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Published in:
Radiotherapy and Oncology

Link to article, DOI:
10.1016/j.radonc.2022.09.015

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Radiotherapy and Oncology 176 (2022) 92–98

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Online adaptive radiotherapy of anal cancer: Normal tissue sparing, target propagation methods, and first clinical experience

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ARTICLE INFO

Article history:
Received 25 July 2022
Received in revised form 20 September 2022
Accepted 20 September 2022
Available online 27 September 2022

Keywords:
Online adaptive radiotherapy
Anal cancer
Normal tissue
Re-optimization
Artificial intelligence
Image-guided radiotherapy

ABSTRACT

Background and purpose: Online adaptive radiotherapy (oART) potentially spares OARs as PTV margins are reduced. This study evaluates dosimetric benefits, compared to standard non-adaptive radiotherapy (non-ART), target propagation methods, and first clinical treatments of CBCT-guided oART of anal cancer.
Materials and methods: Treatment plans with standard non-ART and reduced oART PTV margins were retrospectively generated for 23 consecutive patients with anal cancer. For five patients randomly selected among the 23 patients, weekly CBCT-guided oART sessions were simulated, where the targets were either deformed or rigidly propagated. Preferred target propagation method and dose to OARs were evaluated. Ten consecutive patients with anal cancer were treated with CBCT-guided oART. Target propagation methods and oART procedure time were evaluated.
Results: For the retrospective treatment plans, oART resulted in median reductions in bowel bag V_{45Gy} of 11.4 % and bladder V_{35Gy} of 16.1%. Corresponding values for the simulated sessions were 7.5% and 27.1%. In the simulated sessions, 35% of all targets were deformed while 65% were rigidly propagated. Manual editing and rigid propagation were necessary to obtain acceptable target coverage. In the clinical treatments, the primary and some elective targets were rigidly propagated, while other targets were deformed. The median oART procedure time, measured from CBCT acquisition to completion of plan review and QA, was 23 min.
Conclusions: Simulated oART reduced the dose to OARs, indicating potential reduction in toxicity. Rigid propagation of targets was necessary to reduce the need for manual edit. Clinical treatments demonstrated that oART of anal cancer is feasible but time-consuming.

Radiotherapy (RT) has an essential role in treatment of anal cancer. In combination with chemotherapy, it is the primary treatment option and allows for organ preservation [1–6]. While complete tumor regression rates of 80–90% have been reported, the treatment is often associated with considerable toxicity, as a result of simultaneous irradiation of surrounding healthy tissue (organs at risk, OARs) such as bladder and bowels [7].

Per international standard, the targets in radiotherapy of anal cancer includes the primary target area (gross tumor volume, GTV-T, and clinical target volume, CTV-T), any involved lymph nodes (GTV-N and CTV-N), and an elective area (CTV-E) with pelvic, mesorectal, ischiorectal and inguinal lymph nodes [8]. During the course of treatment, patients display large anatomical variations in pelvic organs, e.g., bladder, rectum and bowels. To compensate for these anatomical changes, among other uncertainties related to the treatment delivery, safety margins are added to the already extensive target area to ensure adequate target coverage. Thus, creating planning target volumes (PTVs), to which the treatment plan is optimized [9].

Over the last decades, technological advances such as stepping from 3-D conformal RT to intensity modulated RT (IMRT) have increased the conformity of the radiation dose to the target, resulting in reduced dose to OARs and radiation-induced toxicity [10,11]. With online adaptive radiotherapy (oART), the OARs may be spared even further. Adapting the treatment to the daily anatomy and thereby accounting for inter-fractional anatomical variations, enables a reduction in the safety margins while ensuring adequate target coverage. Studies have reported on feasibility, dosimetric benefit and possible margin reductions in oART of several pelvic disease sites, including bladder [12,13], prostate [14–16], and rectum [17–19], but reporting on anal cancer is limited. We have previously reported on the feasibility of cone-beam computed tomography (CBCT) guided oART for a larger cohort of pelvic

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https://doi.org/10.1016/j.radonc.2022.09.015
0167-8140/

patients [20], based on treatments of bladder and rectum cancer and simulations of mainly bladder, prostate, and rectum. While the study included simulations of a limited number of anal cases (four patients, one oART session per patient), no margin reduction nor dosimetric evaluation were carried out.

The aim of this study was to evaluate margin reductions, dosimetric benefits and target propagation methods in CBCT-guided oART of anal cancer, for a larger cohort of patients. Furthermore, to evaluate the clinical feasibility. It consisted of three parts: a pre-implementation treatment planning study, a pre-implementation session simulation study, and clinical treatments. We report on OAR sparing and preferred target propagation method in the pre-implementation studies, and on timing, resources, and workflow for the first patients treated.

Materials and methods

Patients

Twenty-three consecutive patients with anal cancer treated with standard non-ART on the Ethos system (Varian Medical Systems, VMS) between January and November 2020 (Table 1) were retrospectively included in the pre-implementation studies.

Additionally, the first 10 patients with anal cancer (Table 1) treated with oART on the Ethos system between January and June 2022 were evaluated. The patients were included in the ROAR-A trial (Re-optimization based Online Adaptive Radiotherapy of Anal cancer), a phase II trial approved by the Danish ethical committee (H-21028093, NCT05438836 on clinicaltrials.gov).

