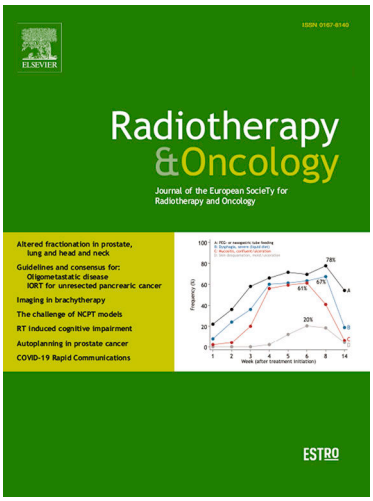

Original Article

Oligorecurrent nodal prostate cancer: radiotherapy quality assurance of the randomized PEACE V-STORM phase II trial

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Oligorecurrent nodal prostate cancer: radiotherapy quality assurance of the randomized PEACE V-STORM phase II trial

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Oligorecurrent nodal prostate cancer: radiotherapy quality assurance of the randomized PEACE V-STORM phase II trial

Abstract

Purpose: Aim of this study is to report the results of the radiotherapy quality assurance program of the PEACE V-STORM randomized phase II trial for pelvic nodal oligorecurrent prostate cancer (PCa).

Material and methods: A benchmark case (BC) consisting of a postoperative case with 2 nodal recurrences was used for both stereotactic body radiotherapy (SBRT, 30 Gy/3 fx) and whole pelvic radiotherapy (WPRT, 45 Gy/25 fx + SIB boost to 65 Gy).

Results: BC of 24 centers were analyzed. The overall grading for delineation variation of the 1st BC was rated as 'UV' (Unacceptable Variation) or 'AV' (Acceptable Variation) for 1 and 7 centers for SBRT (33%), and 3 and 8 centers for WPRT (46%), respectively. An inadequate upper limit of the WPRT CTV (n=2), a missing delineation of the prostate bed (n=1), and a missing nodal target volume (n=1 for SBRT and WPRT) constituted the observed 'UV'. With the 2nd BC (n=11), the overall delineation review showed 2 and 8 'AV' for SBRT and WPRT, respectively, with no 'UV'. For the plan review of the 2nd BC, all treatment plans were per protocol for WPRT. SBRT plans showed variability in dose normalization (Median $D_{90\%}$ = 30.1 Gy, range 22.9-33.2Gy and 30.6 Gy, range 26.8-34.2Gy for nodes 1 and 2 respectively).

Conclusions: Up to 46% of protocol deviations were observed in delineation of WPRT for nodal oligorecurrent PCa, while dosimetric results of SBRT showed the greatest disparities between centers. Repeated BC resulted in an improved adherence to the protocol, translating in an overall acceptable contouring and planning compliance rate among participating centers.

Introduction

Nodal oligorecurrent prostate cancer (PCa) is an emerging disease status generated by the widespread use of molecular imaging to restage biochemical relapse after curative treatment [1-5]. Systemic therapy with androgen deprivation therapy (ADT) remains the standard treatment of these patients [6]. Due to the limited metastatic burden and a good long-term survival [7, 8], metastasis directed therapies (MDT) have been proposed as a therapeutic alternative to improve progression-free survival or postpone use of systemic therapies [9-11]. The optimal MDT strategy remains presently unknown for these patients [1, 11]. In an attempt to provide some answers, the multicenter, randomized phase 2 PEACE V-STORM trial (NCT03569241) opened in 2018 [12]. The aim of this study is to evaluate the potential benefit in terms of metastasis-free survival, of the addition of whole pelvis elective nodal irradiation (WPRT) to MDT (salvage lymph node dissection, sLND or stereotactic body radiotherapy, SBRT) and short-term ADT in patients with oligorecurrent nodal PCa.

Radiotherapy Quality Assurance (RTQA) programs are considered integrative part of clinical trials [12-14]. They can ensure and improve the reliability and robustness of study results, limiting the variability frequently observed among the participating centers of a clinical study (see e.g. [15, 16]). In an effort to improve the quality of our trial for a treatment poorly standardized as the salvage radiotherapy of nodal oligorecurrent PCa, the PEACE-V-STORM trial integrated a dedicated RTQA program, including a study-specific questionnaire (SSQ) and a mandatory benchmark case (BC) [17].

Aim of the present study is to report the results of the RTQA of the PEACE V-STORM randomized phase II trial for pelvic nodal oligorecurrent PCa.

