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Original Article

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Abstract

Aims: Quality assurance in radiotherapy (QART) is essential to ensure the scientific integrity of a clinical trial. This paper reports the findings of the retrospective QART assessment for all centres that participated in PORTEC-3; a randomised controlled trial that compared pelvic radiotherapy with concurrent chemo-radiotherapy to the pelvis followed by adjuvant chemotherapy. The trial showed an overall survival benefit for the addition of the chemotherapy in the management of women with high-risk endometrial cancer.

Materials and methods: Clinicians were invited to upload a randomly selected case/s treated at each of the participating sites. Panel reviewers analysed the contours to certify that the target volumes and organ at risk structures were contoured according to guidelines. The results were categorised into acceptable, minor variation, major variation or unevaluable. The radiotherapy plans were dosimetrically evaluated using the well-established Trans-Tasman Radiation Oncology Group (TROG) protocol.

Results: Between August 2010 and January 2018, data from 146 patients of 686 consecutively treated patients were retrospectively reviewed. All 16 Australia and New Zealand and 71 of 77 international centres uploaded data for evaluation. In total, 3514 dosimetric and contour variables were reviewed. Of these, 3136 variables were deemed acceptable (89.2%), with 335 minor (9.6%) and 43 major variations (1.2%). Major contour variations included the clinical target volume vaginal vault, clinical target volume parametria and differential planning target volume vault expansion.

Conclusion: The results of the QART assessment confirmed high uniformity and low rates of both minor and major deviations in contouring and dosimetry in all sites. This supports the safe introduction of the PORTEC-3 treatment protocol into routine clinical practice.

Key words: PORTEC-3; Quality assurance in radiotherapy

Introduction

Quality assurance in radiotherapy (QART) is important for the design, interpretation and reliability of a randomised

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trial. It ensures that potentially practice-changing results are regarded as robust and generalisable. The importance of protocol compliance has increased in the current era of combined modality, multi-institutional phase III trials. Prior findings highlighting the impact of poor compliance on the trial outcomes [1–3] have necessitated the development of quality assurance protocols to assess both individual and centre compliance in the target volume contours and planning of the radiotherapy treatment.

The PORTEC-3 randomised intergroup phase III trial showed significant improvement in 5-year overall survival (adjusted hazard ratio 0.70, 95% confidence interval 0.51–0.97, $P = 0.034$) and failure-free survival (adjusted hazard ratio 0.70, 95% confidence interval 0.52–0.94, $P = 0.016$) with chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer [4,5].

The PORTEC-3 trial stipulated that the radiotherapy contouring and planning should follow the guidelines published by the Radiation Therapy Oncology Group (RTOG) as a consensus document [6]. Treatment could be delivered using three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy if available. It assumed that all centres participating in this trial had already implemented practices that conformed to the consensus guidelines, so a definitive international quality assurance programme did not form part of the initial trial protocol. However, as Australia and New Zealand (ANZ) centres had yet to adopt these guidelines universally, the ANZ group, together with the Trans-Tasman Radiation Oncology Group (TROG), developed their own protocol to ensure compliance [7]. The success of this programme led to this protocol being adopted for all international centres as a retrospective (post-treatment) review.

This paper reports the findings of the benchmarking and retrospective radiotherapy quality assurance for all centres that participated in PORTEC-3, aiming to reinforce the knowledge and importance of QART in an era of modern, complex, and precise radiotherapy techniques in both routine practice and clinical trials.

Materials and Methods

To facilitate high-quality radiotherapy techniques for ANZ centres, TROG introduced QART to benchmark volumetric contours and assess post-treatment dosimetry and contour compliance. The post-treatment evaluation process was subsequently adopted for all other international participating sites. Details of the variables have been previously reported and are summarised in Table 1 [7].

The QART programme for PORTEC-3 was conducted in two parts. The first (benchmarking exercise and post-treatment quality assurance) was only for sites in ANZ; the second (post-treatment quality assurance) was for all other international sites.

A qualitative analysis was undertaken whereby a TROG panel reviewed the ANZ benchmarking and all participating sites' post-treatment data using the SWAN system provided by TROG [8]. The TROG panel included five radiation oncologists, nine radiation therapists and one medical physicist. Each contour and dosimetric review was carried out by a multidisciplinary team of one radiation oncologist and one radiation therapist or physicist.

