Advances in Radiation Oncology (2024) 9, 101379

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Pretrial Quality Assurance for Hypofractionated Salvage Radiation Therapy After Prostatectomy in the Multi-Institutional PERYTON-trial

Floor H.E. Staal, MD,[a,1,*] Kelvin Ng Wei Siang, PhD,[a,1] Charlotte L. Brouwer, PhD,[a] Jorinde Janssen, MD,[a] Tom C.G. Budiharto, PhD,[b] Dorien M.A.D. Haverkort, MD,[c] Birgit Hollmann, MD,[d] Inge Jacobs, MD,[e] Marianne A.A. De Jong, MD,[f] Mariska A.E. van de Sande, MD,[g] Ben G.L. Vanneste, MD, PhD,[h] Igle Jan De Jong, MD, PhD,[i] J. Fred Verzijlbergen, MD, PhD,[j] Johannes A. Langendijk, MD, PhD,[a] Robert Jan Smeenk, PhD,[k] and Shafak Aluwini, PhD[a]

[a]Department of Radiation Oncology, University Medical Centre Groningen, Groningen, The Netherlands; [b]Department of Radiation Oncology, Catharina Hospital, Eindhoven, The Netherlands; [c]Radiotherapiegroep Arnhem/Deventer, Arnhem, The Netherlands; [d]Department of Radiation Oncology, HAGA Ziekenhuis, Den Haag, The Netherlands; [e]Zuidwest Radiotherapy Institute Vlissingen/Roosendaal, Vlissingen, The Netherlands; [f]Radiotherapy Institute Friesland, Leeuwarden, The Netherlands; [g]Institute Verbeeten, Tilburg, The Netherlands; [h]Department of Radiation Oncology, MAASTRO Clinic, GROW—School for Oncology and Developmental Biology, Maastricht, The Netherlands; [i]Department of Urology, University Medical Centre Groningen, Groningen, The Netherlands; [j]Department of Nuclear Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands; and [k]Department of Radiation Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands

Received 19 April 2023; accepted 12 September 2023

Purpose: The PERYTON trial is a multicenter randomized controlled trial that will investigate whether the treatment outcome of salvage external beam radiation therapy (sEBRT) will be improved with hypofractionated radiation therapy. A pretrial quality assurance (QA) program was undertaken to ensure protocol compliance within the PERYTON trial and to assess variation in sEBRT treatment protocols between the participating centers.

Methods and Materials: Completion of the QA program was mandatory for each participating center (N = 8) to start patient inclusion. The pretrial QA program included (1) a questionnaire on the center-specific sEBRT protocol, (2) a delineation exercise of the clinical target volume (CTV) and organs at risk, and (3) a treatment planning exercise. All contours were analyzed using the pairwise dice similarity coefficient (DSC) and the 50th and 95th percentile Hausdorff distance (HD50 and HD95, respectively). The submitted treatment plans were reviewed for protocol compliance.

Results: The results of the questionnaire showed that high-quality, state-of-the-art radiation therapy techniques were used in the participating centers and identified variations of the sEBRT protocols used concerning the position verification and preparation techniques. The submitted CTVs showed significant variation, with a range in volume of 29 cm^3 to 167 cm^3, a mean pairwise DSC of

Sources of support: The PERYTON trial is sponsored by the Dutch Cancer Society (KWF Kanker Bestrijding grant no. 12649).

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

[1] F.H.E.S. and K.N.W.S. contributed equally to this work.

*Corresponding author: Floor H.E. Staal, MD; E-mail: f.h.e.staal@umcg.nl

https://doi.org/10.1016/j.adro.2023.101379

0.52, and a mean HD50 and HD95 of 2.3 mm and 24.4 mm, respectively. Only in 1 center the treatment plan required adaptation before meeting all constraints of the PERYTON protocol.

