Radiotherapy and Oncology 172 (2022) 1–9

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

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

Vérane Achard [a], Maud Jaccard [a], Frederik Vanhoutte [b], Shankar Siva [c], Reino Heikkilä [d], Piet Dirix [e,f], Nick Liefhooghe [g], François-Xavier Otte [h], Alfonso Gomez-Iturriaga [i], Charlien Berghen [j], Mohamed Shelan [k], Antonio Conde-Moreno [l], Fernando López Campos [m], Alexandros Papachristofilou [n], Matthias Guckenberger [o], Sabine Meersschout [p], Paul Martin Putora [q], Daniel Zwahlen [r], Felipe Couñago [s], Marta Scorsetti [t], Clara Eito [u], Marta Barrado [v], Almudena Zapatero [w], Paolo Muto [x], Lien Van De Voorde [y], Giorgio Lamanna [a], Nikolaos Koutsouvelis [a], Giovanna Dipasquale [a], Piet Ost [b,z], Thomas Zilli [a,*]

[a] *Department of Radiation Oncology, Geneva University Hospital, Switzerland;* [b] *Department of Radiation Oncology, Ghent University Hospital, Belgium;* [c] *EJ Whitten Foundation Prostate Cancer Research Centre, Epworth Healthcare and Sir Peter MacCallum Department of Oncology, University of Melbourne, Australia;* [d] *Department of Oncology, Oslo University Hospital, Norway;* [e] *Department of Radiation Oncology, Iridium Kankernetwerk, Antwerp;* [f] *University of Antwerp, Faculty of Medicine and Health Sciences;* [g] *Department of Radiation Oncology, AZ Groeninge, Kortrijk;* [h] *Department of Radiation Oncology, Jules Bordet Institute and Hôpital Erasme, University Clinics of Brussels, Université Libre de Bruxelles, Belgium;* [i] *Department of Radiation Oncology, Cruces University Hospital (Biocruces Health Research Institute), Barakaldo, Spain;* [j] *Department of Radiation Oncology, University Hospitals Leuven, Belgium;* [k] *Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Switzerland;* [l] *Department of Radiation Oncology, Hospital Universitari i Politècnic la Fe, Valencia;* [m] *Department of Radiation Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain;* [n] *Department of Radiotherapy and Radiation Oncology, University Hospital Basel;* [o] *Department of Radiation Oncology, University Hospital Zürich, University of Zürich, Switzerland;* [p] *Department of Radiation Oncology, AZ-St Jan-Brugge, Belgium;* [q] *Department of Radiation Oncology, Kantonspital St. Gallen;* [r] *Department of Radiation Oncology, Kantonspital Winterthur, Switzerland;* [s] *Department of Radiation Oncology, University Hospital Quironsalud, Universidad Europea de Madrid, Spain;* [t] *Department of Radiation Oncology, Humanitas Clinical and Research Hospital, IRCSS, Radiotherapy and Radiosurgery Department, Rozzano, Italy;* [u] *Department of Radiation Oncology, Instituto Oncólogico Clinica Universitaria IMQ, Bilbao;* [v] *Department of Radiation Oncology, Complejo Hospitalario de Navarra;* [w] *Department of Radiation Oncology, University Hospital La Princesa, Madrid, Spain;* [x] *Department of Radiation Oncology, Napoli Istituto Nazionale Tumori IRCCS Fondazione Pascale, Italy;* [y] *Department of Radiation Oncology, AZ St-Lucas Ghent; and* [z] *Department of Human Structure and Repair, Ghent University, Belgium*

ARTICLE INFO

Article history:
Received 30 January 2022
Received in revised form 29 March 2022
Accepted 19 April 2022
Available online 26 April 2022

Keywords:
Prostate cancer
Radiotherapy
SBRT
Elective nodal
Oligometastases
Randomized trial
Quality assurance

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 22.9–33.2 Gy and 30.6 Gy, range 26.8–34.2 Gy 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.

