculated to determine the correlation between the recommended dose-volume parameters (for the target and OARs) and the volumes of the structures (target, OARs, and overlapping structures). Rho values are given only for significant p values ( $p < 0.05$ ) and when  $\geq 0.2$  analysis.

$V_x$ : volume (in % or cc) of the considered structure receiving x (in % or Gy) of dose; PTV: volumes (in cc) of PTV; CTV: volumes (in cc) of CTV;  $V_{\text{Overlap PTV/Bladder wall}}$ : volume (cc) of overlap between the PTV and the bladder wall;  $V_{\text{Overlap PTV/Rectal wall}}$ : volume (cc) of overlap between the PTV and the rectal wall

**Table 4.2 Correlation between organ at risk dose and volumes of interest (rho values)**

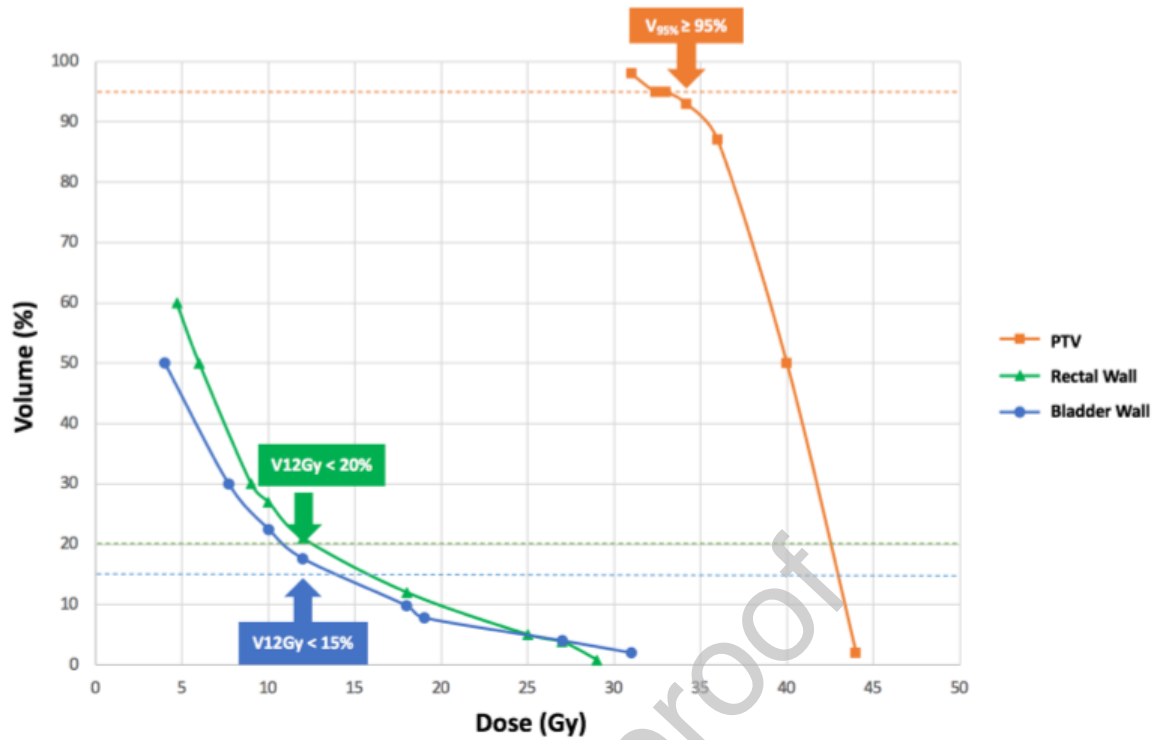
The Spearman correlation coefficient (rho) was calculated to determine the correlation between the recommended dose-volume parameters (for the target and OARs) and the volumes of the structures (target, OARs, and overlapping structures). Rho values are given only for significant p values ( $p < 0.05$ ) and when  $\geq 0.2$  analysis.