Conclusions: The pretrial QA of the PERYTON trial demonstrated that high-quality, but variable, radiation techniques were used in the 8 participating centers. The treatment planning exercise confirmed that the dose constraints of the PERYTON protocol were feasible for all participating centers. The observed variation in CTV delineation led to agreement on a new (image-based) delineation guideline to be used by all participating centers within the PERYTON trial.

Introduction

Salvage external beam radiation therapy (sEBRT) is an established treatment option for patients with a biochemical recurrence after radical prostatectomy. Nevertheless, the 5-year biochemical progression-free survival rate is approximately 60%.[1,2] The PERYTON trial (ClinicalTrials.gov identifier: NCT04642027), a phase 3 randomized controlled trial (RCT), will investigate the potential benefit of a hypofractionated post-prostatectomy sEBRT schedule of 20 × 3 Gy compared with the standard of 35 × 2 Gy. Detailed protocol information is already published.[3]

Protocol variations within an RCT are proven to negatively affect patients' clinical outcome, and pretrial quality assurance (QA) programs have been shown to be an excellent tool to guarantee a high level of protocol compliance within a multicenter RCT.[4-6] Additionally, the PERYTON protocol describes tight dose constraints based on state-of-the-art radiation therapy. Such constraints should be assessed for feasibility in all participating centers (as a condition to start patient inclusion) to ensure safe, high-quality treatment plans.[3]

For these reasons, a pretrial QA program of the PERYTON trial was undertaken with the aim to ensure protocol compliance and reliability of radiation treatment at all steps of the trial and uniform treatment techniques across the participating centers.

Materials and Methods

Completion of the QA program was mandatory for each center before starting the inclusion of patients. The QA program evaluated multiple elements of sEBRT using the following 3 steps:

1. A questionnaire on the current (pretrial) center-specific radiation therapy sEBRT treatment protocol
2. A delineation benchmark exercise for organs at risk (OARs) and clinical target volume (CTV)
3. A treatment-planning benchmark exercise

Questionnaire

The questionnaire was designed to detect interinstitutional treatment variation in sEBRT and consisted of 20 questions on the current (pretrial) local sEBRT treatment protocols used within each participating center (N = 9) (Appendix E1).

Delineation benchmark exercise

All centers received an identical anonymized planning computed tomography (CT) scan of a postprostatectomy patient eligible for the PERYTON trial. The CT-scan was downloaded in DICOM format from a central server by the participating institutions and loaded into their local delineation systems. Centers were instructed to delineate the CTV according to their locally used delineation guideline, because the PERYTON protocol allows all published guidelines for CTV delineation.[7-11] OARs were delineated in compliance with the PERYTON protocol.[3] The received contours were compared based on volume and analyzed using the Dice similarity coefficient (DSC) and the 50th and 95th percentile Hausdorff distance (HD50 and HD95, respectively) for all observer pairs. The DSC, defined as the volume of the union of the compared contours normalized by the average of the 2 volumes, ranges from 0 to 1; a value of 0 indicates no overlap, and a value of 1 means that the contours are perfectly matched. The HD50 and HD95 are the percentiles obtained from the distribution of shortest distances between 2 contours using all contour points; a smaller HD value signifies more similar contours.

Planning benchmark exercise

For the treatment-planning exercise, centers were provided with an identical predelineated planning CT scan of a patient eligible for the PERYTON trial. The CT scan was downloaded in DICOM format from a central server and loaded into each participating institution's local treatment planning system. The OARs were predelineated as per PERYTON protocol and the CTV was predelineated according to the guideline of the Genitourinary Radiation Oncologists of Canada (GUROC).[3,9] Centers were asked to generate a treatment plan for the hypofractionated treatment arm in accordance with the PERYTON protocol, using a planning target volume (PTV) margin according to their local protocol (Table 1).[3] Submitted treatment plans

Table 1 Overview of the PERYTON trial protocol dose constraints per treatment arm