The panel radiation oncologists analysed the contours to certify that the target volumes and organ at risk (OAR) structures were contoured according to guidelines. In the ANZ benchmarking exercise, if a radiation oncologist was found to have three or more major variations, they were requested to submit their first recruited patient to the trial for a 'real-time review', i.e. assessment prior to the patient starting treatment.

The dosimetric panel (radiation therapist and physicist) reviewed each plan to ensure that the appropriate dose constraints were met for the target volume and OAR, as well as ensuring that the overall treatment time was within the trial's specification.

Results were categorised into acceptable, minor variation or major variation. The post-treatment plans were dosimetrically evaluated using the well-established TROG protocol (Supplementary Table S1) [8,9].

Australia and New Zealand

As part of the ANZ appendix to the PORTEC-3 protocol, all radiation oncologists who were planning to enrol and treat patients on this study were required to undertake a benchmarking exercise prior to starting recruitment. For post-treatment quality assurance, a sampling protocol was designed to include the first five patients enrolled in the trial at each site, to be followed by the next one-in-three randomly selected patients.

The contouring variables evaluated for both the benchmarking and the post-treatment quality assurance were identical and were selected from the guidelines in the trial protocol. Although these variables have not been externally validated, they were extensively reviewed by the TROG ANZ Trial Management Committee (TMC) and subsequently by the international principal investigator and deemed appropriate for this type of assessment. It is acknowledged that in 2021 these criteria would be more comprehensive and detailed, as recognition of the importance of QART in trials has increased, unlike in 2008.

The TROG TMC elected to use the RTOG Consensus Guidelines [6] as the framework for assessment. The decision to determine a major versus minor variation was made based on the reference guideline parameters. A major deviation was defined as one that completely violated the guideline. Any deviation that did not meet this measure became a minor variation.

All radiation oncologists were provided with written feedback regarding the evaluation undertaken and as an aid for any changes that they wished to make when treating future patients in the trial. As the quality assurance in the trial was a post-treatment review, no change could then be instituted to improve the patient plan.

International Quality Assurance (UK, the Netherlands, Italy, Canada, France)

Following a review of the results of the benchmarking exercise and the early improvement in the post-treatment reviews from the ANZ cohort, the international TMC determined that the quality assurance protocol should be voluntarily adopted by all international sites.

The sample size selected for the ANZ cohort was felt to be onerous in the international cohort, given that the post-treatment quality assurance started after the initiation of the trial and sites were already enrolling patients. The international TMC decided that a minimum of one case per site would be required to ensure validity in this setting. Provision was made that if an international site was recruiting rapidly, a further one in five cases might be selected for quality assurance review; however, due to the time needed to obtain and evaluate a first plan, there were no additional cases evaluated in the international quality assurance assessment.

TROG invited all international sites participating in PORTEC-3 to upload a randomly selected case treated at the site to the TROG platform. All plans were uploaded using DICOM-RT and additional information regarding the surgery and pathology for each case was also requested. If the original reports were not in the preferred language (English), then the PORTEC-3 trial forms were used for reference. The same variables and dosimetric evaluation used to assess the ANZ patients were adopted for all international sites. As for the ANZ radiation oncologists, written feedback was provided regarding the evaluation undertaken, noting that no correction could be undertaken as this was a post-treatment review.

As part of the wider PORTEC-3 trial, written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society and the ethics committees of the participating groups or centres. Participating groups obtained their institutional review board and ethics approvals and were funded by separate grants.

Results

A retrospective quality assurance analysis was conducted between August 2010 and January 2018, when the data from 146 of 686 consecutively treated patients were reviewed.

All 16 ANZ centres and 71 of the 77 participating international centres complied and uploaded their data to TROG for evaluation by the reviewers' panel. Six international centres did not submit any data.

In total, 3514 dosimetric and contours variables were reviewed by the panel. Of these, 3136 variables were deemed acceptable (89.2%), 335 had minor variations (9.6%) and 43 had major variations (1.2%). The results of the key dosimetry reviews are detailed here and summarised in Figure 1 (see Supplementary Tables S2, S3).