$V_x$ : volume (in % or cc) of the considered structure receiving x (in % or Gy) of dose; PTV: volumes (in cc) of PTV; CTV: volumes (in cc) of CTV;  $V_{\text{Overlap PTV/Bladder wall}}$ : volume (cc) of overlap between the PTV and the bladder wall;  $V_{\text{Overlap PTV/Rectal wall}}$ : volume (cc) of overlap between the PTV and the rectal wall

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**Table 5. New proposal for OARs dose-volume constraints**

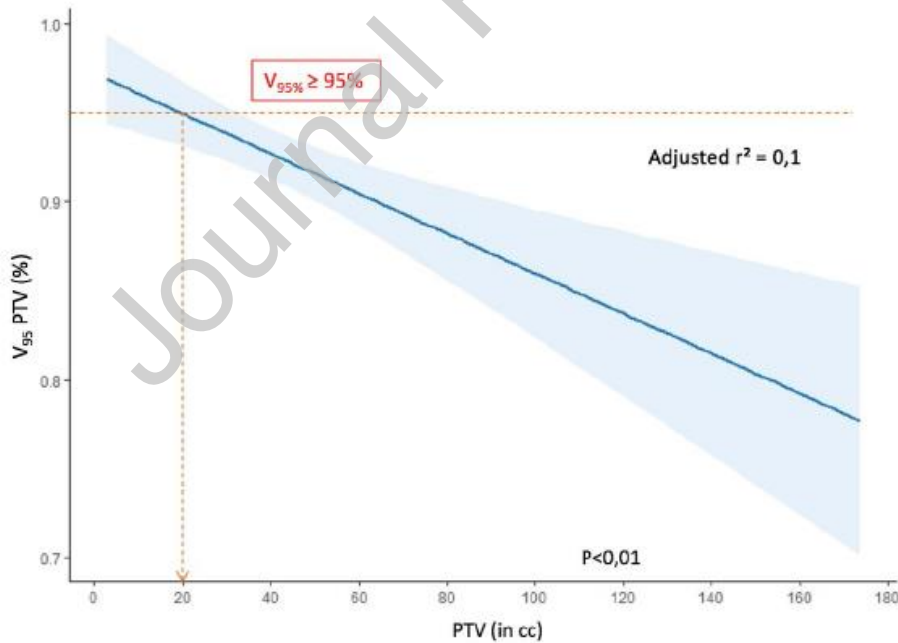
DVCs: dose-volume constraints.  $V_x$ : volume (in % or cc) of the considered structure receiving x (in % or Gy) dose.



**Fig 1. Dose-volume histogram for the PTV, bladder and rectum in our series when delivering 36 Gy in 6 fractions**

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$V_x$ : volume (in % or cc) of the considered structure receiving x (in % or Gy) dose.