Target / Organ	Arm 1 (35 × 2 Gy)	Arm 2 (20 × 3 Gy)
CTV	V95 ≥ 100%	V95 ≥ 100%
PTV	V95 ≥ 99%	V95 ≥ 99%
Rectum	V70 < 5%	V60 < 5%
	< 15%	V55 <15%
Rectal wall	V30 < 80%	V25 < 80%
	V41 < 50%	V35 < 50%
	V60 < 25%	V50 < 25%
	D_{mean} < 30 Gy	D_{mean} < 25 Gy
Anus	D_{mean} < 25 Gy	D_{mean} < 22 Gy
Anal wall	V30 < 30%	V25 < 30%
Bladder	$Dose_{0.1cc}$ < 105%	$Dose_{0.1cc}$ < 105%
	V70 < 25%	V60 < 25%
	V60 < 50%	V50 < 50%
Femoral head	V55 < 10%	V45 < 10%
Penile bulb	ALARA	ALARA

Abbreviations: ALARA = as low as reasonably achievable; CTV = clinical target volume; PTV = planning target volume; Vx = volume receiving *x* dose.

were reviewed for protocol variations, of which minor protocol variations were accepted and major variations required resubmission. Variations exceeding ≤5% the PERYTON protocol OAR dose constraints were considered minor, and only rectal volumes exceeding the protocol by >5% were considered major (Table 1). Variation in PTV coverage was accepted if it was necessary to meet the OAR constraints, provided that at least 95% of the PTV should receive 95% of the prescribed dose.[3]

Results

Questionnaire

All 9 participating centers (of 18 Dutch radiation therapy centers) responded to the questionnaire. Three centers used, as the standard of care, moderately hypofractionated sEBRT (28-30 × 2.25-2.5 Gy). Five centers used the conventional treatment schedule of the PERYTON trial (35 × 2 Gy), and 1 center used 36 × 2 Gy. For delineation of the CTV, centers used 3 different guidelines: (1) the guidelines of the European Organization for the Research and Treatment of Cancer (EORTC) (4 centers), (2) the guidelines of the Radiation Therapy Oncology Group (RTOG) (4 centers), and (3) the CTV definition from GUROC (1 center).[7-9] All answers are summarized in Table 2.

A variety of patient preparation methods were used. Two centers used an endorectal balloon, of which 1 used bisacodyl, 10 mg, for rectal preparation. Two centers placed markers in the prostate bed before treatment. The applied CTV-PTV margins varied from 5 to 10 mm. Eight centers used volumetric-modulated arc therapy as the treatment-planning technique, and 1 used intensity

Table 2 Outcomes of the questionnaire concerning the treatment protocols for salvage radiation therapy

Variable	Centers, No.	Variable	Centers, No.	Variable	Centers, No.
Patients/y, No.		CTV guideline		PTV margin, mm	
10-20	1	EORTC	4	5	1
20-40	3	RTOG	4	7	2
>40	5	GUROC	1	9	1
Follow-up		Positioning		10	5
3 mo	1	Knee support	9	Planning technique	
1 y	1	Foot lock	3	VMAT	8
3 y	1	Mattress	0	IMRT	1
5 y	6	Head support	3	Verification technique	
Planning imaging		Preparation		Online	6
CT	9	Markers	2	Offline	3
MRI, dedicated	4	Rectal balloon	2	Registration	
-		Bisacodyl, 10 mg	1	Surgical clips	3
-		Full bladder	9	Bony anatomy	6

Abbreviations: CT = computed tomography; CTV = clinical target volume; EORTC = European Organization for the Research and Treatment of Cancer; GUROC = Genitourinary Radiation Oncologists of Canada; IMRT = intensity modulated radiation therapy; MRI = magnetic resonance imaging; PTV = planning target volume; RTOG = Radiation Therapy Oncology Group; VMAT = volumetric-modulated arc therapy.