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

* Corresponding author at: Department of Radiation Oncology, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, CH-1211 Genève 14, Switzerland.
E-mail address: Thomas.Zilli@hcuge.ch (T. Zilli).

https://doi.org/10.1016/j.radonc.2022.04.020
0167-8140/

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.

Table 1
Dose constraints to PTV and OAR for both arms of PEACE-V-STORM trial.

Arm B (WPRT)			
	Per Protocol	***Acceptable Variation***	***Unacceptable Variation***
Target volume coverage			
PTV (PTV_PB, PTV_LNN, PTV_node)	$D_{98} \geq 95\%\ D_{prescribed}$ $D_2 \leq 107\%\ D_{prescribed}$	$D_{95} \geq 95\%\ D_{prescribed}$ or $D_{98} \geq 90\%\ D_{prescribed}$ $D_5 \leq 107\%\ D_{prescribed}$	$D_{95} < 95\%\ D_{prescribed}$ or $D_{98} < 90\%\ D_{prescribed}$ $D_5 > 107\%\ D_{prescribed}$
OAR			
Bladder wall	V_{65Gy} (%) ≤ 50%	x	V_{65Gy} (%) > 50%
Rectal wall	V_{50Gy} (%) < 50% V_{60Gy} (%) < 35% V_{65Gy} (%) < 25% V_{70Gy} (%) < 20% V_{75Gy} (%) < 15%		V_{50Gy} (%) ≥ 50% V_{60Gy} (%) ≥ 35% V_{65Gy} (%) ≥ 25% V_{70Gy} (%) ≥ 20% V_{75Gy} (%) ≥ 15%
Bowel	V_{45Gy} < 195cc		V_{45Gy} ≥ 195cc
Femoral head	V_{50Gy} (%) < 5%		V_{50Gy} (%) ≥ 5%
Arm A (SBRT)[&]			
Target volume coverage			
PTV_SBRT	D_{max} = 30 Gy/80% Gy = 37.5 Gy V_{30Gy} (%) = 90%		
OAR			
Sigmoid PRV	$D_{0.03cc}$ < 28.2 Gy		
Bowel loop PRV	$D_{0.03cc}$ < 25.2 Gy		

Abbreviations: OAR, organs at risk; PB, prostate bed; PRV, planning organ at risk volume; PTV, planning target volume; LNN, lymph nodes; SBRT, stereotactic body radiotherapy, D_x = dose covering x % volume, V_{xGy} = Volume receiving a dose > x Gy, V_{xGy} (%) = percentage of volume receiving a dose ≥ x Gy, $D_{0.03cc}$ = Maximal dose covering 0.03cc, D_{max} = Maximum radiation dose;; AV, acceptable variation; UV, unacceptable variation; PP, per protocol.

[&] For arm A, there was no rating (AV, UV, PP). Because of the proximity of OAR, it was the choice of the centers to favor either PTV_SBRT coverage or respect of OAR dose constraints.