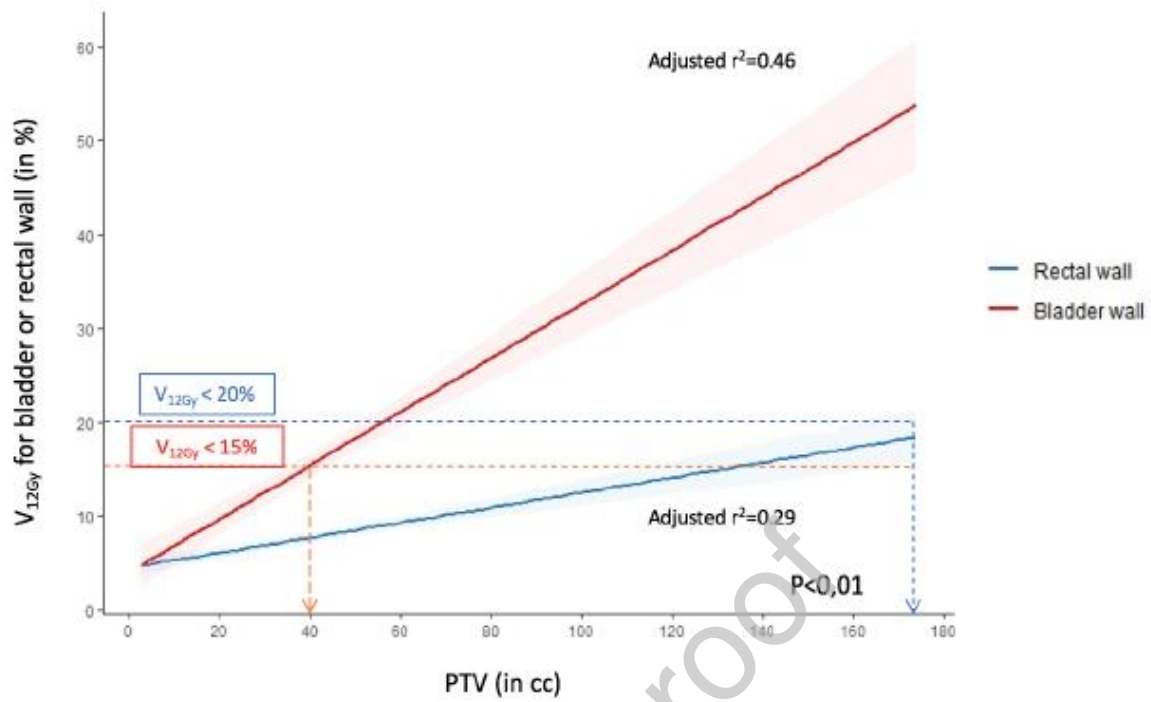


**Fig. 2.1. Correlation between PTV coverage ( $V_{95\%}$ ) and PTV (cc)**

The correlation method used the linear regression model with the Pearson's test.

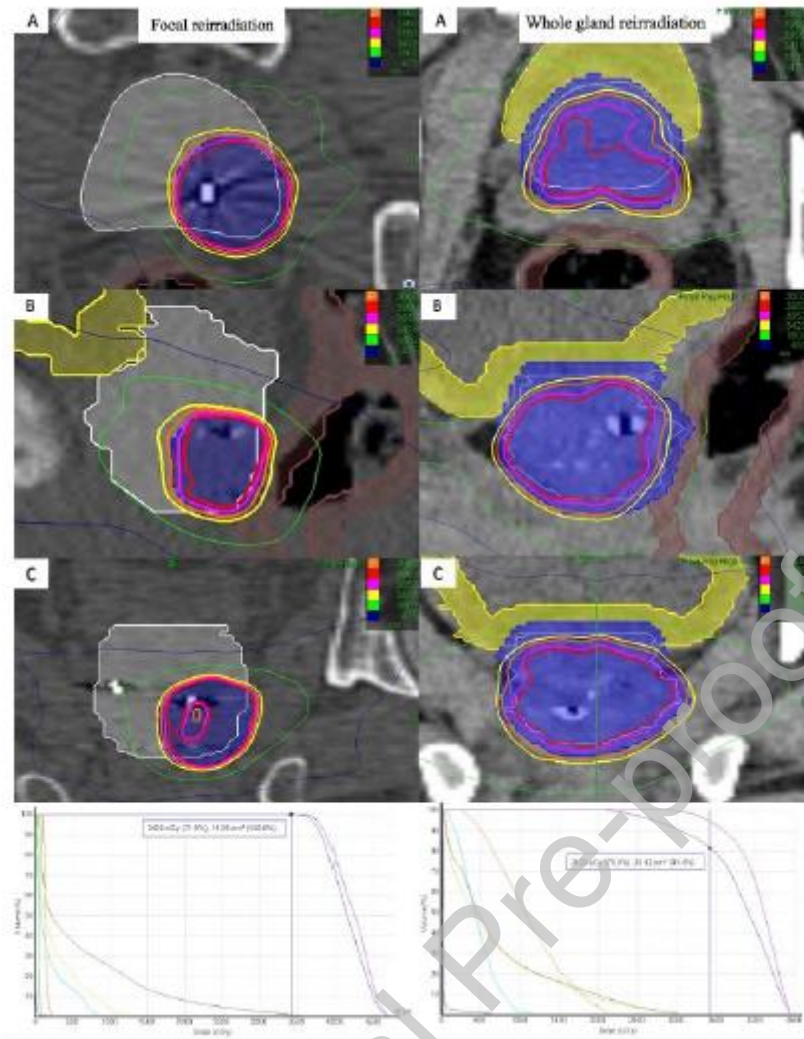
$V_x$ : volume (in % or cc) of the considered structure receiving x (in % or Gy) dose.





