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Adaptive sequential plan-on-plan optimization during prostate-specific antigen response guided radiotherapy of recurrent prostate cancer

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ABSTRACT

Background: Treatment adaptation based on tumour biomarker response during radiotherapy of prostate cancer, could be used for both escalation and de-escalation of radiation doses and volumes. To execute an adaptation involving extension of treatment volumes during radiation can however be restricted by the doses already delivered. The aim of this work was to develop a treatment planning method that addresses this challenge.
Material and methods: A volumetric-modulated-arc-therapy (VMAT) planning method with sequential plan-on-plan optimization was developed for a prospective phase II trial including 100 patients on salvage radiotherapy (SRT) for prostate cancer recurrence. A treatment adaptation was performed after five weeks of SRT based on prostate-specific antigen response during this phase of the treatment. This involved extension of treatment volumes for non-responders (n = 64) to include pelvic lymph nodes and boost to ^{68}Gallium-Prostate-Specific-Membrane-Antigen-Positron-Emission-Tomography positive lesions. This method was evolved by introducing an EQD2 (equivalent dose in 2.0 Gy fractions) correction of the base plan for improved dose coverage.
Results: All dose-volume criteria for target coverage were met for the non-responders when based on physical dose. An EQD2 correction of the base plan for non-responders, implemented for the final 29 patients, led to a statistically significant improvement in dose coverage as compared to the 35 patients treated without EQD2 correction.
Conclusions: This is to our knowledge the only study presented on biomarker-guided sequential VMAT radiotherapy using a plan-on-plan technique in the pelvis. By using a biologically adapted technique an improved target coverage was achieved without compromising doses to organs at risk.

Introduction

An increase in prostate-specific antigen (PSA) during surveillance after radical prostatectomy, termed biochemical recurrence (BCR) [1,2], is an early sign of a prostate cancer relapse. Patients with BCR, where no radiological evidence of extra-prostatic tumour location is detected, are assumed to have a local recurrence and are most commonly treated with salvage radiotherapy (SRT) delivering 66–70 Gy to the prostate bed [3,4]. The expected biochemical recurrence-free survival 3–5 years after SRT is approximately 50–60% [4]. The decision to treat patients with BCR with SRT is currently based on pre-treatment clinical tumour-related factors according, for example, to the Stephenson nomogram [5]. New positron emission tomography (PET) tracers such as ^{68}Gallium-Prostate-Specific-Membrane-Antigen-HBED-CC-ligand (^{68}Ga-PSMA-11), which binds to and inhibits the prostate-specific membrane antigen (PSMA), are promising in detecting prostate cancer lesions. They have demonstrated a higher detection rate of tumour manifestations than previous tracers and could thus improve the selection of patients for curatively intended treatment with SRT extended to include regional lymph nodes and boost to local recurrence [6–10].

Previous retrospective studies have shown an association between decreasing PSA during SRT and long-term clinical control [11,12]. Based on weekly PSA measurements during prostate bed SRT, we recently confirmed these findings in a prospective clinical trial [13]. We

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showed that the change in PSA, expressed as a PSA decay constant is the single strongest factor predicting treatment outcome after SRT, already three weeks after starting SRT. Based on these results, and PSMA-PET data, we designed a new treatment schedule where the delivery of SRT was adapted based on PSA response, and on the pre-therapy PET findings. This approach allowed us to extend the treatment volumes (e.g. including regional lymph nodes) in cases of inadequate treatment response, as assessed by the change in PSA already during SRT. This is a new treatment concept that involves modification of the treatment volumes and/or RT dose levels during the SRT course. Adaptation of an on-going course of radiotherapy demands advanced treatment planning techniques. In volumetric modulated arc therapy (VMAT) [14,15], previously delivered dose distributions can be taken into account during treatment plan optimization with a "plan-on-plan" function after a change in treatment conditions [16].

In this paper we present results of such an adaptive sequential treatment planning technique for inclusion of pelvic lymph nodes (based on treatment response) in the target volume during SRT of the prostate bed.