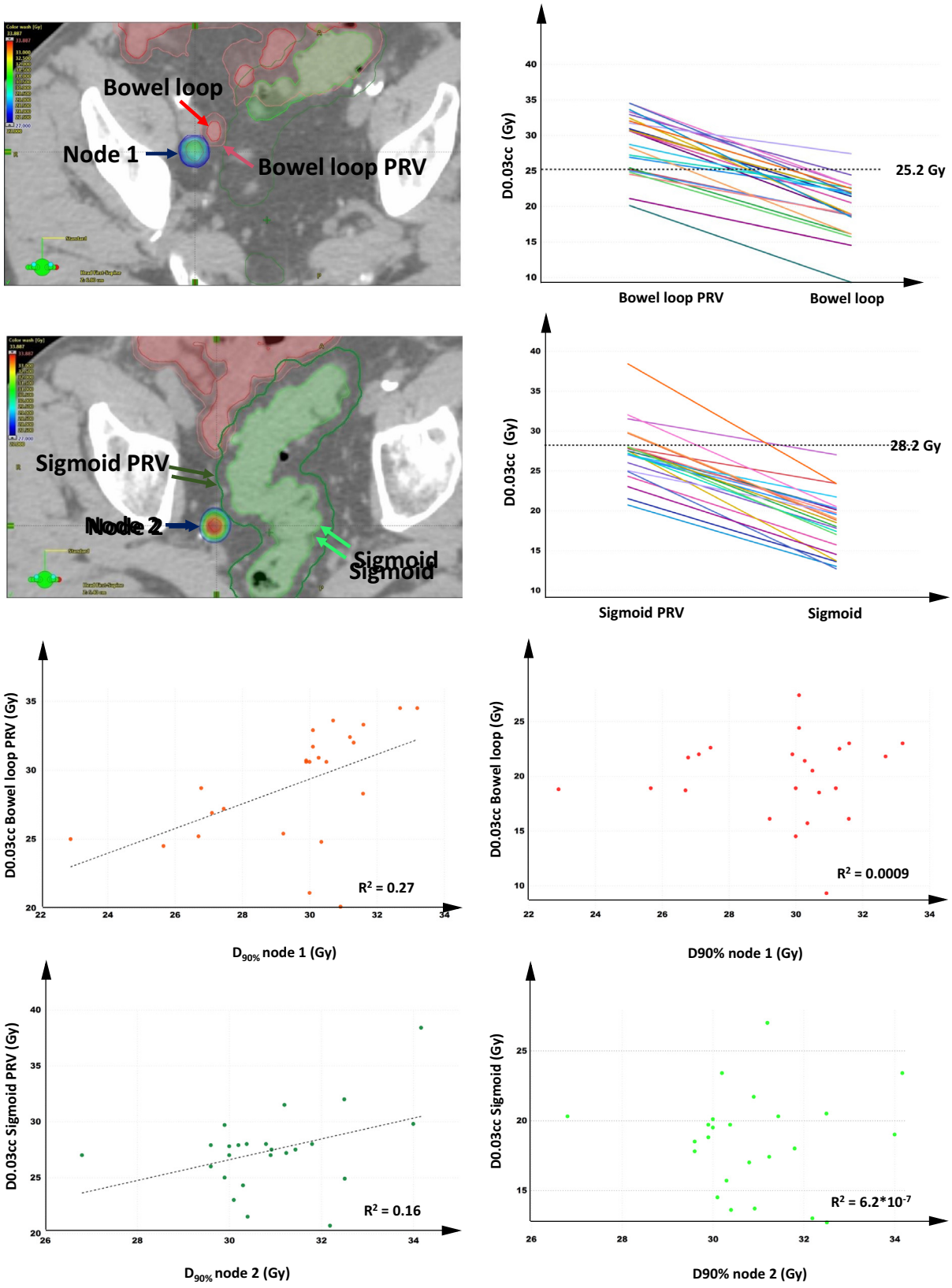

Fig. 1. (a) Color wash representation (90% of 30 Gy) of the arm A treatment for both nodes with OARs contouring (University Hospitals of Geneva); (b) Variation between the maximal dose to the OARs PRV and the OARs for 24 plans of the benchmark case; (c) Correlation between doses to the bowel loop and sigmoid versus PTV $D_{90\%}$ of node 1 and 2 for the 24 plans of the benchmark case. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).

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) (Fig. 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 Fig. 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