Materials and Methods

Trial

In the PEACE V-STORM trial, oligorecurrent prostate cancer patients with 5 or less pelvic positive lymph node detected by positron emission tomography (PET) imaging were randomized 1:1 to MDT (sLND or SBRT) alone (arm A) or to MDT with WPRT (arm B), both arms combined with 6 months of ADT [12]. Twenty-four centers in Belgium (7, 29%), Norway (1, 4%), Italy (2, 8%), Spain (7, 29%), Australia (1, 4%), and Switzerland (6, 25%) completed the quality assurance (QA) part of the trial (ClinicalTrials.gov NCT03569241). The trial was open in June 2018 and closed in May 2021 with 196 patients who have been included [18].

Radiotherapy procedures have been extensively detailed in the study protocol [12]. In arm A, SBRT was delivered to the node with a 3-mm PTV margin to a dose of 30 Gy in 3 fractions 3 times a week (80% of the max dose (= 30 Gy), covering at least 90% of the PTV_SBRT). Use of a planning risk volume (PRV) of 5 mm was mandatory for organs at risk (OAR), with dose constraints based on the AAPM task group 101 report - 3 fraction schedule [19] applied to these PRV.

For arm B, the CTV_LNN consisted out of the pelvic lymph node regions as described in the RTOG guidelines [20], with the exception that delineation of the common iliac should start at the L4/L5 interspace [21]. The dose prescribed to the PTV_LNN was 45 Gy in 25 daily fractions of 1.8 Gy, while the nodes with a 5 mm margin received an integrated boost to a median dose of 65 Gy in 25 fractions, 2.6 Gy per fraction.

For both arms, the prostate bed clinical target volume (CTV_PB) was defined by any of the published consensus guidelines such as EORTC [22], RTOG [23], or ANZUP [24]. Prescribed dose to the prostate bed (PB) planning target volume (PTV_PB) was 66 Gy in 33 fractions (for arm B, treated at the same time as the WPRT with 50 Gy in 25 fractions followed by a sequential boost of 16 Gy in 6 fractions).

Dose constraints to the OAR contoured as per RTOG guidelines were following the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) group recommendations [25-27]. Bladder wall (BW) and rectal wall (RW) were defined by the external wall (5-mm thickness) of the bladder and the rectum respectively. The dose specification criteria for the target volumes and the OAR for both arms are given in Table 1.

QA procedures

Anonymized DICOM images of the CT and PET-CT scan together with a description of the clinical case of an eligible patient were sent to the participating centers. The BC consisted of PCa patient previously treated with radical robot-assisted laparoscopic prostatectomy and bilateral pelvic lymphadenectomy (prostate adenocarcinoma, Gleason 4+3, pT3b pN0 (0/6) R1) and relapsing with two pelvic lymph nodes (one right external iliac lymph node, node 1 and a right obturator lymph node, node 2) positive on choline PET/CT. Node 1 was located very close to a bowel loop (~ 6 mm), while the node 2, located posteriorly, was in proximity to the sigmoid (~ 10 mm) (Figure 1a) .

The centers had to delineate the volumes of interest and to perform treatment planning for each arm according to the trial protocol described above and including the PB. Then they had to submit electronically their DICOM-RT structures, RT-dose and RT-plan files as well as the trial dedicated SSQ. These data were centrally archived for subsequent analyses. The QA was conducted independently by two experienced radiation oncologists (TZ and VA) with the assistance of three medical physicists (NK, MJ, GD). The Eclipse™ (Varian Medical System, Palo Alto, US) software was used for reviewing. According to the Global Harmonization Group Guidelines [17], structures were considered an unacceptable variation (UV) if there was any contouring variation which did not correspond to what is stated in the protocol and influences the clinical outcome. The overall grade for target OAR delineations was considered an acceptable variation (AV) if there were any variations from the protocol definition with no influence on the clinical outcome. AV were communicated to the centers which were activated for patient inclusion. In case of UV in delineation and/or dosimetry, centers were asked to submit a new BC version with the needed changes. Descriptive statistics and plots were generated using the PowerBI software (Microsoft).