Materials and methods

The PROPER study

The present study is part of a prospective phase II clinical trial (PROPER trial, NCT02699424). The PROPER trial is an ongoing, single-centre, open-label, phase II trial including patients with BCR after prostatectomy at a tertiary referral centre, Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden. The aim of the trial is to test personalized radiotherapy based on PSA response during SRT, and ^{68}Ga-PSMA-11 PET/CT imaging performed before commencing SRT. Patients with BCR who were eligible for SRT were invited to participate during the inclusion period March 2016 to December 2019. The study was approved by the Regional Ethics Review Board in Lund (Ref. No. 2015/431). One hundred men were included. Two withdrew their consent and were thus excluded from further analysis. Patient characteristics are presented in Supplementary Table S1. Of the 98 evaluable patients, 34 were classified as responders and received 70.0 Gy to the prostate bed only. The remaining 64 patients were classified as non-responders, all of whom received additional irradiation to the pelvic lymph nodes and to ^{68}Ga-PSMA-11 PET-positive lesions, if present. This was done with a sequential plan-on-plan optimization described below. To improve dose coverage, a biologically adaptive base plan was used for the last 29 patients.

Treatment preparation and prescription

Prior to treatment, all patients underwent ^{68}Ga-PSMA-11 PET/CT. One hour after an intravenous injection of 2,5 MBq/kg body weight (maximum 300 MBq) ^{68}Ga-PSMA-11, patients were scanned from mid-thigh to the top of the skull on a GE Discovery 690 (GE Healthcare, Milwaukee, WI, USA) with a PET acquisition time of 4 min per bed position. Uptakes not typical for normal physiological or reported unspecific uptake patterns were regarded as suspicious for malignancy [17,18]. PET findings were not included in the initial treatment plan, but instead taken into account after five weeks of SRT in cases when the patient did not respond to treatment, according to the required decrease in PSA based on weekly measurements from start of SRT. This was done to minimize the risk of treating those with false positive PET findings as PSA response would be highly unlikely in case of disease spread outside of the prostate bed [13]. Treatment planning CT was performed with intravenous contrast medium with the patient in a supine position, with the arms on the chest and the legs immobilized with Combifix^{TM}3 (CIVCO Radiotherapy, Orange City, IA, USA). The scanning volume extended from the second lumbar vertebra to 5 cm caudal of the trochanter minor with a CT slice thickness of 3 mm. All patients received written information regarding bowel preparations (start with stool bulking agents at least two weeks prior to CT simulation and continuing through the whole treatment period) and bladder preparations (empty the bladder one hour before the CT scan and before each treatment for comfortably filled bladder).

The clinical target volumes (CTVs) of the prostate bed (CTV-P_{70Gy}) (all patients) and lymph nodes (CTV-N_{50Gy}) (non-responders only) were defined according to the RTOG guidelines [19]. Gross target volume (GTV) for lymph node metastases (GTV-$Lmet_{60Gy}$) and local recurrence (GTV-T_{70Gy+}) were delineated for non-responders based on information from baseline CT and PET examinations. The corresponding CTVs, CTV-$Lmet_{60Gy}$ and CTV-T_{70Gy+}, were obtained by adding 3 mm isotropic margins to the respective GTV. Planning target volumes (PTVs) were generated by adding 10 mm isotropic margins to CTV-P_{70Gy} (PTV-P_{70Gy}), 8 mm to CTV-N_{50Gy} (PTV-N_{50Gy}), 5 mm to CTV-$Lmet_{60Gy}$ (PTV-$Lmet_{60Gy}$), and 3 mm to CTV-T_{70Gy+} (PTV-T_{70Gy+}).

Rectum, bowel bag, and bladder were defined as organs at risk (OARs). They were segmented according to the RTOG pelvic normal tissue contouring guidelines [20]. Femoral heads were defined as spherical structures.