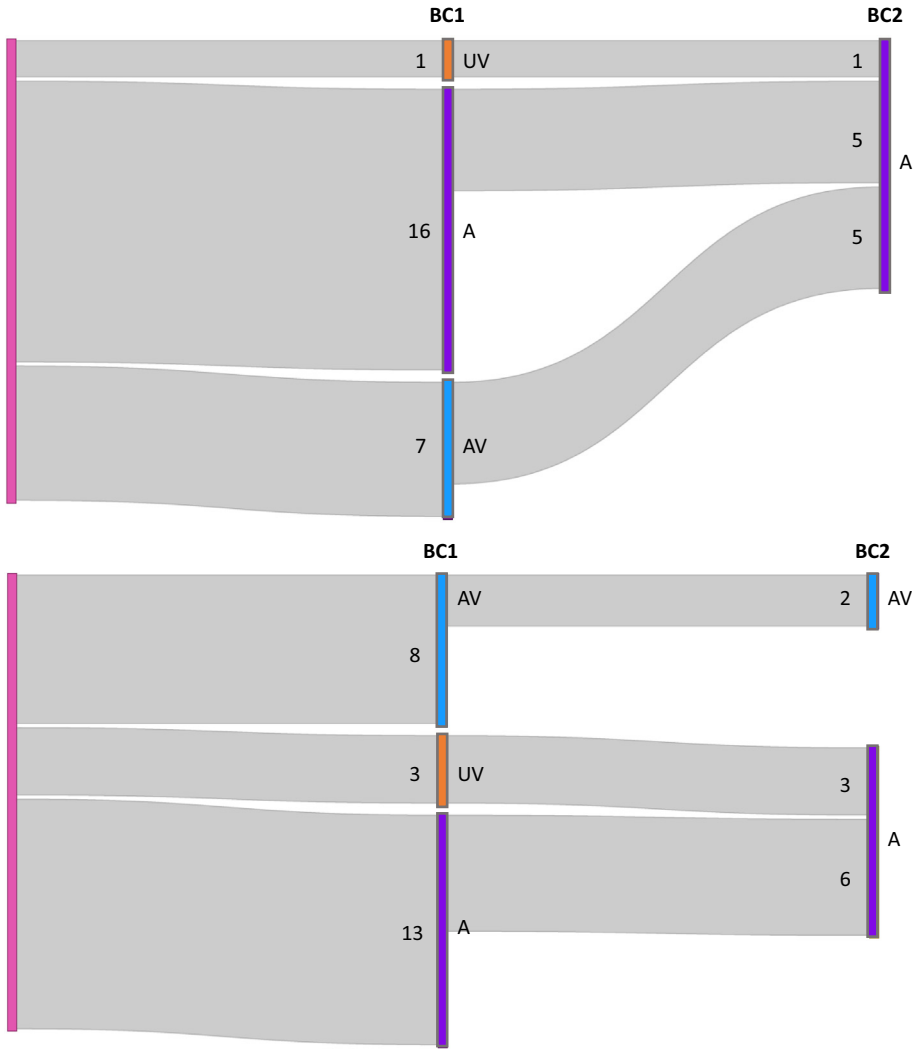

Fig. 2. Sankey diagrams of the 2 benchmark cases for arm A (a) and arm B (b) contouring. *Abbreviations: A, as per protocol; AV, acceptable variation; UV, unacceptable variation; BC, Benchmark case.*

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 Fig. 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. Fig. 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 64 cc, 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 (Fig. 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 (Fig. 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

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

(a)