Results

As regards the delineation unacceptable variations in the first submitted version of the BC (BC1), the overall grading for delineation review was rated as 'UV' for 1 center for arm A and for 3 centers for arm B, respectively (see Figure 2). PB and external iliac lymph node contours were missing for 1 center, which constituted an UV for both arms. The cranial limit of the CTV_LNN located at the L5-S1 interspace instead of L4-L5 as per protocol constituted an UV for two other centers for arm B. In the second BC (BC2) (required for 11 centers), these 3 centers corrected the delineation which was therefore rated as per protocol.

For the delineation acceptable variations, overall grading for delineation review in BC1 was rated AV for 7 centers for arm A and 8 centers for arm B, respectively. For arm A, besides an incomplete sigmoid (n=1) and a missing PRV for sigmoid and bowel loop (n=1), inappropriate PTV_SBRT margins (n=5) around the GTV

nodes were the cause of most acceptable variations: the PTV margins were larger (4-5 mm) than pre-specified for the SBRT treatment (3 mm). Five out of these 7 centers corrected these variations in BC2, while for 2 remaining centers a larger PTV margin for the GTV node (n=1) and an incomplete sigmoid (n=1) contouring continued to be rated as AV in the BC2. For arm B, delineation of the CTV_LNN (n=3), of the CTV_PB (n=2), of OARs (n=6), and inappropriate PTV margins either for PB or for nodes (n=4) were the cause of AV and remained overall unchanged in the BC2. The most common AV in the delineation of the CTV_LNN were the inclusion of the obturator fossa (n=1), an incomplete coverage of the iliac external nodes (n=1), and a cranial border situated above the L4-L5 interspace (n=1). The AV of the CTV_PB were a PB CTV apex too close from the vesico-urethral anastomosis (n=2), and an upper anterior limit not cranial enough (n=1). Other AV were observed in bladder (n=2), bowel bag (n=2), and sigmoid (n=2) delineation. Finally, 3 centers used a 3-4 mm margin for defining the PTV_1/2 nodes instead of the 5 mm margins used in the protocol and one center used a 4 mm cranial margin for defining the PTV_PB.

The AV and UV for BC1 are summarized in Table 2 and the Sankey diagrams of the 2 BCs for arm A and arm B contouring are illustrated in Figure 2.

Concerning the target volumes, the median radius of the volume equivalent sphere of the nodal GTV_1 and GTV_2 was 5.23 mm (range, 4.15–6.59 mm) and 3.34 mm (range, 2.88–5.23 mm), respectively. Figure 3 shows the variation in submitted volumes for GTV_1 and GTV_2 and their corresponding PTV for arm A (PTV_SBRT 1 and PTV_SBRT 2, 3 mm margin) and arm B (PTV_1 node and PTV_2 node, 5 mm margin) in BC 2. The median CTV_LNN volume was 420 cc (range, 302 – 606 cc, standard deviation 81 cc), while the CTV_PB ranged from 23 to 108 cc (median 64cc, standard deviation 27 cc) in BC2.

All dosimetric parameters for arm A were reported at the end of the BC2 or BC1 for patients not undergoing BC2. For 23 out of 24 centers the SBRT was planned with C-arm linac, while a robotic delivery technique was used for a patient. The mean PTV_SBRT 1 V_{30Gy} for node 1 was 77.3%, below the recommended 90% because some centers preferred to decrease the prescribed dose to the node 1 in order to respect the dose constraints on the bowel loop PRV (Figure 4). However, prioritization on the PTV node coverage over OAR was adopted in the majority of the centers, as illustrated by a median V_{30Gy} for node 1 estimated at 91.5%. For node 2, both median and mean V_{30Gy} were above 90% (96.2% and 90.7%, respectively). This can be explained by the fact that the dose constraints on the sigmoid PRV were easier to achieve while covering correctly the PTV_SBRT 2, for geometric reasons (Fig. 1a). Seven centers out of 24 respected the AAPM task group 101 report dose constraints for the bowel loop PRV. When applied to the bowel loop itself, 23 centers out of 24 respected the dose constraint. Twenty centers out of 24 respected the AAPM report 101 dose constraints for the sigmoid PRV and all centers respected the dose constraint for the sigmoid itself (Figure 1b). Within the set of 24 plans for the benchmark cases there is little correlation between $D_{0.03cc}$ bowel loop/sigmoid PRV and $D_{90\%}$ for nodes 1 and 2 (R^2 = 0.27 and 0.16), and none between $D_{0.03cc}$ bowel loop/sigmoid and $D_{90\%}$ node 1 and 2 (R^2 = 0.0009 and $6.2.10^{-7}$), suggesting a rapid dose fall-off outside the nodal PTV (Figure 1c).