Figure 1 illustrates the key dosimetric review for both the ANZ and international cohorts. Within the ANZ cohort, we examined a total of 605 variables. Of these, 578 variables (95.6%) were acceptable, 22 variables were categorised as minor variations (3.6%) and five variables as major variations (0.8%). Within the international cohort, we examined a total of 741 variables. Of these, 710 variables (95.8%) were acceptable, 24 variables were categorised as minor variations (3.2%) and seven variables as major variations (1%). Those variables not shown included beam energy, prescribed dose and OARs including spinal cord and kidney.

In total, 2168 contour variables were examined by the panel reviewers. Of these, 1848 variables were deemed acceptable (85.2%), 289 were categorised as minor variations (13.3%) and 31 as major variations (1.4%).

Table 1
Description of major and minor variations for benchmarking and post-treatment evaluation

Variation	Structure	Description
Major	Lymph nodes	CTV extends significantly (>0.5 cm) into bone
		Missing an iliac vessel group
		CTV as contoured included entire muscle or whole bowel loop prior to PTV expansion
	Parametrium	Not contoured
	Vaginal vault	Not contoured
	CTV	Not contoured
		Extends significantly into bone (>0.5 cm)
		>3 cm from common iliac bifurcation
	PTV	No volume created
		Expansion of lymph nodes >1 cm or differential too large
Minor	Lymph nodes	Inadequate margins on vessels
		External iliac nodes contoured beyond pelvis
		CTV partially into muscle (<0.5 cm); or partial voluming of bowel
		CTV as contoured was not edited to exclude bone (<0.5 cm) prior to PTV expansion
		Missing obturator strip
		No pre-sacral nodal volume marked with positive pathological cervical stromal involvement
	Parametrium	CTV does not reach pelvic sidewall
		CTV extends <1 cm superior of vagina
	Vaginal vault	CTV covers more than three-quarters of vagina
		CTV covers less than a quarter of vagina
	CTV	Upper level >2 cm superior to the most superior part of S1 body
	PTV	Differential vault PTV margin not used
		Expansion (other than vault) is <0.7 cm or >1.0 cm

CTV, clinical target volume; PTV, planning target volume.

Adequate coverage of the protocol-defined clinical target volume (CTV) was one of the most difficult items to be reviewed. Figure 2 (see Supplementary Tables S4, S5) illustrates the contour reviews of the Australasian and international cohorts. Adequate coverage in the Australasian cohort was achieved in 1006 variables (90.6%), with 99 (8.9%) reported to have minor variations and five (0.5%) in the major category. Within the international cohort, acceptable coverage was achieved in 828 variables (76.8%), with 187 (17.3%) reported to have minor variations and 63 (5.8%) with major variations.

Figure 3 (Supplementary Table S6) compares the contours reviewed between the ANZ benchmarking exercise and the retrospective QART of ANZ and international sites.

In the ANZ benchmarking exercise, the minor variations noted included planning target volume (PTV) expansion margins for the vaginal vault (17/44), pelvic nodal CTV contours (11/44) and CTV parametrial contours (10/44). Major variations included CTV lymph node contours (5/12), incorrect superior CTV boundary (4/12), CTV parametrial contour (1/12), PTV nodes (1/12) and PTV expansion greater than 1 cm (1/12) [7]. When comparing the ANZ benchmarking exercise with the retrospective international contours, similar minor variations were noted in the contours of CTV nodes, CTV parametria and PTV vault differential volume expansion. In the ANZ post-treatment QART review, although an overall improvement was noted, minor variation continued to be observed with PTV vault differential volume expansion, contours of CTV nodes and CTV parametria.

Discussion

This retrospective review of QART confirmed a high uniformity of target volume contouring and dosimetry, and low rates of both minor and major deviations in centres participating in the PORTEC-3 trial.

The benchmarking exercise highlights the importance of having a quality assurance programme for a radiotherapy department. Pre-trial benchmarking allows the participating centres to assess if they have adequately comprehended the protocol and have sufficient resources in place to deliver the radiotherapy according to the trial's protocol. The PORTEC-3 benchmarking exercise improved the post-treatment QART assessment, especially in the items showing major variations. In the benchmarking Australasian exercises previously reported by Jameson *et al.* [7], a manual review of 495 individual target structures showed acceptable rate of 85%, a minor variation rate of 11.8% and a major variation rate of 3.2%. Post-treatment QART-acceptable CTV coverage was achieved in 90.6%, with 8.9% reported to have over/under CTV coverage, but only 0.5% in the major variation category.