Color	Volume (cm3)	Guideline
Red	167	GUROC
Yellow	149	RTOG
Orange	137	RTOG
Light blue	69	EORTC
Dark blue	69	EORTC
Pink	34	EORTC
Green	32	RTOG
Purple	29	EORTC

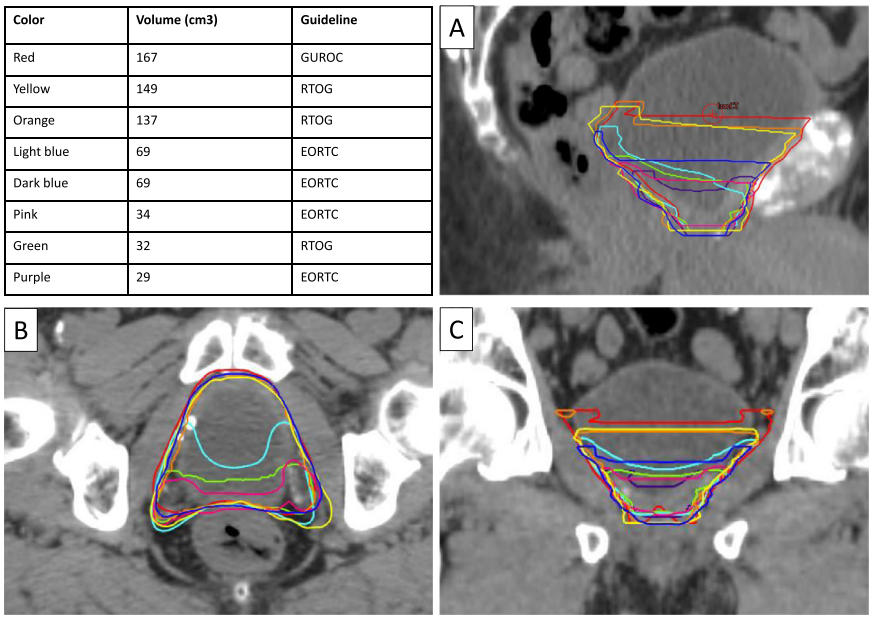

Figure 1 All submitted clinical target volume contours in the delineation exercise. Each color represents a participating center in the (A) sagittal plane, (B) axial plane, and (C) coronal plane.

modulated radiation therapy. Three different treatment-planning systems were used: 2 centers used Pinnacle (Philips), 4 used RayStation (RaySearch Laboratories), and 3 used Eclipse (Varian). In 4 centers, position verification was carried out using online verification with daily cone beam computed tomography (CBCT). Two centers performed CBCT only during the first week and before the first fraction of every week. Offline verification protocols using CBCT, 2D kilovoltage (kV), or megavoltage (MV) imaging were used by 3 centers. All centers indicated that they conduct QA procedures for treatment planning on a randomized basis.

Delineation benchmark exercise

All inclusion centers (n = 8) completed the delineation benchmark exercise; the submitted contours are depicted in Fig. 1. The volumes of the CTV ranged from 29 cm^3 to 167 cm^3, with the largest variation shown in the superior boundary (Fig. 1). The CTV volumes delineated according to the EORTC guideline (4 centers) ranged from 29 cm^3 to 69 cm^3, whereas the CTV volumes delineated according to the RTOG guideline (3 centers) had a wider range (32 cm^3 to 148 cm^3).[7,8] All CTV contours resulted in a mean pairwise DSC of 0.52 (median, 0.52; range, 0.27-0.89) and a mean HD95 and HD50 value of 24.4 mm and 2.3 mm, respectively, indicating low agreement in the delineation of the CTV.

All centers delineated the OARs according to the PERYTON protocol, and the delineation of the rectum and bladder did not show any systematic variation, resulting in an average pairwise DSC of 0.85 and 0.96, respectively (Fig. 2). The pretrial QA delineation results were presented and discussed with the participating centers during a consensus meeting, and all centers agreed on the need for a new, unambiguous, and consistent definition of the CTV.