The prescription scheme for the PROPER study is shown in Fig. 1. Initially, all patients were prescribed 70.0 Gy to the prostate bed (PTV-P_{70Gy}) in 35 fractions. After 50.0 Gy, patients were defined as responders or non-responders based on the PSA change during the first five weeks of SRT. The treatment of responders (PSA after five weeks < 0.15 ng/ml) continued according to the initial prescription (70.0 Gy to the prostate bed). Non-responders (PSA after five weeks ≥ 0.15 ng/ml) were treated with a new prescription including the initial 70.0 Gy to the prostate bed (PTV-P_{70Gy}) and an additional 50.0 Gy in 25 fractions to adjuvant lymph nodes (PTV-N_{50Gy}). In the case of lymph node metastases detected with pre-therapy PET, a simultaneously integrated boost of 60.0 Gy (PTV-$Lmet_{60Gy}$) was added in fractions of 2.4 Gy, corresponding to equivalent dose 2.0 Gy (EQD2) ($\alpha/\beta = 3.0$ Gy) of 64.0 Gy. Local recurrence (PTV-T_{70Gy+}) was treated to a total EQD2 ($\alpha/\beta = 3.0$ Gy) of 74.0–78.0 Gy. All target volumes were treated with 1 fraction/day and 5 fractions/week. PET findings in the responder group were considered false positive.

Treatment planning

The aim of this work was to demonstrate the feasibility of this new type of planning, which we call "sequential VMAT treatment planning with biologically adaptive plan-on-plan optimization". To evaluate feasibility, we used both physical and equivalent dose in 2.0 Gy fractions (EQD2) in relation to the study specific dose-constraints. We specifically analysed the robustness of the dose distribution in the inter-phase junction used in this planning method. We report treatment planning results using this technique when including pelvic lymph node irradiation in patients who do not show an adequate reduction in PSA following the delivery of SRT to the prostate bed only.

Sequential VMAT treatment planning with plan-on-plan optimization for non-responders was carried out in a three-phase process: for prostate bed (phase 1), for the prostate bed and the adjuvant lymph nodes (phase 2), and for the adjuvant lymph nodes (phase 3), (Fig. 1).

In phase 1 a plan to 50.0 Gy in 25 fractions was created for the prostate bed (PTV-P_{70Gy}). The isocentre position was placed at the centre of the most cranial PTV-P_{70Gy} slice to minimize the divergence affecting the dose plan in phase 3. The plan was normalized to the median PTV dose. A smooth, homogeneous dose distribution with a maximum dose $< 103\%$ in the cranial part of PTV-P_{70Gy} is important for the treatment planning of phase 3.

In phase 2 a plan to 20.0 Gy in 10 fractions was created to the prostate bed (PTV-P_{70Gy}) and adjuvant lymph nodes (PTV-N_{50Gy}), 24.0 Gy to lymph node metastases (PTV-$Lmet_{60Gy}$) if present, and an individualized boost in cases of local recurrence (PTV-T_{70Gy+}) (Supplementary Fig. S1). To achieve high dose conformity on the target and to spare the OARs, a maximum field size of about 15 cm in the MLC