Poortmans *et al.* [10] observed that the number of systematic protocol deviations was reduced in trial patients compared with benchmarking cases in the treatment of breast cancer, and an improved interinstitutional dose variation for individual case review than encountered on a dummy run. Treatment response can be estimated by reviewing the impact of contour variations on planning dosimetry. Peters *et al.* [1] evaluated a post-treatment review of radiotherapy plans for protocol compliance in the Tirapazamine Head and Neck trial. They found worse overall survival for patients who received suboptimal dose due to major deficiencies in contouring of gross tumour volume and/or inadequate dose coverage of the tumour. Gkika *et al.* [11] also reported recently on the impact of major deviations on long-term survival in the management of patients with inoperable non-small cell lung cancer. These patients had inferior overall survival; however, the contouring issues appear to be related to OAR delineation and dose constraints. Additionally, it was alluded that low volume centres appeared to have more major deviations compared with higher volume centres.

Despite the improvement in the major variation category in the post-treatment QART review, minor variations continued to be noted. It was an interesting observation that the benchmarking exercises did not entirely prevent the minor inconsistencies seen in the post-treatment reviews. Potential reasons for the difference include insufficient training and feedback to the participating sites, changes in the team members involved at the sites or the absence of an online real-time contour and plan review. It is also possible that this variability is related to the manual review and some inter-observer variability with the assessment. The SCOPE1 oesophageal cancer trial's quality assurance programme [12] of pre-trial and on-trial quality assurance made similar observations. The rate of major deviations declined and consistency in radiotherapy practice improved, but they too failed to eliminate minor variations. The benchmark case was able to identify a participating centre's inconsistent technique, which resulted in no more than a single major deviation for patients treated within SCOPE1. The quality assurance programme has contributed to greater consistency in oesophageal radiotherapy practice in the UK.

Okamoto *et al.* [13] noted substantial deviations in the contouring of the nodal and vaginal cuff CTV in intensity-modulated radiotherapy for gynaecological cancer. Although the guidelines they used in the protocol differ from the TROG guidelines used in PORTEC-3, they noted that deviations of CTV delineation accounted for about 50% of the total. They also found that the dummy-run is essential to ensure the quality of the study and confirm understanding of the protocol in participating institutions. Naismith *et al.* [14] noted in the CHHiP Trial that 71 of 100 outlining cases required amendment prior to treatment, leading them to comment that a pre-trial benchmarking exercise would have been beneficial. They also noted that as the centres became accustomed to the trial requirements, the number of additional reviews for major variations significantly decreased.

The results from our international post-treatment QART were remarkably similar to the Australasian benchmarking exercises and we hypothesised that if the international centres had undergone a pre-trial benchmarking quality assurance programme, we may have identified areas of the radiotherapy technique and contours that were inconsistent with the trial's protocol. Although most of the

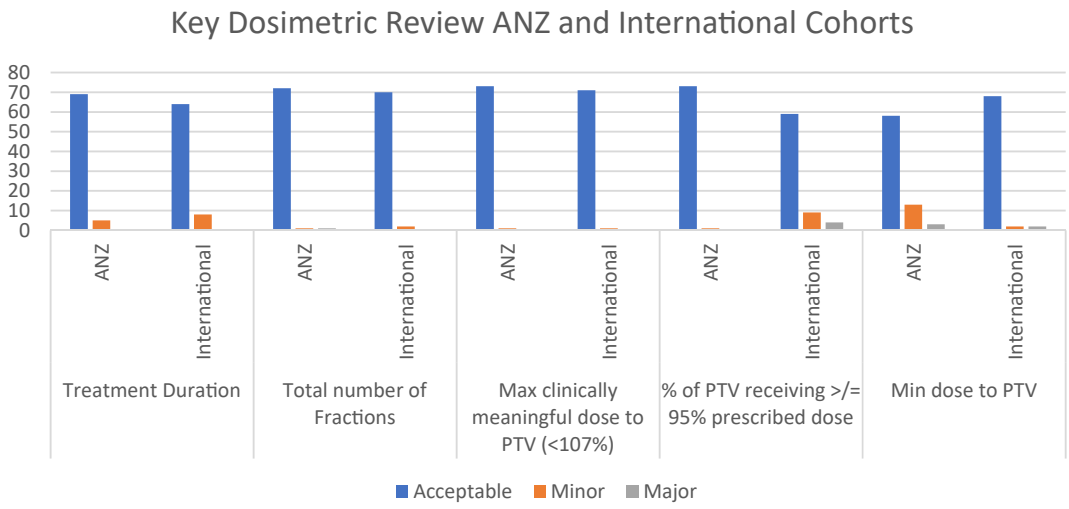

Fig 1. Key dosimetric variables.