Treatment-planning benchmark exercise

All 8 inclusion centers completed the treatment-planning exercise. All treatment plans met both the PTV and CTV coverage constraints. Seven treatment plans met all dose constraints of the OARs, of which 5 reported (acceptable) minor protocol variations of rectal and bladder constraints (Fig. 3). One treatment plan showed a major protocol variation exceeding the rectal-wall dose constraint by 6.25% (V50 <25%) and a PTV coverage of 99% of the prescribed dose. The dose-volume histograms for rectum and bladder for all treatment plans are presented in Fig. 4. A plan adaptation with lower PTV coverage (according to protocol) was advised, and the resubmitted plan was according to protocol, with a PTV coverage of 98%.[3]

Discussion

The pretrial QA of the PERYTON trial demonstrated that the dose constraints of the PERYTON protocol are feasible and clinically applicable in all centers. Despite that the participating centers were not familiar with the

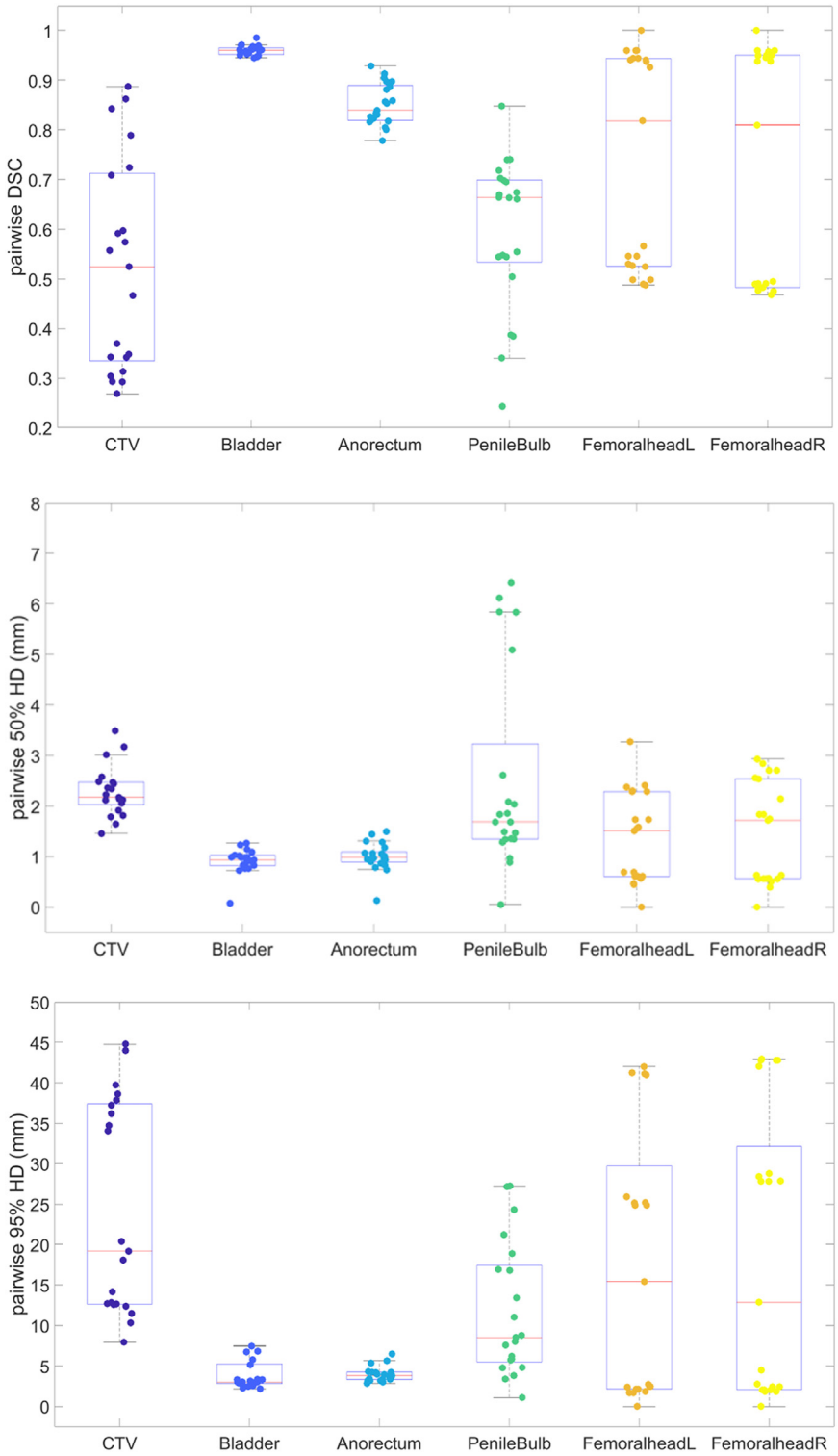

Figure 2 Box-and-whisker plot of the mean pairwise dice similarity coefficient (DSC), pairwise 50% Hausdorff distance (HD), and 95% HD of the submitted clinical target volumes (CTVs) and organs at risk.

use of the tight PERYTON dose constraints, all centers were able to meet the PERYTON protocol. Furthermore, the QA identified variable but high-quality and state-of-the-art radiation therapy infrastructures, treatment-planning systems, and verification protocols in each participating center. However, significant variability in the delineation of the CTV was found, with a wide range in volume of 29 cm^3 to 167 cm^3.

The current PERYTON trial protocol allows all published CTV delineation guidelines for sEBRT, because the

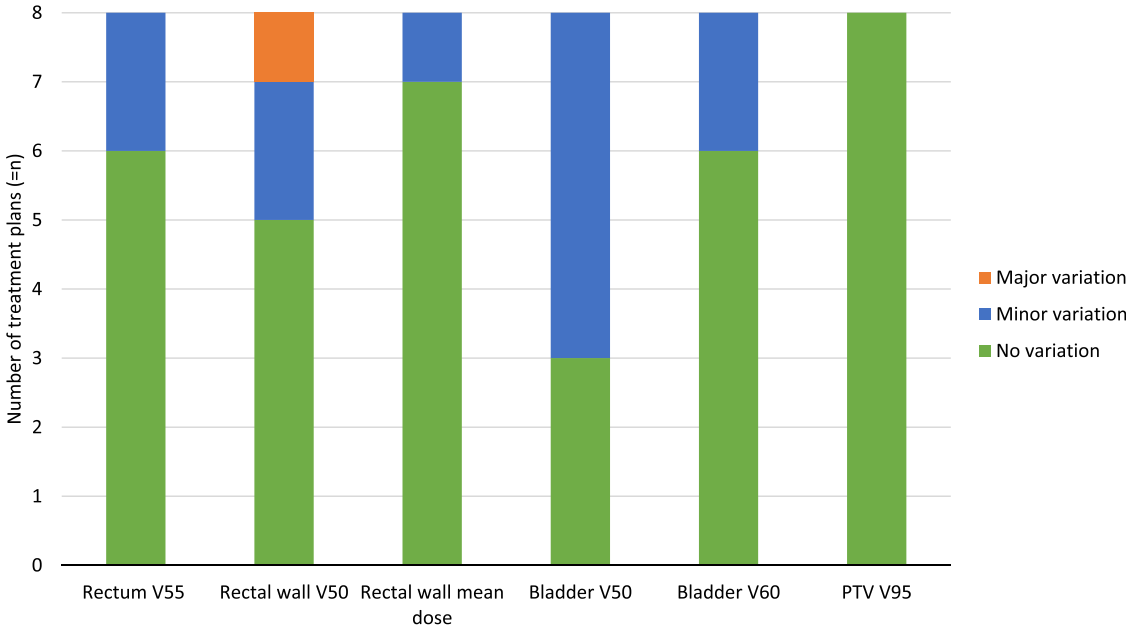

Figure 3 Number of protocol variations within the 8 submitted treatment plans.