**Fig. 2.2. Correlation between OARs sparing ( $V_{12Gy}$ ) and PTV volume**

The correlation method used the linear regression model with the Pearson's test.  
 $V_x$ : volume (in % or cc) of the considered structure receiving x (in % or Gy) dose.



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**Fig. 3. Two examples of dose distribution of salvage SBRT with CyberKnife®(Accuray) depending on PTV volume**

In the 3D dose distribution figures (transversal (A), sagittal (B), and coronal (C) views), the PTV is blue, the rectal wall is brown, the bladder wall is yellow, and the prostate is white. In the DVH figures, the **Table 1. Fractionation schedule and dose-volume constraints in case of prostate reirradiation in the literature**

Total dose (Gy) / Number of fraction	Target volumes (PTV) and prescription isodose (PI)	Rectum	Bladder	Urethra	Others OARs
25 / 5 [28]	NR	D <sub>30%</sub> <13.8Gy D <sub>60%</sub> <6.69Gy	D <sub>max</sub> <120% D <sub>50%</sub> <10.58Gy	NR	NR
20-30 / 2-5 [58]	NR	D <sub>30%</sub> <13.5Gy D <sub>60%</sub> <6.7Gy V <sub>100%</sub> <5%	D <sub>30%</sub> <10.6Gy		
30 / 5 [27,32,34,36,61,66, 67]	V <sub>100%</sub> ≥ 95% V <sub>95%</sub> ≥ 95% PI: 80%	D <sub>max</sub> <100% or <35Gy or 40Gy D <sub>30%</sub> <13.8Gy or 13,5Gy D <sub>60%</sub> <6.69Gy V <sub>10Gy</sub> < 40%	D <sub>max</sub> <120% or <35Gy D <sub>50%</sub> <10.58Gy V <sub>10Gy</sub> < 25% or 20% V <sub>18Gy</sub> < 15% V <sub>12Gy</sub> < 15% V <sub>27Gy</sub> < 5cc D <sub>30%</sub> <10Gy	D <sub>max</sub> <120% or <35Gy V <sub>36Gy</sub> < 1 cc Urethra+3mm: D <sub>max</sub> (35 mm <sup>3</sup> ) < 39 Gy V <sub>24Gy</sub> < 30%	-Femoral heads: V <sub>24Gy</sub> <10% -Penile bulb: V <sub>24Gy</sub> <50% -Small bowel: V <sub>1cc</sub> <21 Gy V <sub>18Gy</sub> <5cc