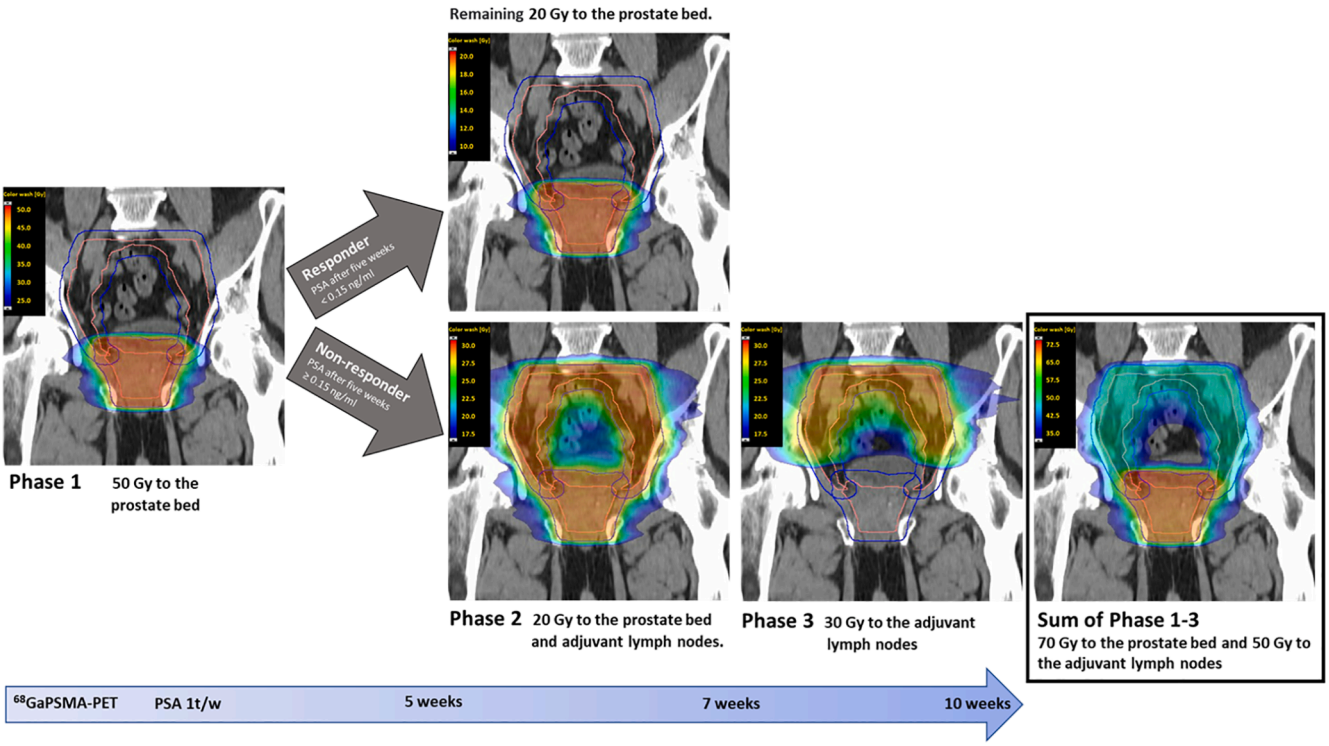

Fig. 1. Prescription scheme the PROPER trial. Computed tomography images (frontal views) showing dose distributions for phases 1–3.

direction was used due to limitations of the equipment. This was achieved by decreasing X1 for arc one to obtain a field size of 15 cm, and vice versa for X2 in arc two, where X1 and X2 are as defined in IEC 61217 [21]. The dose plan was normalized to the median PTV dose as in phase 1.

In phase 3 a plan to 30.0 Gy in 15 fractions was created to the lymph nodes (PTV-N_{50Gy}) and 36.0 Gy to lymph node metastases (PTV-$Lmet_{60Gy}$) (if any). In this phase, the Base Dose Plan function in Eclipse was applied to allow the dose from a previous plan to be accounted for during optimization. The dose plan in phase 1 served as the base plan in phase 3. The field width was decreased to about 15 cm, as in phase 2. No plan normalization was applied in phase 3 due to dose inhomogeneity arising from the plan-on-plan optimization. This process was further developed during the study by including an EQD2 correction of the dose distribution from phase 1. The physical dose distribution in phase 1 was converted to EQD2 with $\alpha/\beta = 3.0$ Gy for both tumour and normal tissues. This was performed with an inhouse software that multiplies the total physical dose in each voxel of the dose matrix with $(d + \alpha/\beta)/(2 + \alpha/\beta)$, where d is the dose per fraction in the voxel [22]. This new approach with EQD2 correction was implemented with the aim to improve dose coverage further as compared to when using a base plan with physical dose, although we consider the latter clinically acceptable fulfilling physical dose-constraints. The EQD2 approach was implemented when fully tested with patient simulations in January 2018.

The CT-based VMAT planning was carried out in Eclipse versions 13.6 and 15.6 (Varian Medical Systems, Palo Alto, CA, USA) with the anisotropic analytical algorithm versions 10.0.28 and 13.6.23, and the photon optimization algorithm versions 10.0.28 and 13.6.23.

Dose volume constraints for the summed dose distribution are presented in Table 1. Optimization volumes were generated for all OARs by excluding the OAR-PTV overlapping region with an additional 5 mm margin. Optimization and dose calculation grid sizes were 0.25 cm. The Arc Geometry Tool was used for all three plans to define a field geometry with two full arcs and a collimator rotation of five degrees. The complementary angle was used for the second arc. The same isocentre position was used in all plans. The Normal Tissue Objective was used in manual mode. Starting parameters for optimization objectives are given in Supplementary Table S2. Dose metrics for target and OARs, according to the dose volume constraints given in Table 1, were extracted with the MICE toolkit, version 0.5.1.3 (NONPI Medical AB, Sweden).