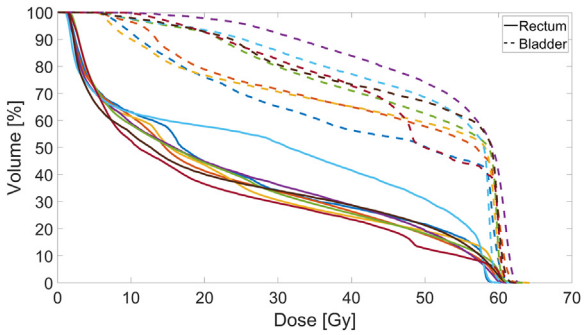

Figure 4 Dose-volume histograms for rectum (solid) and bladder (dashed) for all centers. Each color represents a participating center.

study is performed in different centers using different delineation guidelines. However, these guidelines have important differences in the definition of the boundaries of the CTV.[7-13] Studies evaluating these delineation guidelines reported major intraobserver and interobserver variability, which points out the difficulty in interpretation of the per-guideline prescribed anatomic landscape.[14-16] These variabilities are underlined in our observed interobserver differences in the delineation of the CTV. Because major deviations in CTV delineation may lead to a higher risk of toxicity, it is of high importance to use a consequent, uniform, and imaging-based delineation guideline for the CTV, especially in the framework of conducting an RCT.[16,17] Therefore, for upcoming clinical trials focusing on postprostatectomy sEBRT, it is advisable to consider adopting a single comprehensive CTV guideline.

Acceptance of all existing delineation guidelines could be a shortcoming of the PERYTON trial, but is also a practical consideration fitting to Dutch clinical practice. Moreover, the obligation of only 1 specific guideline within the study does not guarantee a uniform CTV delineation; our results reported significant interobserver variation with the use of the same guideline (in 2 different centers). This issue was also demonstrated in the postinclusion QA of the SAKK 09/10 trial, with a protocol deviation in 48.8% of cases (using only the EORTC guideline for CTV delineation).[16,17]

To improve consistency in CTV delineation in the PERYTON study, a new and consequent (based on prostate-specific membrane antigen positron emission tomography / CT scan) CTV definition (the PERYTON delineation guideline) has been developed and will be implemented and submitted for publication soon.

Because of its multicentric design, the PERYTON trial aims to treat patients with prostate cancer on different types of linear accelerators available in the Netherlands with different position verification equipment. Therefore, the study protocol allows a small range in CTV-PTV margins (5-8 mm).[3] As we strive for uniformity of all elements of the sEBRT treatment within the PERYTON trial, the PTV margin range is a subject of research at this moment.

The results of the questionnaire highlighted some gaps in our current knowledge about the use of preparation in postprostatectomy sEBRT. All participating centers used almost identical bladder preparation protocols, whereas rectal preparation methods (the use of diet, laxation, or endorectal balloons) varied. Data on rectal preparation

methods in the postprostatectomy setting is sparsely reported with different results, which is why all rectal preparation methods are allowed within the PERYTON trial.[18,19] The verification protocols used in the participating centers were, as expected, variable and depended on the available equipment. In all centers, advanced, state-of-the-art verification protocols are in use.

A shortcoming of this study was that only 1 clinical case was used, which might not reflect the range of clinical practice in patients with different anatomic and pathologic features. In view of workload, the use of 1 representative clinical case was requested by the participating centers. To continuously improve the protocol adherence within the PERYTON trial, a prospective individual case review will be performed after including the first 20 patients per center during the inclusion period.

Conclusion

The pretrial QA of the PERYTON trial demonstrated the high feasibility of the dose constraints in the PERYTON protocol and showed that high-quality treatment techniques are in use in each participating center. Our results identified a significant variability in the delineation of the CTV. The implementation of the new CTV delineation guideline as soon as possible is expected to improve the consistency in delineation. The ongoing QA program will ensure continued protocol compliance during the PERYTON trial.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101379.