For arm B dosimetry, 3 treatment plans could not be assessed in the BC1 because of incorrect volumes (UV rating for delineation), 1 because of a missing plan sum and 5 were rated as UV. Of the UV plans, 1 was an incorrect PB dose and 4 presented an incorrect dose to the PTV nodes. Among the 4 centers which did not deliver a correct dose to the PTV nodes, 1 center did not perform a SIB to the suspicious nodes, and for 3 centers, a SIB was performed but 98% of the PTV nodal volume was covered only by the 90% isodose line. Fifteen treatment plans were rated per protocol. With the BC2, all treatment plans were as per protocol. Dose constraints were respected for all plans (already in BC1) with a mean V_{65Gy} for the BW at 25.9 ± 13.6 %. The mean V_{50Gy}, V_{60Gy} and V_{65Gy} for the RW were 26.1 ± 8.4 %, 16.7 ± 5.9 %, and 7.2 ± 4.5 % respectively. No femoral head received a dose superior to 50 Gy. Finally, the mean V_{45Gy} for the bowel bag was 92.6 ± 56.2 cc (values reported for BC2).

Discussion

Results of the PEACE V-STORM phase II multi-center randomized trial are expected to define the best treatment approach for patients with nodal oligorecurrent PCa. Implementation of a rigorous QA program was therefore mandatory to improve the reliability of the trial and quality of practice by promoting uniformity in nodal pelvic treatment. Noteworthy, radiotherapy protocol deviations have been associated with an increased risk of treatment failure and overall mortality [14, 28].

Pelvic lymph node irradiation is a common practice in the post-prostatectomy setting. The RTOG developed a consensus-based contouring atlas in 2009 [20] and the PEACE V-STORM trial participant centers were asked to follow this atlas with the exception of the inclusion of the common iliac nodes starting at the L4/L5 interspace. Although for two centers contouring were rated UV in BC1 because of insufficient coverage of the common iliac stations, the overall rating of this BC exercise was good, suggesting an acceptable agreement among centers in defining the elective nodal pelvic regions as per protocol guidelines.

Limitations of guidelines in defining volumes of elective nodal pelvic irradiation should be acknowledged. The OligoPelvis – GETUG P07 trial used the RTOG consensus guidelines [20] modified by the GETUG group [29], similar to the elective nodal CTV volumes used in our trial. Among the 67 patients included in the French trial, 28% of the relapses were located in the pelvis (pelvic nodes or PB) [30]. This rate is in line with the 20% of nodal recurrences missed by standard elective WPRT templates in the study by De Bruycker *et al.* [31]. Inclusion in the CTV volume of the transition region from the external iliac to the inguinal nodes is supposed to improve nodal coverage, although perirectal nodes, accounting for 11% of pelvic lesions, will not be covered by any template [32].

Target volumes recommendations for postoperative PB radiotherapy have been established by several groups [22-24]. However, it has been shown that even with a specific contouring atlas, the interobserver agreement of PB delineation remains moderate [33]. This is confirmed by our data, showing a high standard deviation of the PB volume dataset, certainly explained also by the use in the study trial of different guidelines for PB definition. Development of new and more reproducible consensus guidelines for PB CTV definition is expected to homogenize practices [34].

As for node delineation, we observed some variability in nodal contouring among centers, however with probably no major clinical impact considering the isotropic expansion generated by the PTV. Noteworthy, the 2-year local control rates of pelvic lymph nodes treated with SBRT in retrospective studies range between 70% to 100% [1], with the majority of relapses that are again nodal, oligometastatic, and in close proximity to the previously treated node [35, 36].

Optimal conformity of the prescription isodose to the target volume and a steep dose gradients surrounding the target volumes are the hallmarks of SBRT planning [37]. In our trial, V_{30Gy} had to cover 90% of the PTV node as per protocol unless in case of violation of dose constraints to the surrounding OAR. In the selected benchmark case, optimization of SBRT to respect dose constraints to the OAR was challenging, considering the close proximity of node 1 to the bowel loop, almost overlapping with the corresponding PRV (Figure 1). Among the 24 centers, only 7 centers decided to decrease the prescribed dose to node 1 in order to meet the dose constraints to the bowel loop PRV. Nevertheless, dose constraints to the bowel loop were respected for 23 centers, reflecting the steep dose gradient surrounding the target volume and the quality of the SBRT plans. Similarly, for node 2, less close to the OAR, only two 2 centers decided to decrease the prescribed dose in order to respect dose constraints on the sigmoid PRV, while for 17 centers a correct nodal coverage according to the protocol without violating dose constraints to the sigmoid PRV was possible. On the other hand, dose constraints to the sigmoid were respected for all 24 centers. Although 30 Gy in 3 fractions is the most commonly