		V <sub>18Gy</sub> < 20% or ≤35% V <sub>28Gy</sub> ≤10% V <sub>12Gy</sub> < 20% V <sub>27Gy</sub> < 2cc			
34 / 5 [37,38]	V <sub>100%</sub> ≥ 95% D <sub>max</sub> > 150% V <sub>125%</sub> : 50-60% V <sub>150%</sub> : 15-25% V <sub>200%</sub> : 0-2%  PI: 50-60 %	D <sub>max</sub> < 100%*	D <sub>max</sub> < 100%*	D <sub>max</sub> < 120% D <sub>50%</sub> < 105%	NR
35 / 5 [31,69]	V <sub>95%</sub> ≥ 99%	D <sub>max</sub> < 38 Gy V <sub>10Gy</sub> < 40% V <sub>18Gy</sub> < 20% V <sub>25Gy</sub> < 20cc V <sub>26Gy</sub> < 10%	D <sub>max</sub> < 38 Gy* V <sub>10Gy</sub> < 25% V <sub>18Gy</sub> < 15% V <sub>18.3Gy</sub> < 15cc* V <sub>26Gy</sub> < 10%	NR	-Femorals heads : V <sub>10Gy</sub> < 1% -Penile bulb: V <sub>10Gy</sub> < 5%
36 / 6 [30,35,39,40,45]	PI: 80-100%  V <sub>95%</sub> ≥ 95%  D <sub>95%</sub> ≤ 100% D <sub>0.1mL</sub> ≤ 115%	V <sub>12Gy</sub> < 20% ± * V <sub>27Gy</sub> < 2cc ± *  V <sub>27Gy</sub> < 20 cc D <sub>max</sub> = 40.5Gy  D <sub>0.1mL</sub> ≤ 33Gy D <sub>0.5mL</sub> ≤ 28Gy D <sub>1mL</sub> ≤ 24Gy D <sub>2mL</sub> ≤ 18Gy	V <sub>12Gy</sub> < 15% ± * V <sub>27Gy</sub> < 5cc ± *  V <sub>19Gy</sub> < 15cc V <sub>40Gy</sub> < 5cc  D <sub>0.1mL</sub> ≤ 33 Gy D <sub>0.5mL</sub> ≤ 28Gy D <sub>1mL</sub> ≤ 24Gy D <sub>2mL</sub> ≤ 18Gy	V <sub>36Gy</sub> < 1 cc <b>Urethra+3mm:</b> D <sub>max</sub> (35 mm3) < 39 <b>Gy</b> V <sub>24Gy</sub> < 30%  D <sub>max</sub> < 33 Gy	NR
36.2 / 5 [33]	NR	NR	NR	NR	Downloaded for Anonymous User (n/a) at R4L.Afghanistan For personal use only. No other uses without permission.
36.25 / 5 [29]	V <sub>100%</sub> ≥ 95%  PI: 80%	V <sub>18.1Gy</sub> < 50% V <sub>29Gy</sub> < 20% V <sub>36Gy</sub> < 1cc	V <sub>18.1Gy</sub> < 40% V <sub>37Gy</sub> < 10cc	NR	Femoral heads: V <sub>14.5Gy</sub> < 5%
36 / 6 then 38 / 6 [40]	D <sub>95%</sub> ≤ 100% D <sub>0.1mL</sub> ≤ 115%  PI: 100%	D <sub>0.1mL</sub> ≤ 33Gy D <sub>0.5mL</sub> ≤ 28Gy D <sub>1mL</sub> ≤ 24Gy D <sub>2mL</sub> ≤ 18Gy	D <sub>0.1mL</sub> ≤ 33Gy D <sub>0.5mL</sub> ≤ 28Gy D <sub>1mL</sub> ≤ 24Gy D <sub>2mL</sub> ≤ 18Gy	D <sub>max</sub> < 33Gy  Urethra + PRV: D <sub>max</sub> < 36Gy	

All OAR constraints are given for the entire organ, except for \*, which considers the wall of the organ. Fr: fractions; V<sub>x%</sub> ≥ y%: the volume (in %) of the considered VOI receiving x% of the prescribed dose should be more than y%. PI: prescription isodose; NR: not reported. In bold: dose constraints used in the study, according to the GETUG-31 phase I/II trial.

**Table 2. Dosimetric values in our series in case of prostate reirradiation at a total dose of 36 Gy in six fractions**

Volumes of interest		Dosimetric Index (unit)	Values		
			Mean	SD	Range
Target Volume	GTV#	Volume (cc)	23	18	0.2 - 94
		V <sub>100%</sub> (%)	95.3	8.5	50 - 100
	CTV	Volume (cc)	26	18	0.7 - 94
		V <sub>100%</sub> (%)	94.7	9.4	38 - 100
	PTV	Volume (cc)	40.5	25	3 - 174
		V <sub>100%</sub> (%)	87	11	37 - 99.8
		V <sub>95%</sub> (%)	<b>93</b>	<b>11</b>	<b>50 - 100</b>
		V <sub>90%</sub> (%)	95	7	60 - 100
	D <sub>98%</sub> (Gy)	31	5	8 - 37	