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

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

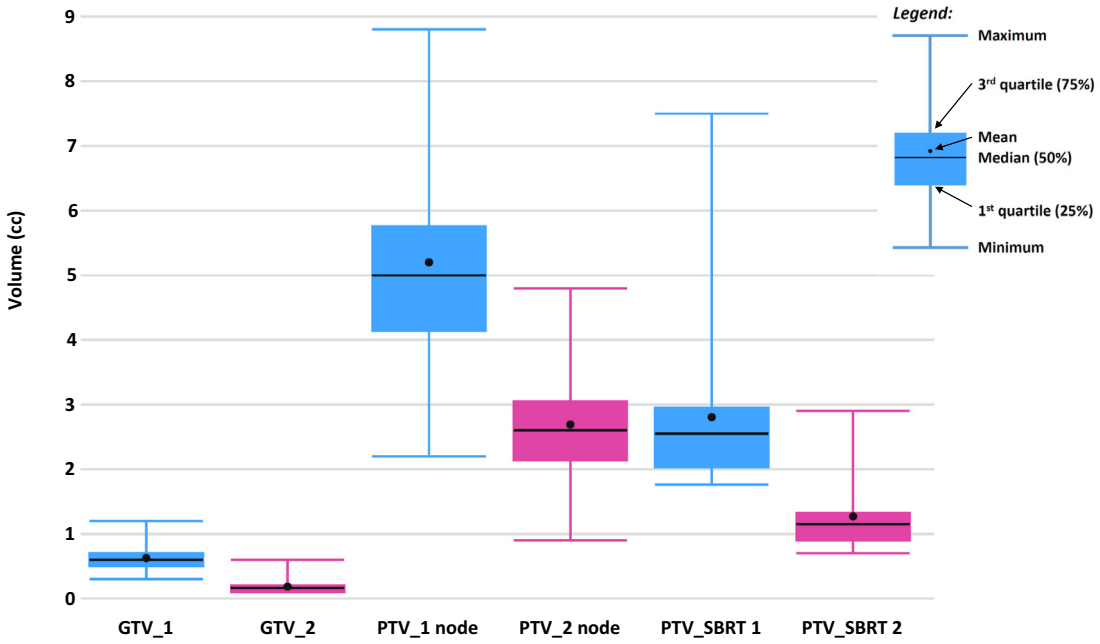

Fig. 3. Boxplots showing the variation in nodal volumes (GTV and PTV) for arm A (GTV + 3 mm isotropic margin to generate PTV_1/2_SBRT) and for arm B (GTV + 5 mm isotropic margin to generate PTV_1/2_node).

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 (Fig. 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% and 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