used SBRT schedule [1], dose de-escalation delivering 24 Gy [38] or 27 Gy [35] in 3 fractions has also been used with excellent local control rates. In our trial, only a minority of the centers decided to decrease the dose to the node, probably giving a priority to the OAR itself instead of the OAR PRV considering the confidence on repositioning and image-guided techniques. Use of mandatory dose prescription in case of non-respect of dose constraints to surrounding OARs may be advisable for future study protocols.

The present analysis has some limitations. First, the QA program of the PEACE-V-STORM trial included only the evaluation of a BC, without implementation of a prospective individual case reports (ICR) analysis. Although a prospective BC can help to highlight protocol ambiguities and to improve plan protocol compliance, rigorous application of the study protocol during the trial remains matter of uncertainty. Of note, a BC-ICR correlation has not always been observed in clinical trials [39, 40], suggesting the need of implementing prospective ICR evaluations in the RTQA program to prevent protocol deviations. Although deviations observed in the present BC analysis were considered acceptable in most cases, the true impact of the overall quality of radiotherapy treatment plans on long-term clinical results remains unknown and it will require a dedicated analysis. Second, our study does not implement quantitative and objective contouring evaluation methods like the Sorensen-Dice Similarity Index (DSI) or the 95th percentile Hausdorff distance (HD) that may certainly help to reduce interobserver variability and lead to a more rigorous analysis. Nevertheless, each BC was reviewed separately by two experienced radiation-oncologist, and further discussed to reach a consensus in case of divergent evaluation.

In conclusions, to the best of our knowledge, this is the first RTQA study providing valuable insights into the level of congruence for delineation and treatment planning for treating patients with nodal oligorecurrent PCa. Overall, the contouring and planning BC procedure of the multicenter phase II PEACE-V-STORM trial showed an acceptable compliance rate among the participating centers, reinforcing confidence in the overall quality of treatment plans of patients included in the trial. WPRT was more subject to variations, mostly considered acceptable, with up to 46% of protocol deviations in delineation of the BC1 and with a clear improvement in the adherence to the protocol after BC2, while dosimetric results of SBRT plans showed large variations with different balancing between the target coverage and the respect of dose constraints to the OAR PRV.

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Figure legend

Figure 1. a: Color wash representation (90% of 30 Gy) of the arm A treatment for both nodes with OARs contouring (University Hospitals of Geneva); b: Variation between the maximal dose to the OARs PRV and the OARs for 24 plans of the benchmark case; c: Correlation between doses to the bowel loop and sigmoid versus PTV $D_{90\%}$ of node 1 and 2 for the 24 plans of the benchmark case.

Figure 2. Sankey diagrams of the 2 benchmark cases for arm A (Fig. 2a) and arm B (Fig. 2b) contouring.

Abbreviations: A, as per protocol; AV, acceptable variation; UV, unacceptable variation; BC, Benchmark case.

Figure 3. Boxplots showing the variation in nodal volumes (GTV and PTV) for arm A (GTV + 3 mm isotropic margin to generate PTV_1/2_SBRT) and for arm B (GTV + 5mm isotropic margin to generate PTV_1/2_node).

Figure 4. Boxplots displaying variations in dose delivered to the nodal lesions (Fig. 4a) and organs at risk (Fig. 4b) for arm A.

Abbreviations: V_{30Gy} ,percentage of target volume receiving 30 Gy; PRV, planning target volume.

Declarations

Ethics approval and consent to participate

Signature of the informed consent will be obtained from all patients before inclusion in the study. This study was approved by the Ethics committee of the Ghent University Hospital (EC/2018/0130) and for all participating centers. The study is registered on Clinicaltrials.gov (NCT03569241) and Swiss National Clinical Trials Portal (SNCTP000002947).