All dose plans were assessed prior to treatment with the diode-array-based Delta^4 phantom or Delta^4 phantom+ (ScandiDos, Uppsala, Sweden). The measured dose was compared with the Eclipse calculated dose using the gamma index (global, 3%/2 mm, lower cut-off 15%) [23], with a pass rate tolerance limit of 90%.

Table 1
Dose volume objectives (physical dose).

Priority	VOI	Prescribed dose (dose/fraction)	Dose/volume recommendation
1	GTV-T	78.0 Gy (2.0 + Gy)	$D_{99\%}$ ≥76.0 Gy
2	CTV-T	78.0 Gy (2.0 + Gy)	$D_{98\%}$ ≥76.0 Gy
3	PTV-T	78.0 Gy (2.0 + Gy)	$D_{98\%}$ ≥74.0 Gy
4	CTV-P	70.0 Gy (2.0 Gy)	$D_{99\%}$ ≥68.0 Gy
5	PTV-P	70.0 Gy (2.0 Gy)	$D_{98\%}$ ≥66.0 Gy
6	GTV-Lmet	60.0 Gy (2.4 Gy)	$D_{99\%}$ ≥58.0 Gy
7	CTV-Lmet	60.0 Gy (2.4 Gy)	$D_{98\%}$ ≥58.0 Gy
8	PTV-Lmet	60.0 Gy (2.4 Gy)	$D_{98\%}$ ≥57.0 Gy
9	Fixed bowel loop		V_{50Gy} <17 cm^3 $D_{2\%}$ ≤60.0 Gy
10	Rectum		V_{70Gy} <20%
11	CTV-N	50.0 Gy (2.0 Gy)	$D_{99\%}$ ≥47.5 Gy
12	Rectum		V_{75Gy} <15%
13	PTV-N	50.0 Gy (2.0 Gy)	$D_{99\%}$ ≥46.5 Gy
14	Femoral heads		D_{max} ≤55.0 Gy
15	BowelBag - PTV5mm		V_{30Gy} <300 cm^3 V_{40Gy} <150 cm^3 V_{45Gy} <100 cm^3 V_{50Gy} <35 cm^3
16	Rectum		V_{60Gy} <35%
17	BODY		D_{max} ≤82.0 Gy
18	Bladder		D_{medel} ≤62.0 Gy

Image guidance

Image guidance during treatment was based on cone-beam CT (CBCT) with automatic bone matching and manual adjustment if required. A No Action Level protocol with averaging shifts and an adaptive maximum likelihood factor of 0.75 was used for the first three fractions together with weekly imaging [24]. Action level for redefinition of the isocenter position from fraction four and onwards was 3 mm. The assessment of patient position accuracy over the whole course of treatment was based on set-up shifts from the weekly imaging in the longitudinal, lateral and vertical directions. The robustness of the dose distribution in the inter-phase junction between phase 1 and phase 3, due to patient positioning, was analysed by adjusting the longitudinal isocentre position ± 4 mm between these two plans for five patients.

Statistics

For dose-volume data analysis, comparisons between groups were done with the Wilcoxon rank sum test. The statistical softwares used were IBM SPSS Statistics Version 25 and MedCalc Statistical Software version 19.3.1.

Results

The treatment planning results for the initial 35 of the 64 patients treated without correction for fractionation effects of the base plan showed that all dose-volume criteria for target coverage were met when calculated in physical dose. When EQD2-corrected, all dose-volume criteria were still met with the exception for CTV-N_{50Gy} and PTV-N_{50Gy}. The dose coverage for these nodal volumes were slightly below the dose-volume recommendations in the area of the inter-phase junction. The median $D_{99\%}$ in the EQD2-corrected CTV-N_{50Gy} volume was 44.0 Gy EQD2 (IQR: 43.1–44.5 Gy) (Table 2 and Fig. 2a and b). The introduction of an EQD2-corrected base plan for the remaining 29 patients led to a statistically significant improvement in dose coverage ($P < 0.0001$) as compared to the patients treated without an EQD2 correction of the base plan. The median $D_{99\%}$ in the CTV-N_{50Gy} was 47.2 Gy EQD2 (IQR: 46.8–47.8 Gy). This improvement in target coverage was performed without increasing doses to the OARs (Table 2 and Fig. 2c and d).