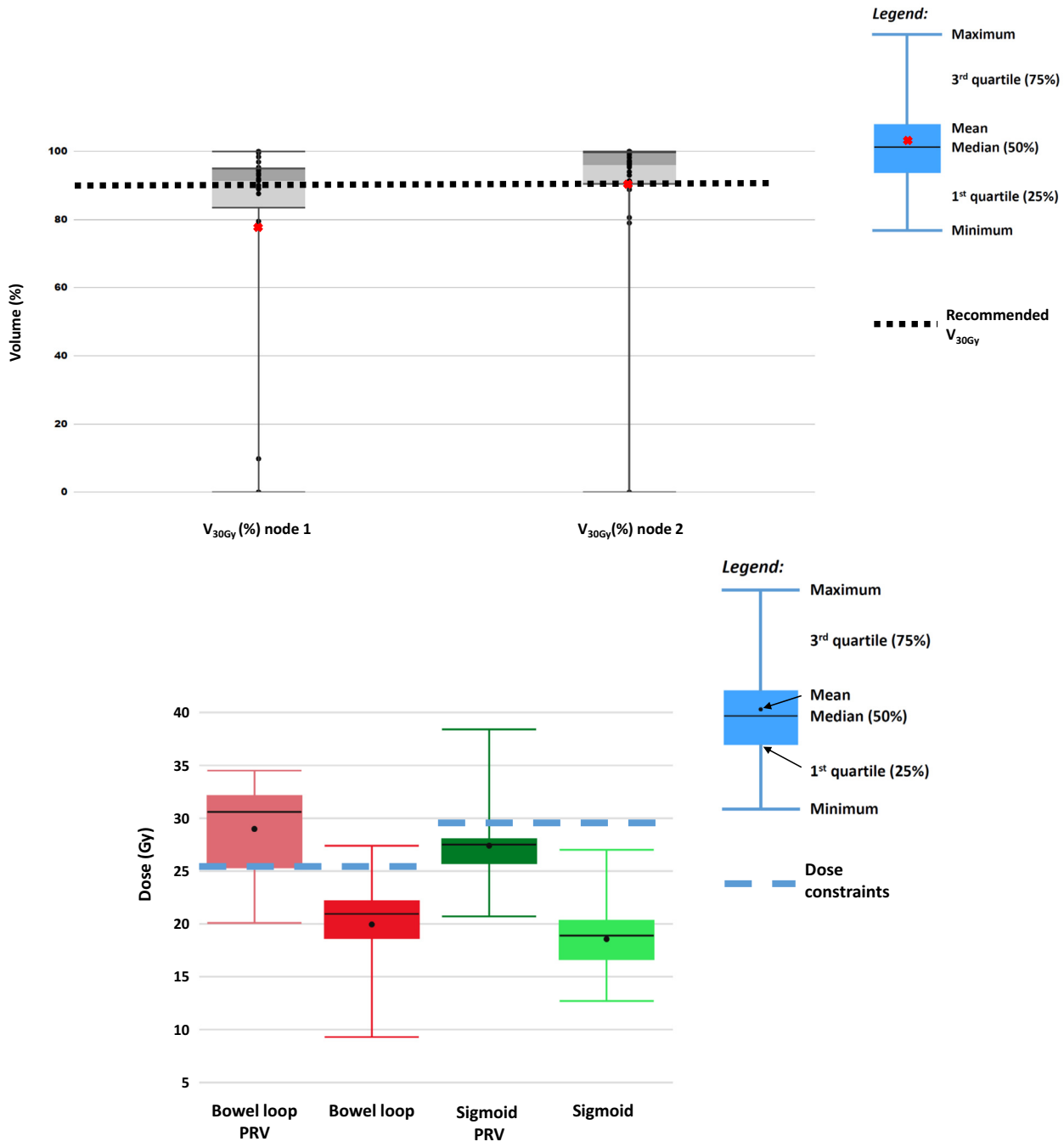

Fig. 4. Boxplots displaying variations in dose delivered to the nodal lesions (a) and organs at risk (b) for arm A. *Abbreviations: V_{30Gy}, percentage of target volume receiving 30 Gy; PRV, planning target volume.*

to the OAR was challenging, considering the close proximity of node 1 to the bowel loop, almost overlapping with the corresponding PRV (Fig. 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.

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).

Funding

This study is funded by a Swiss Prostate Cancer Award grant from the Movember Foundation https://de.movember.com/report-cards/view/?id=3399, by the Belgian 'Kom Op Tegen Kanker' and by a young investigator grant from the Scientific Association of Swiss Radiation Oncologists (SASRO).

Conflict of interest

No competing interests concerning the submitted work.

Acknowledgements

We thank all the patients and the referring physicians whose willingness to participate made this study possible. We thank for its special contribution Isabelle Semac, PhD, and Laurence Zulianello, PhD, Department of Radiation oncology, Geneva University Hospital, Switzerland and Johan Adnet, Unité de Méthodologie, Biostatistiques et Data Management, CRC, Centre Georges François Leclerc, Dijon, France.