		<b>D<sub>95%</sub> (Gy)</b>	<b>33</b>	<b>4</b>	<b>12 - 37</b>
		D <sub>50%</sub> (Gy)	40	1.8	33 - 46
		D <sub>2%</sub> (Gy)	44	2	39 - 51
		D <sub>Mean</sub> (Gy)	40	2	31 - 47
		nCI	1.34	0.3	1 - 3.4
		GI	4.4	1	0.4 - 11
		HI	1.26	0.1	1.1 - 1.5
	Prostate	Volume (cc)	38	16	11 - 94
	Ratio: CTV/prostate volume	Ratio	0.7	0.3	0.03 - 1.1
OARs	Rectum whole organ/wall*	Volume (cc)	59 / 38*	24 / 12*	9 - 143 / 9 - 85*
		D <sub>max</sub> (0.03cc) (Gy)	31 / 31*	5 / 5*	5 - 41 / 5 - 41*
		D <sub>max</sub> (2%) (Gy)	29 / 29*	6 / 6*	5 - 37 / 6 - 41*
		D <sub>Mean</sub> (Gy)	7.8 / 8*	2.6 / 2.7*	0.6 - 21 / 0.6 - 21*
		D <sub>30%</sub> (Gy)	8.9 / 9*	3 / 3*	1.7 - 25 / 1.8 - 25*
		D <sub>50%</sub> (Gy)	6 / 6*	2.8 / 2.7*	0.2 - 21 / 0.2 - 20*
		D <sub>60%</sub> (Gy)	5 / 4.7*	2.5 / 2.5*	0 - 19 / 0.1 - 18*
		V <sub>10Gy</sub> (%)	26 / 27*	13 / 13*	0 - 97 / 0 - 97*
		<b>V<sub>12Gy</sub> (%)</b>	<b>19 / 21*</b>	<b>11.5 / 11*</b>	<b>0 - 91 / 0 - 90*</b>
		V <sub>18Gy</sub> (%)	9.7 / 12*	9 / 7*	0 - 65 / 0 - 62*
		V <sub>25Gy</sub> (%)	3.8 / 5*	4 / 4.5*	0 - 31 / 0 - 32*
		<b>V<sub>27Gy</sub> (cc)</b>	<b>1.4 / 1.4*</b>	<b>1.6 / 1.3*</b>	<b>0 - 15 / 0 - 9*</b>
		V <sub>27Gy</sub> (%)	2.7 / 3.8*	3.4 / 3.8*	0 - 25 / 0 - 24*
		V <sub>29Gy</sub> (%)	0.9 / 0.8*	1.2 / 0.9*	0 - 7 / 0 - 7*
		V <sub>36Gy</sub> (cc)	0.1 / 0.1*	0.2 / 0.2*	0 - 3.4 / 0 - 2.2*
		D <sub>20cc</sub> (Gy)	7.6 / 5*	3.5 / 2.5*	0 - 24 / 0 - 15*
		Bladder Whole organ/wall*	Volume (cc)	160 / 85*	92 / 34*
	D <sub>max</sub> (0.03cc) (Gy)		32.2 / 33*	8.7 / 8*	0.17 - 44 / 0 - 44*
	D <sub>max</sub> (2%) (Gy)		29 / 31*	8 / 8*	0.5 - 43 / 0.5 - 43*
	D <sub>Mean</sub> (Gy)		6 / 6.8*	2.7 / 2.6*	0 - 19 / 0 - 19*
	D <sub>30%</sub> (Gy)		6.9 / 7.7*	3.3 / 3.4*	0 - 27 / 0 - 29*
	D <sub>50%</sub> (Gy)		4.2 / 4*	3.2 / 2.8*	0 - 24 / 0 - 18*
	V <sub>10Gy</sub> (%)		19 / 22.5*	12 / 11*	0 - 79 / 0 - 73*
	<b>V<sub>12Gy</sub> (%)</b>		<b>14 / 17.6*</b>	<b>9 / 9*</b>	<b>0 - 71 / 0 - 67*</b>
	V <sub>18Gy</sub> (%)		6.8 / 9.8*	5.5 / 6*	0 - 47 / 0 - 45*
	V <sub>19Gy</sub> (%)		6.2 / 7.8*	5 / 6.6*	0 - 44 / 0 - 41*
	<b>V<sub>27Gy</sub> (cc)</b>		<b>4 / 4*</b>	<b>5.7 / 4*</b>	<b>0 - 51 / 0 - 33*</b>
	V <sub>27Gy</sub> (%)		2.5 / 4*	3 / 4*	0 - 29 / 0 - 33*
	V <sub>36Gy</sub> (cc)		0.5 / 0.7*	0.9 / 2.5*	0 - 8 / 0 - 8*
	V <sub>37Gy</sub> (cc)	0.3 / 0.4*	0.7 / 0.7*	0 - 6 / 0 - 5.7*	
	V <sub>40Gy</sub> (cc)	0.1 / 0.1*	0.1 / 0.1*	0 - 0.6 / 0 - 0.6*	
	D <sub>15 cc</sub> (Gy)	14 / 12*	6 / 6*	0.9 - 35 / 0.1 - 34*	
	Femorals Heads	D <sub>Mean</sub> (Gy)	4	1.8	0.6 - 9
		D <sub>max</sub> (2%) (Gy)	12	3	1.8 - 22
		D <sub>5%</sub> (Gy)	9.6	3	1.3 - 17
	Sigmoide	D <sub>1cc</sub> (Gy)	2.7	2.6	0.1 - 14
		D <sub>5cc</sub> (Gy)	1.6	1.8	0.1 - 10
	Small Bowel	D <sub>1cc</sub> (Gy)	5.4	3.8	0.04 - 16
		D <sub>5cc</sub> (Gy)	3.9	3	0.03 - 12
	Bulbe	D <sub>Mean</sub> (Gy)	9	8	0.2 - 34.7
D <sub>max</sub> (2%) (Gy)		15	11	0.2 - 40	
V <sub>24Gy</sub> (%)		8	22	0 - 100	
V <sub>29.5Gy</sub> (%)		2.6	9	0 - 59	
Urethra	D <sub>max</sub> (0.03cc) (Gy)	32	10	6 - 43	