The treatment planning data for boost volumes treated in the study are presented separately in Supplementary Table 3a (local recurrences) and Supplementary Table 3b (lymph node metastases).

The robustness test of the inter-phase junction resulted in an overdosage ($D_{2\%}$) of median (range) 5.2% (3.3–6.4%) for the body and an underdosage ($D_{98\%}$) of median (range) −6.8% (−10.6% to −4.2%) for CTV-N_{50Gy}. CBCT positioning data of all non-responders showed that weekly longitudinal shifts greater than 4 mm were observed in 21 of 815 fractions with CBCT imaging. The number of image fractions with shifts greater than 4 mm was three for two patients, two for four patients, and one for seven patients. The maximum longitudinal shift during one fraction was 6.5 mm.

All treatment plans except one (reoptimized), passed quality assurance measurements prior to treatment, 196 measurements (Supplementary Fig. S2).

Discussion

In this phase ll study, we have demonstrated the feasibility of sequential dose planning with a plan-on-plan technique, i.e., changing the treatment strategy and including irradiation to pelvic lymph nodes during the course of radiotherapy. We demonstrated that adequate target coverage was achieved with acceptable doses to the OARs, although the local (GTV-T) recurrence should be covered from the start of radiotherapy for optimal dose coverage of the PTV-T. The procedure was further optimized by fractionation-corrected adjustment of the base plan to give even better target coverage. The robustness of abutting fields was evaluated and showed minimal influence on the final treatment plan.

In the initial part of this study, we used the physical dose in the base dose plan, and target coverage was achieved according to the trial criteria. For reasons of safety, we accepted a somewhat lower EQD2-adjusted target coverage in the periphery of CTV-N_{50Gy} and PTV-N_{50Gy} at the inter-phase junction. The EQD2 criteria were met for all other target volumes, with acceptable doses to OARs, although, not surprisingly, the low-dose bowel-bag constraints (V_{30Gy}) were difficult to achieve in some cases. Due to the fairly low EQD2-adjusted coverage of the PTV-N_{50Gy} in the inter-phase junction we introduced a new planning method using biologically adaptive plan-on-plan optimization. This allowed the optimizer to improve the dose coverage in the low-dose area without significantly increasing doses to the OARs. The use of sequential plans introduces inter-phase junction areas, i.e. between phase 1 and 3. To ensure that this did not lead to an unacceptably high risk of overdosage, we investigated the reproducibility in the treatment set-up, and found it to be high with robust treatment plans using 4 mm displacements.

There are several reports describing VMAT treatment planning of prostate cancer, both for focal treatment and for inclusion of pelvic lymph nodes in the target [14,25–27]. The method presented in this paper differs from these studies as the target volumes are changed

Table 2
Physical and EQD2-corrected dose-volume data for the 35 non-responders with physical dose in the base plan and for the 29 non-responders with EQD2-corrected dose in the base plan.