References

[1] Achard V, Bottero M, Rouzaud M, Lancia A, Scorsetti M, Filippi AR, et al. Radiotherapy treatment volumes for oligorecurrent nodal prostate cancer: a systematic review. Acta Oncol 2020;59:1224–34.
[2] Fendler WP, Ferdinandus J, Czernin J, Eiber M, Flavell RR, Behr SC, et al. Impact of (68)Ga-PSMA-11 PET on the management of recurrent prostate cancer in a prospective single-arm clinical trial. J Nucl Med 2020;61:1793–9.
[3] Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. LancetOncol 2020;21:e18–28.
[4] Lancia A, Zilli T, Achard V, Dirix P, Everaerts W, Gomez-Iturriaga A, et al. Oligometastatic prostate cancer: The game is afoot. Cancer Treat Rev 2019;73:84–90.
[5] le Guevelou J, Achard V, Mainta I, Zaidi H, Garibotto V, Latorzeff I, et al. PET/CT-based salvage radiotherapy for recurrent prostate cancer after radical prostatectomy: impact on treatment management and future directions. Front Oncol 2021;11:742093.
[6] Patrikidou A, Zilli T, Baciarello G, Terisse S, Hamilou Z, Fizazi K. Should androgen deprivation therapy and other systemic treatments be used in men with prostate cancer and a rising PSA post-local treatments? Ther Adv Med Oncol 2021;13:17588359211051870.
[7] Halabi S, Kelly WK, Ma H, Zhou H, Solomon NC, Fizazi K, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. J Clin Oncol 2016;34:1652–9.
[8] Ost P, Decaestecker K, Lambert B, Fonteyne V, Delrue L, Lumen N, et al. Prognostic factors influencing prostate cancer-specific survival in non-castrate patients with metastatic prostate cancer. Prostate 2014;74:297–305.
[9] Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–53.
[10] Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: The ORIOLE phase 2 randomized clinical Trial. JAMA Oncol 2020;6:650.
[11] De Bleser E, Jereczek-Fossa BA, Pasquier D, Zilli T, Van As N, Siva S, et al. Metastasis-directed therapy in treating nodal oligorecurrent prostate cancer: A multi-institutional analysis comparing the outcome and toxicity of stereotactic body radiotherapy and elective nodal radiotherapy. Eur Urol 2019;76:732–9.
[12] De Bruycker A, Spiessens A, Dirix P, Koutsouvelis N, Semac I, Liefhooghe N, et al. PEACE V - Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM): a study protocol for a randomized controlled phase II trial. BMC Cancer 2020;20.
[13] Weber DC, Poortmans PMP, Hurkmans CW, Aird E, Gulyban A, Fairchild A. Quality assurance for prospective EORTC radiation oncology trials: the challenges of advanced technology in a multicenter international setting. Radiother Oncol 2011;100:150–6.
[14] Weber DC, Tomsej M, Melidis C, Hurkmans CW. QA makes a clinical trial stronger: evidence-based medicine in radiation therapy. Radiother Oncol 2012;105:4–8.
[15] Jaccard M, Zilli T, Dubouloz A, Escude L, Jorcano S, Linthout N, et al. Urethra-sparing stereotactic body radiation therapy for prostate cancer: quality assurance of a randomized phase 2 trial. Int J Radiat Oncol Biol Phys 2020;108:1047–54.
[16] Khalil AA, Bentzen SM, Bernier J, Saunders MI, Horiot J-C, Van Den Bogaert W, et al. Compliance to the prescribed dose and overall treatment time in five randomized clinical trials of altered fractionation in radiotherapy for head-and-neck carcinomas. Int J Radiat Oncol Biol Phys 2003;55:568–75.
[17] Melidis C, Bosch WR, Izewska J, Fidarova E, Zubizarreta E, Ulin K, et al. Global harmonization of quality assurance naming conventions in radiation therapy clinical trials. Int J Radiat Oncol Biol Phys 2014;90:1242–9.
[18] Zilli T, Dirix P, Heikkilä R, Liefhooghe N, Siva S, Gomez-Iturriaga A, et al. The multicenter, randomized, phase 2 PEACE V-STORM trial: defining the best salvage treatment for oligorecurrent nodal prostate cancer metastases. Eur Urol Focus 2021;7:241–4.
[19] Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 2010;37:4078–101.
[20] Lawton CAF, Michalski J, El-Naqa I, Buyyounouski MK, Lee WR, Menard C, et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2009;74:383–7.
[21] Spratt DE, Vargas HA, Zumsteg ZS, Golia Pernicka JS, Osborne JR, Pei X, et al. Patterns of lymph node failure after dose-escalated radiotherapy: implications for extended pelvic lymph node coverage. Eur Urol 2017;71:37–43.
[22] Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, et al. Guidelines for target volume definition in post-operative radiotherapy for