		$D_{\text{Mean}}$ (Gy)	21	12	1.3 - 38
		$V_{24\text{Gy}}$ (%)	46	38	0 - 100
		$V_{36\text{Gy}}$ (cc)	1	2	0 - 9
Overlaps	PTV/Rectal wall	Volume (cc)	0.51	0.8	0 - 7.2
	PTV/Bladder wall	Volume (cc)	1.4	3.3	0 - 35

$V_x$ : volume (in % or cc) of a considered VOI receiving  $x$  (in % or Gy) of dose;  $D_x$ : dose (in Gy) received in  $x\%$  of the considered volume; GTV<sup>#</sup>, defined on MRI ± PET imaging; nCI, new conformity index; GI, gradient index; HI, homogeneity index.

All constraints are given for the entire organ, except for \*, which considers the organ wall.

In bold: dose constraints used in the study, according to the GETUG-31 phase I/II trial.

**Table 3.** Description of patients not respecting volume-dose constraints defined in the GETUG-31 trial, when prescribing a total dose of 36 Gy in 6 fractions

Volumes of interest		GETUG-31 DVC	Patients not respecting the DVC		
			% of patients	Parameters values	% of patients with CTV/ prostate ratio >0.5
<b>Target Volume</b>	<b>PTV</b>	$V_{95\%} \geq 95\%$	52%	$V_{95} = 87\% \pm 9$ (50-94.9)	53%
<b>OARs</b>	<b>Rectum wall</b>	$V_{12Gy} < 20\%$	53%	$V_{12Gy} = 29\% \pm 16$ (20.1-91)	89%
		$V_{27Gy} < 2$ cc	13%	$V_{27Gy} = 3.6cc \pm 2.4$ (2.1-9)	98%
	<b>Bladder wall</b>	$V_{12Gy} < 15\%$	64%	$V_{12Gy} = 22\% \pm 8$ (15.1-67)	73%
		$V_{27Gy} < 5$ cc	16%	$V_{27Gy} = 11cc \pm 7$ (5.2-31)	96%
	<b>Urethra + 3mm</b>	$D_{max} (35 \text{ mm}^3) < 39$ Gy	11%	$D_{max} (35 \text{ mm}^3) = 42Gy \pm 1.4$ (40-43)	98%
		$V_{24Gy} < 30\%$	42%	$V_{24Gy} = 84\% \pm$ (44-100)	98%

DVC: dose-volume constraint. Values are presented as mean  $\pm$  standard deviation (range).  $V_x$ : volume (in % or cc) of a considered VOI receiving x (in % or Gy) dose