References

1. Abdollah F, Suardi N, Cozzarini C, et al. Selecting the optimal candidate for adjuvant radiotherapy after radical prostatectomy for prostate cancer: A long-term survival analysis. *Eur Urol*. 2013;63:998-1008.
2. Zattoni F, Heidegger I, Kasivisvanathan V, et al. Radiation therapy after radical prostatectomy: What has changed over time? *Front Surg*. 2021;8: 691473.
3. Staal FHE, Janssen J, Brouwer CL, et al. Phase III randomised controlled trial on PSMA PET/CT guided hypofractionated salvage prostate bed radiotherapy of biochemical failure after radical prostatectomy for prostate cancer (PERYTON-trial): Study protocol. *BMC Cancer*. 2022;22:416.
4. Marcello M, Ebert MA, Haworth A, et al. Association between measures of treatment quality and disease progression in prostate cancer radiotherapy: An exploratory analysis from the TROG 03.04 RADAR trial. *J Med Imaging Radiat Oncol*. 2018;62:248-255.
5. Grant W, Hurkmans CW, Poortmans PM, et al. Quality assurance standards drive improvements in the profile of radiation therapy departments participating in trials of the EORTC Radiation Oncology Group. *Radiother Oncol*. 2014;112:376-380.
6. Kearvell R, Haworth A, Ebert MA, et al. Quality improvements in prostate radiotherapy: Outcomes and impact of comprehensive quality assurance during the TROG 03.04 "RADAR" trial. *J Med Imaging Radiat Oncol*. 2013;57:247-257.
7. Poortmans P, Bossi A, Vandeputte K, 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;84:121-127.
8. Michalski JM, Lawton C, El Naqa I, 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;76:361-368.
9. Wiltshire KL, Brock KK, Haider MA, et al. Anatomic boundaries of the clinical target volume (prostate bed) after radical prostatectomy. *Int J Radiat Oncol Biol Phys*. 2007;69:1090-1099.
10. Robin S, Jolicoeur M, Palumbo S, 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;109:1243-1253.
11. Sidhom MA, Kneebone AB, Lehman M, et al. Post-prostatectomy radiation therapy: Consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. *Radiother Oncol*. 2008;88:10-19.
12. Latorzeff I, Sargos P, Loos G, Supiot S, Guerif S, Carrie C. Delineation of the prostate bed: The "invisible target" is still an issue? *Front Oncol*. 2017;7:108.
13. Malone S, Croke J, Roustan-Delatour N, et al. Postoperative radiotherapy for prostate cancer: A comparison of four consensus guidelines and dosimetric evaluation of 3D-CRT versus tomotherapy IMRT. *Int J Radiat Oncol Biol Phys*. 2012;84:725-732.
14. Ost P DMG, Vercauteren T, De Gersem W, et al. Delineation of the postprostatectomy prostate bed using computed tomography: Interobserver variability following the EORTC delineation guidelines. *Int J Radiat Oncol Biol Phys*. 2011;81:e143-e149.
15. Symon Z, Tsvang L, Wygoda M, et al. An interobserver study of prostatic fossa clinical target volume delineation in clinical practice: Are regions of recurrence adequately targeted? *Am J Clin Oncol*. 2011;34:145-149.
16. Sassowsky M, Gut P, Holscher T, 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;87:534-541.
17. Beck M, Sassowsky M, Schar S, et al. Adherence to contouring and treatment planning requirements within a multicentric trial: Results of the quality assurance of the SAKK 09/10 trial. *Int J Radiat Oncol Biol Phys*. 2022;113:80-91.
18. Smeenk RJ, van Lin EN, van Kollenburg P, McColl GM, Kunze-Busch M, Kaanders JH. Endorectal balloon reduces anorectal doses in post-prostatectomy intensity-modulated radiotherapy. *Radiother Oncol*. 2011;101:465-470.