prostate cancer, on behalf of the EORTC Radiation Oncology Group. Radiother Oncol 2007;84:121–7.
[23] Michalski JM, Lawton C, El Naqa I, Ritter M, O'Meara E, Seider MJ, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;76:361–8.
[24] Sidhom MA, Kneebone AB, Lehman M, Wiltshire KL, Millar JL, Mukherjee RK, et al. Post-prostatectomy radiation therapy: consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. Radiother Oncol 2008;88:10–9.
[25] Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys 2010;76:S123–9.
[26] Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. Int J Radiat Oncol Biol Phys 2010;76:S116–22.
[27] Kavanagh BD, Pan CC, Dawson LA, Das SK, Li XA, Ten Haken RK, et al. Radiation dose-volume effects in the stomach and small bowel. Int J Radiat Oncol Biol Phys 2010;76:S101–7.
[28] Fairchild A, Straube W, Laurie F, Followill D. Does quality of radiation therapy predict outcomes of multicenter cooperative group trials? A literature review. Int J Radiat Oncol Biol Phys 2013;87:246–60.
[29] Sargos P, Guerif S, Latorzeff I, Hennequin C, Pommier P, Lagrange J-L, et al. Definition of lymph node areas for radiotherapy of prostate cancer: A critical literature review by the French Genito-Urinary Group and the French Association of Urology (GETUG-AFU). Cancer Treat Rev 2015;41:814–20.
[30] Supiot S, Vaugier L, Pasquier D, Buthaud X, Magné N, Peiffert D, et al. OLIGOPELVIS GETUG P07, a multicenter phase II trial of combined high-dose salvage radiotherapy and hormone therapy in oligorecurrent pelvic node relapses in prostate cancer. Eur Urol 2021;80:405–14.
[31] De Bruycker A, De Bleser E, Decaestecker K, Fonteyne V, Lumen N, De Visschere P, et al. Nodal oligorecurrent prostate cancer: anatomic pattern of possible treatment failure in relation to elective surgical and radiotherapy treatment templates. Eur Urol 2019;75:826–33.
[32] Hall WA, Paulson E, Davis BJ, Spratt DE, Morgan TM, Dearnaley D, et al. NRG Oncology Updated International Consensus Atlas on pelvic lymph node volumes for intact and postoperative prostate cancer. Int J Radiat Oncol Biol Phys 2021;109:174–85.
[33] Sassowsky M, Gut P, Hölscher T, Hildebrandt G, Müller A-C, Najafi Y, et al. Use of EORTC target definition guidelines for dose-intensified salvage radiation therapy for recurrent prostate cancer: results of the quality assurance program of the randomized trial SAKK 09/10. Int J Radiat Oncol Biol Phys 2013;87:534–41.
[34] Robin S, Jolicoeur M, Palumbo S, Zilli T, Crehange G, De Hertogh O, et al. Prostate bed delineation guidelines for postoperative radiation therapy: on behalf of the Francophone Group of Urological Radiation Therapy. Int J Radiat Oncol Biol Phys 2021;109:1243–53.
[35] Pasqualetti F, Panichi M, Sainato A, Matteucci F, Galli L, Cocuzza P, et al. [(18)F] Choline PET/CT and stereotactic body radiotherapy on treatment decision making of oligometastatic prostate cancer patients: preliminary results. Radiat Oncol 2016;11.
[36] Ost P, Jereczek-Fossa BA, Van As N, Zilli T, Tree A, Henderson D, et al. Pattern of progression after stereotactic body radiotherapy for oligometastatic prostate cancer nodal recurrences. Clin Oncol 2016;28:e115–20.
[37] Nagata Y, Matsuo Y, Takayama K, Norihisa Y, Mizowaki T, Mitsumori M, et al. Current status of stereotactic body radiotherapy for lung cancer. Int J Clin Oncol 2007;12:3–7.
[38] Jereczek-Fossa BA, Fanetti G, Fodor C, Ciardo D, Santoro L, Francia CM, et al. Salvage stereotactic body radiotherapy for isolated lymph node recurrent prostate cancer: single institution series of 94 consecutive patients and 124 lymph nodes. Clin Genitourin Cancer 2017;15:e623–32.
[39] Fairchild A, Collette L, Hurkmans CW, Baumert B, Weber DC, Gulyban A, et al. Do results of the EORTC dummy run predict quality of radiotherapy delivered within multicentre clinical trials? Eur J Cancer 2012;48:3232–9.
[40] Coskun M, Straube W, Hurkmans CW, Melidis C, de Haan PF, Villà S, et al. Quality assurance of radiotherapy in the ongoing EORTC 22042–26042 trial for atypical and malignant meningioma: results from the dummy runs and prospective individual case Reviews. Radiat Oncol 2013;8.