**Table 4.1 Correlation between target volume coverage (dose) and volumes of interest (rho values)**

	V <sub>95</sub> PTV (%)	V <sub>100</sub> PTV (%)	V <sub>100</sub> CTV (%)
PTV (cc)	-0.47	-0.50	-0.54
CTV (cc)	-0.46	-0.49	-0.56
CTV/Prostate (ratio volume)	-0.44	-0.48	-0.52
V <sub>Overlap</sub> PTV/Bladder wall (cc)	-0.47	-0.44	-0.40
V <sub>Overlap</sub> PTV/Rectal wall (cc)	-0.40	-0.32	-0.26

The Spearman correlation coefficient (rho) was calculated to determine the correlation between the recommended dose-volume parameters (for the target and OARs) and the volumes of the structures (target, OAR, and overlapping structures). Rho values are given only for significant p values ( $p < 0.05$ ) and when  $\geq 0.2$  analysis.

V<sub>x</sub>: volume (in % or cc) of the considered structure receiving x (in % or Gy) of dose; PTV: volumes (in cc) of PTV; CTV: volumes (in cc) of CTV; V<sub>Overlap PTV/Bladder wall</sub>: volume (cc) of overlap between the PTV and the bladder wall; V<sub>Overlap PTV/Rectal wall</sub>: volume (cc) of overlap between the PTV and the rectal wall

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**Table 4.2 Correlation between organ at risk dose and volumes of interest (rho values)**

	Bladder wall		Rectal wall	
	V <sub>12Gy</sub> (%)	V <sub>27Gy</sub> (cc)	V <sub>12Gy</sub> (%)	V <sub>27Gy</sub> (cc)
PTV (cc)	0.64	0.49	0.71	0.23
CTV (cc)	0.64	0.44	0.70	0.20
V <sub>Overlap</sub> PTV/Bladder wall (cc)	0.49	0.52	0.45	0.20
V <sub>Overlap</sub> PTV/Rectal wall (cc)	0.20	0.21	0.32	0.38

The Spearman correlation coefficient (rho) was calculated to determine the correlation between the recommended dose-volume parameters (for the target and OARs) and the volumes of the structures (target, OAR, and overlapping structures). Rho values are given only for significant p values ( $p < 0.05$ ) and when  $\geq 0.2$  analysis.

V<sub>x</sub>: volume (in % or cc) of the considered structure receiving x (in % or Gy) of dose; PTV: volumes (in cc) of PTV; CTV: volumes (in cc) of CTV; V<sub>Overlap PTV/Bladder wall</sub>: volume (cc) of overlap between the PTV and the bladder wall; V<sub>Overlap PTV/Rectal wall</sub>: volume (cc) of overlap between the PTV and the rectal wall

**Table 5. New proposal for OARs dose-volume constraints**

Volumes of interest		GETUG-31 DVC	Proposed DVC	% of pts not respecting DVC
OARs	Rectal wall	$V_{12Gy} < 20\%$	-	53%
		-	$V_{12Gy} < 25\%$	12%
		$V_{27Gy} < 2 \text{ cc}$	$V_{27Gy} < 2 \text{ cc}$	13%
	Bladder wall	$V_{12Gy} < 15\%$	-	64%
		-	$V_{12Gy} < 25\%$	10%
		$V_{27Gy} < 5 \text{ cc}$	$V_{27Gy} < 5 \text{ cc}$	16%

DVCs: dose-volume constraint.  $V_x$ : volume (in % or cc) of the considered structure receiving x (in % or Gy) dose.

CTV was pink, PTV was blue, rectal wall was brown, bladder wall was yellow, penile bulb was orange, femoral heads were cyan, sigmoid was green, and small bowel was purple.

Left, focal reirradiation for isolated left lateral prostate relapse. The CTV corresponded to the GTV, with an isotropic additional margin of 2 mm. The CTV/prostate volume ratios were 0.15. PTV was defined as the CTV with a margin of 2 mm. The PTV  $V_{95\%}$  was 99%, and all the dose-volume constraints were considered.



On the right, whole-gland reirradiation was delineated as the CTV. The CTV/prostate volume ratios were 1. The isotropic margin of the PTV was 2 mm. The PTV V95% was 81%, limited by the constraints on the bladder, with V12Gy equal to 20%.

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