Structure		Non-responders, physical dose in base plan. n = 35		Non-responders, EQD2-corrected dose in base plan. n = 29	
		Median (IQR) physical	Median (IQR) EQD2	Median (IQR) physical	Median (IQR) EQD2
CTV-P_{70Gy}	$D_{99\%}$ (Gy)	70.4 (70.1–70.6)	70.0 (69.5–70.2)	70.2 (70.0–70.3)	69.5 (69.5–69.8)
PTV-P_{70Gy}	$D_{98\%}$ (Gy)	69.3 (69.0–69.6)	68.2 (67.8–68.7)	68.9 (68.7–69.1)	67.5 (67.3–68.0)
CTV-N_{50Gy}	$D_{99\%}$ (Gy)	49.6 (49.0–49.8)	44.0 (43.1–44.5)	49.6 (49.4–49.9)	47.2 (46.8–47.8)
PTV-N_{50Gy}	$D_{99\%}$ (Gy)	47.3 (47.1–47.8)	42.0 (41.4–42.4)	47.9 (47.6–48.3)	44.7 (43.9–45.2)
Rectum	V_{60Gy} (%)	32.0 (26.9–34.7)	28.9 (24.4–31.2)	33.0 (27.2–34.5)	29.6 (24.3–30.6)
	V_{70Gy} (%)	19.7 (16.4–22.3)	16.7 (13.7–18.5)	17.0 (15.0–19.9)	12.3 (9.3–16.2)
Femoral heads	D_{max} (Gy)	48.4 (46.1–50.8)	43.6 (41.0–46.2)	50.3 (47.7–53.3)	43.8 (41.1–45.9)
BowelBag -PTV5mm	V_{30Gy} (cm^3)	319.7 (253.5–371.6)	221.1 (177.6–267.5)	290.4 (237.0–327.8)	206.8 (169.8–231.7)
	V_{40Gy} (cm^3)	127.1 (101.2–163.0)	61.0 (47.6–95.0)	132.3 (81.9–146.1)	55.7 (39.0–82.9)
	V_{45Gy} (cm^3)	43.9 (31.4–68.9)	18.7 (12.3–28.8)	52.5 (29.9–65.5)	13.1 (7.2–19.1)
	V_{50Gy} (cm^3)	3.1 (0.7–12.0)	0.9 (0.1–6.6)	6.6 (1.1–12.7)	1.0 (0.0–4.2)
BODY	D_{max} (Gy)	76.4 (75.7–77.0)	75.7 (75.1–76.6)	76.8 (76.4–77.7)	75.9 (75.5–77.2)
Bladder	D_{mean} (Gy)	63.0 (56.3–66.1)	60.1 (52.4–63.6)	64.8 (60.2–68.2)	62.7 (56.3–66.3)