international centres involved in PORTEC-3 had already implemented volumetric contouring according to the published protocols [6,15,16], some had only just implemented target volume contouring before participation in the trial, which may also have contributed to the variation observed. In contrast, the benchmarking review undertaken in EMBRACE II [17] displayed greater variation between clinicians, with only 41% deemed acceptable at first attempt. Forty-four per cent 'passed' after one revision, whereas 6% required two or more revisions. Of note, the variations noted by the expert reviewers also documented similar 'errors' to the ones we encountered in our review.

In the PORTEC-3 trial, most of the patients were treated using 3DCRT techniques rather than intensity-modulated radiotherapy/volumetric modulated arc therapy. We hypothesised that the minor variations noted were unlikely to have an adverse impact on planning dosimetry and, therefore, treatment outcomes. However, we acknowledge that if all patients had been treated using intensity-modulated radiotherapy/volumetric modulated arc therapy, where the potential for sculpting dose around OARs exists, there may be an effect on toxicity outcome caused by contour variations. This has been tested in the ANZ benchmarking exercise cases and detailed in Jameson *et al.*'s study [7]. Cloak *et al.* [18] undertook a similar comparison for the RAVES trial (post-prostatectomy radiotherapy). Like Jameson *et al.*'s study, they compared the benchmarking contours with a simultaneous truth and probabilistic level estimate and consensus volume. They found that variation in CTV and rectum delineation could affect dosimetric compliance with RAVES's protocol.

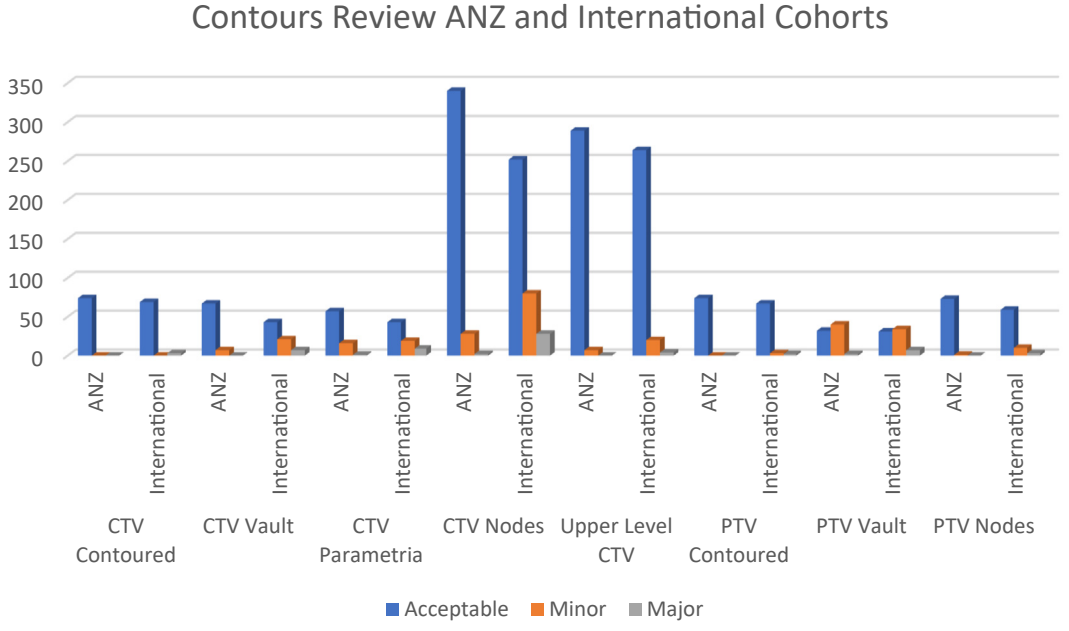

Fig 2. Review of contours.