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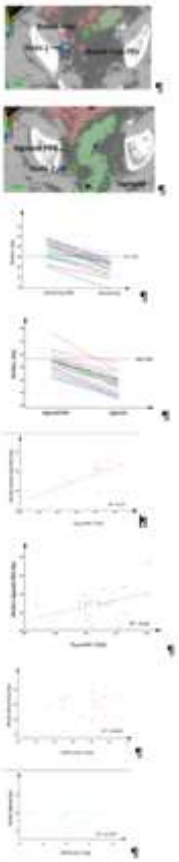

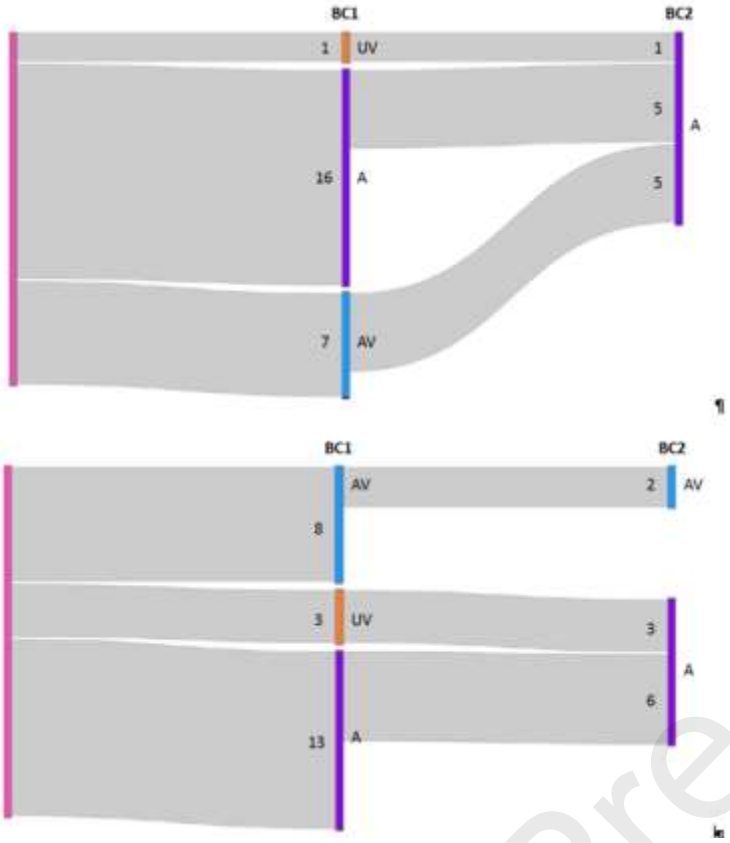

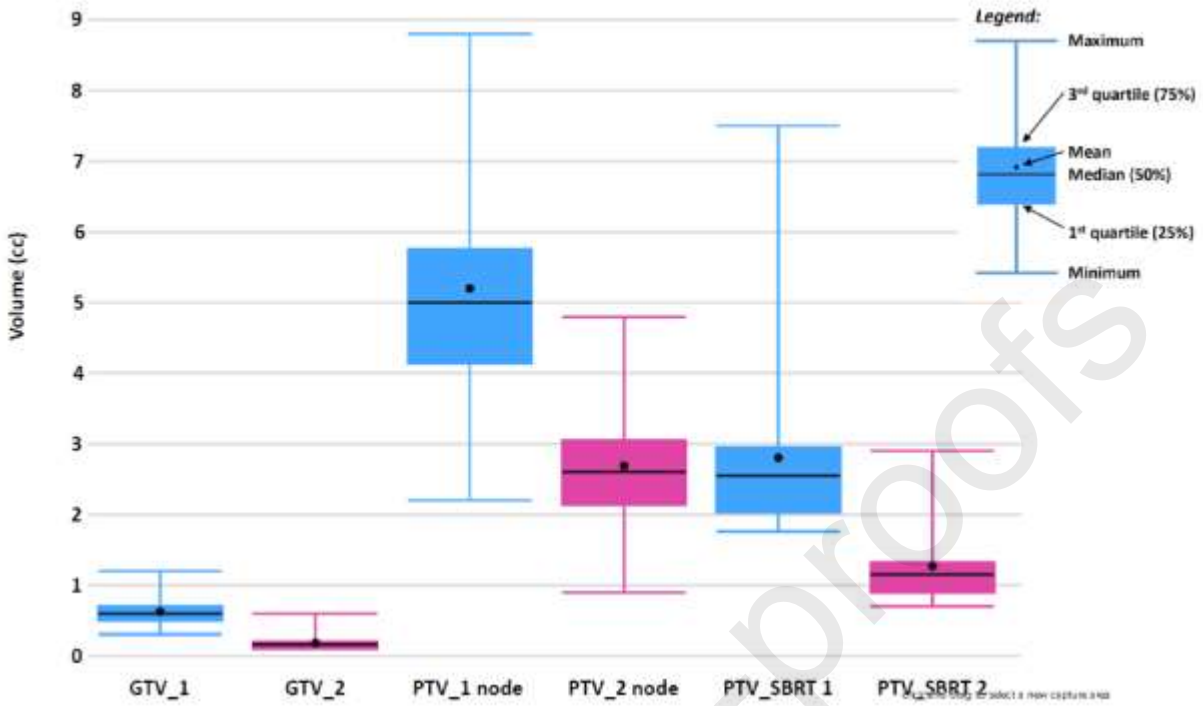

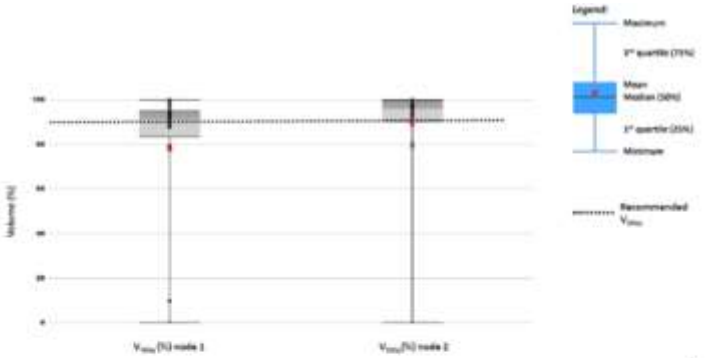

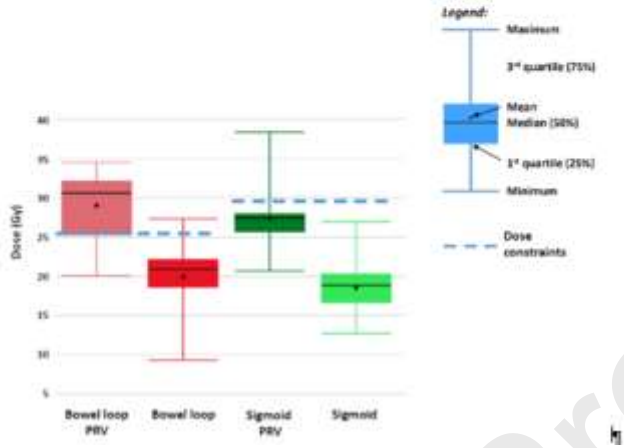

(a)

Number of BCs containing 1 or more protocol variations BC 1	
Unacceptable Variation	**Acceptable Variation**
1	7

	Occurrences	
Variation	**Unacceptable Variation**	**Acceptable Variation**
OAR contouring inappropriate	0	
- Bladder		
- Bowel bag		
- Sigmoid		1
Missing contours	1	1
PTV margins inappropriate	0	5 (PTV_node)

(b)

Number of BCs containing 1 or more protocol variations BC 1	
Unacceptable Variation	**Acceptable Variation**
3	8

	Occurrences	
Variation	**Unacceptable Variation**	**Acceptable Variation**
CTV LNN delineation	2	3
CTV PB delineation	1	2

	OAR contouring inappropriate		
	- Bladder	1	2
	- Bowel bag	1	2
	- Sigmoid		2
	Missing contours	1	0
	PTV margins inappropriate	0	4 (3 PTV_node and 1 PB)

Table 2. Acceptable and Unacceptable variations of BC 1 arm A (a) and arm B (b) contouring for (a center can present multiple variations).

Abbreviations: BC, benchmark case; OAR, organ at risk; PB, prostate bed; CTV, clinical target volume; PTV, planning target volume; LNN, lymph nodes.

- A radiotherapy quality assurance program was conducted in the PEACE V-STORM trial
- Benchmark case results were analyzed for 24 centers as part of a dummy run procedure
- Benchmark case consisted of a pelvic nodal oligorecurent prostate cancer patient
- WPRT and SBRT delineation and dosimetry were assessed
- Contouring for WPRT was more subject to variations compared to SBRT
- SBRT plans showed more dosimetric disparities between centers due to OAR proximity