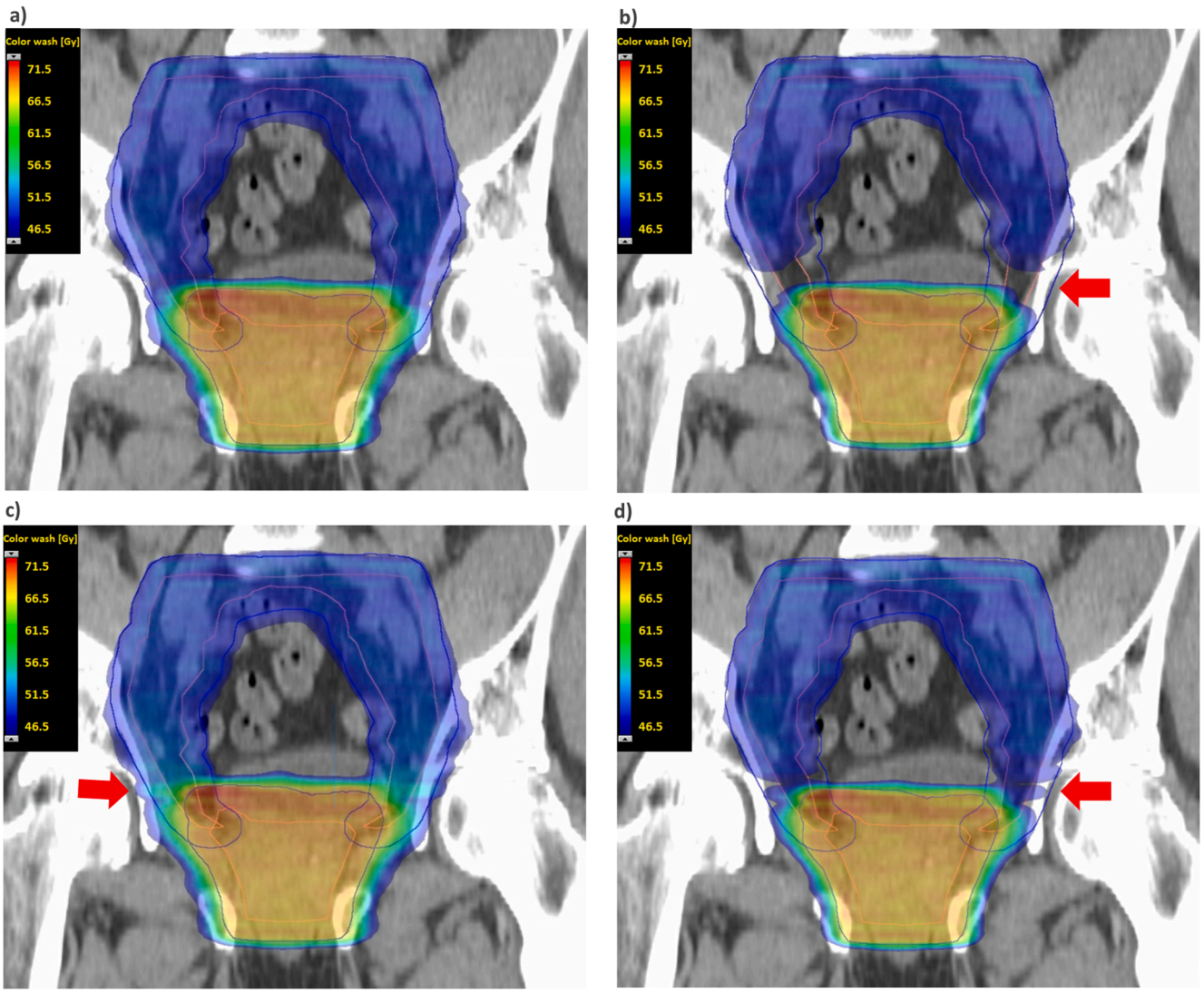

Fig. 2. Computed tomography images (frontal views) showing summed dose distributions in phases 1–3. a) Dose distribution expressed as physical dose when physical dose is used in the base plan. All target objectives are fulfilled. b) As in a) but in terms of the EQD2-corrected dose, showing lower target coverage in the inter-phase junction (red arrow). c) Dose distribution expressed in physical dose when using the biologically adaptive base plan. All target objectives are met, but with a slightly increased dose in the inter-phase junction (red arrow). d) As in c) but in terms of the EQD2 corrected dose, showing improved dose coverage in the inter-phase junction, and without the hotspots observed in c) (red arrow).

during radiation according to treatment response. Our personalized PSA-guided treatment approach in the PROPER study can spare future patients from receiving unnecessary pelvic lymph node irradiation. From a treatment planning point of view however, this is a challenge as it demands a plan-on-plan optimization based on the radiation already delivered. The EQD2 based planning method described in this paper improved dose coverage to meet dose-volume constraints.

New imaging methods with improved sensitivity and specificity will affect radiotherapy planning for future patients with recurrent prostate cancer. The diagnosis of lymph node metastases enables treatment planning upfront of both local recurrence and lymph node metastases [28,29]. However, still a large proportion of these patients will have either no lymph node metastases or possibly findings of uncertain value. This is more pronounced at low baseline PSA levels [10]. The mean PSA level at start of radiotherapy in this study is 0.3 ng/ml and positive lymph nodes were treated in 14% of the cohort. The sequential biomarker-based approach will enable a selection of patients with high risk of lymph node metastases despite uncertain or no PET-findings and enable lymph node irradiation while avoiding unnecessary treatment for treatment responders.

These findings can be used to develop future treatment regimens allowing individualized radiotherapy, based on an early treatment response. This approach could also be of use in the re-irradiation of patients [30,31], irrespective of cancer diagnosis, in order to achieve sufficient target coverage, while sparing normal tissue.

An additional finding during the study was the problem of delivering adequate dose to the PET-positive local recurrence(s) when initiated after five weeks of radiotherapy. This can be solved by initiating treatment at baseline or earlier in the treatment with SRT. There were no corresponding difficulties in dose delivery to the lymph nodes, despite the phase-wise planning.

One limitation of this study is the relatively small sample size. However, we believe that the prospective nature of this trial guarantees high quality of the data. Another limitation of our study is the no action level protocol used. This applies primarily for the boost volumes with small PTV margins. However, as they are included in the PTV-N_{50Gy} or PTV-P_{70Gy} we do think that the dose coverage is adequate but daily imaging should be used in the future for these patients. Daily imaging will also minimize the risk of under/over-dosage in the inter-phase junction.

In conclusion, to the best of our knowledge, this is the only study presented to date on sequential VMAT treatment planning with biologically adaptive plan-on-plan optimization in the pelvis. The results show that good target coverage and acceptable doses to the OARs can be achieved when using a biologically adapted base plan. The clinical benefits of this treatment method are being tested within the ongoing phase II PROPER trial, where further follow-up will be undertaken.

Declaration of Competing Interest

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2021.03.001.

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