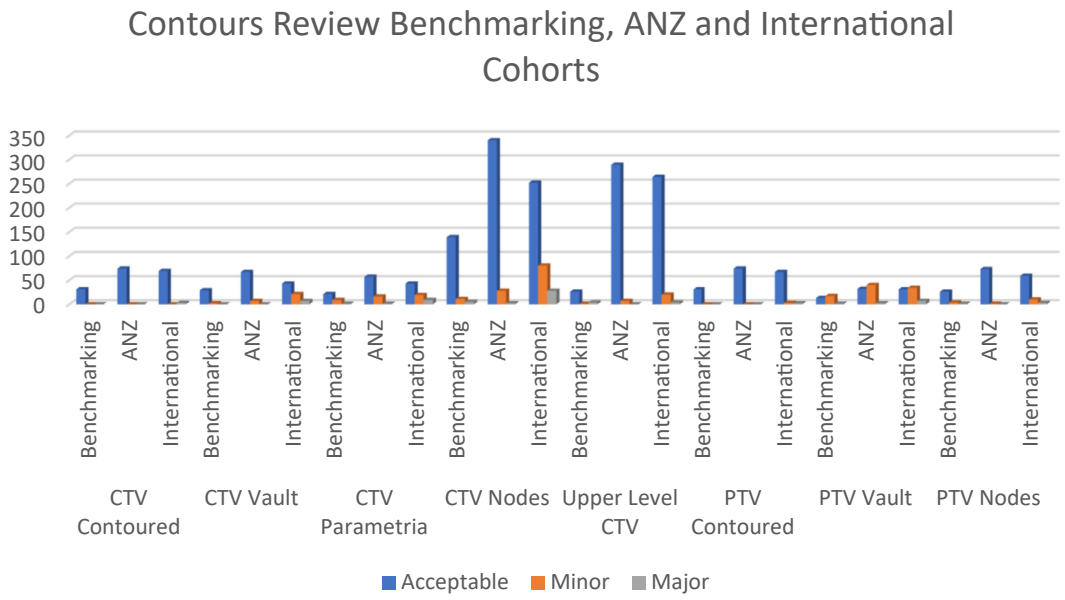

Fig 3. Comparison of contour review: Australia and New Zealand (ANZ) benchmarking, ANZ and international cohorts.

Although QART for the ANZ Gynaecologic Oncology Group cases was carried out for 74/122 patients (61%), only a limited number of cases were assessed in the international post-treatment QART (72/560 patients or 13%) due to the retrospective introduction, workload and cost limitations, which is a limitation to our review. This raises the possibility of improving QART for future trials using automated atlases [19] or algorithms that could quickly identify major contour variations and provide feedback. It would also minimise the interobserver variability noted in manual review. Studies are currently underway to develop this capacity [20].

Given the retrospective nature of the international QART, there remains the concern that, had implementation of a full QART programme been instituted from trial initiation, this would have improved the overall quality assurance of this trial. Even though no major variations were seen to affect the overall trial outcome due to predominant use of 3DCRT techniques and the voluntary nature of submission reducing overall cases available for review, future trials using intensity-modulated techniques will probably require comprehensive QART as part of their protocol due to the variations detected in trials like PORTEC-3. Trial costs will need to include this important step to ensure that the results can be considered rigorous and valid. This is supported by Sanuki *et al.* [21] who reported on the QART of a randomised trial of locally advanced oesophageal cancer. They suggested that improvement in protocol adherence and reduction of contouring variations will balance the increased cost by decreasing the exclusion loss from the analysis. Based on their QART's experience, the authors argued for a pre-trial benchmarking for all participating centres in a cooperative trial and recommended what would now be termed a 'real-time review' of most cases enrolled into a trial.

In conclusion, the results of the QART assessment confirm high uniformity and low rates of both minor and major deviations in contouring and dosimetry in international sites. This supports the safe introduction of the PORTEC-3 treatment protocol into routine clinical practice. Further improvements with the introduction of benchmarking exercises and prospective, interactive QART will improve radiotherapy quality, especially when using highly conformal intensity-modulated techniques.

Conflicts of interest

The authors declare no conflict of interest.

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These results were initially presented at IGCS 2018 in Kyoto, Japan and subsequently at the TROG 2021 ASM (virtual).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2021.11.015.

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