Each patient simultaneously received 60 Gy to the primary target, 60 or 54 Gy to any involved lymph nodes, and 48 Gy to the elective area, in 30 fractions. Reference CT (ref-CT) and magnetic resonance (ref-MR) scans were acquired approximately-one week prior to treatment. The patients were fixated with a pelvic vacuum cushion, in supine position. They followed a preparatory protocol aiming at a moderately filled bladder and an empty rectum during reference scans and treatments.

The Ethos system includes an O-ring linear accelerator, a template-based automatic treatment planning system (TPS), and a novel solution for CBCT-guided oART. Detailed descriptions of the technical characteristics of the system [21], as well as previous clinical utilizations and evaluations of it [12,20,22] have been reported elsewhere.

Target and OAR delineations

GTV-T was defined as the common tumor volume as identified on ref-CT, ref-MR, and diagnostic positron emission tomography (PET)/CT scans. GTV-T was divided into an upper and lower part, separated by the anocutaneous border, due to difference in intra-fractional motion. CTV-T was defined as GTV-T plus an isotropic margin of 10 mm to the upper part and 15 mm to the lower part and included the circumference of anal canal and rectum. CTV-E included pre-sacral, ischiorectal, inguinal (left and right), iliac (internal and external), mesorectal and obturator regions. CTV-E also included the anal canal if its entire cranio-caudal extension was not included in CTV-T. GTV-N was defined as any involved lymph node(s) as identified on diagnostic PET/CT, ref-CT and ref-MR. CTV-N was obtained by adding a 5 mm isotropic margin to GTV-N, and subsequently excluding muscles and bones.

The main OARs included bowel bag, bladder, and femoral heads as seen on ref-CT. The bowel bag was defined as the peritoneal space from the most caudal slice with visible bowel to at least

Table 1
Patient characteristic including sex, age, whether the patient had any positive lymph nodes (CTV-N) or CTV-E anal canal, and number of clinical oART fractions. *Received 54 Gy to CTV-N to comply with updated national guideline, remaining patients received 60 Gy to CTV-N.

	Patient	Sex	Age [y]	CTV-N	CTV-E anal canal	# oART fx
Pre-implementation studies	1	Male	74	Yes	Yes	-
	2	Male	62	No	No	-
	3	Female	75	No	No	-
	4	Female	71	No	No	-
	5	Female	65	Yes	Yes	-
	6	Female	69	No	No	-
	7	Male	73	Yes	No	-
	8	Female	58	Yes	Yes	-
	9	Female	60	Yes	No	-
	10	Female	64	Yes	No	-
	11	Female	75	Yes	No	-
	12	Female	76	Yes	No	-
	13	Female	72	No	No	-
	14	Female	55	Yes	Yes	-
	15	Female	55	Yes	Yes	-
	16	Female	76	Yes	No	-
	17	Male	59	Yes	No	-
	18	Female	72	Yes	No	-
	19	Female	68	Yes	No	-
	20	Female	78	Yes	No	-
	21	Female	75	Yes	No	-
	22	Male	77	Yes	No	-
	23	Male	72	No	Yes	-
Clinical treatments	1	Female	71	Yes	No	30
	2	Male	55	Yes	Yes	28
	3	Male	68	No	No	28
	4	Male	72	No	No	30
	5	Female	62	Yes*	No	27
	6	Female	82	Yes	Yes	27
	7	Female	59	Yes	Yes	27
	8	Male	70	Yes*	Yes	26
	9	Male	54	Yes*	Yes	26
	10	Female	74	No	No	25

1 cm cranially from PTV-E. Remaining OARs were sacrum, penile bulb, vagina, testis, and sacroiliac joint.

Initial contouring was conducted in Eclipse TPS (VMS). Segmentations were subsequently imported to Ethos TPS for treatment planning and session simulations.

Margins and pre-implementation treatment planning study

Two reference treatment plans based on the ref-CT and reference delineations were generated per patient in Ethos TPS v1.0; one with PTV margins clinically used for non-ART ("non-ART reference plan") and another with PTV margins as expected to be used for oART ("oART reference plan").

Non-ART reference plans followed institutional standard with population-based PTV margins. CTV-T and CTV-N were each expanded 10 mm isotropically to generate PTV-T and PTV-N. CTV-E was expanded 10 mm anteriorly and 5 mm in other directions to generate PTV-E. In oART reference plans, the bladder was subtracted from CTV-E, and an isotropic margin of 5 mm was added to CTV-E and CTV-N to generate PTV-E and PTV-N. The PTV-T margin was 10 mm, i.e., identical to the non-ART margin, due to poor visibility of GTV-T on CBCT.

Ethos TPS automatically generated three IMRT plans (7, 9, and 12 fields) based on user-defined planning templates, which included structures, constraints, and priorities. All non-ART and oART reference plans were generated using the same planning templates. The plans were normalized to achieve a PTV-T mean dose of 60 Gy. Dose calculations were carried out using AcurosXB algorithm (v15.6.03, VMS), calculating dose to medium with a 2.5 mm calculation resolution. The most optimal plan according to constraints and priorities (Table 2) was selected. Bowel bag V_{30Gy} and V_{45Gy}, and bladder V_{35Gy} and V_{50Gy} were compared between non-ART and oART reference plans.

Pre-implementation session simulation study

Treatment sessions were simulated using six weekly CBCTs for five patients randomly selected among the cohort of 23 patients. The selection was carried out using the randsample function in Matlab (R2019a, The MathWorks, Inc.).

The sessions were simulated in an emulator with a pre-released version of the Ethos treatment management system v2.1. Body outline, OARs, and CTVs were re-generated on the CBCT anatomy at each session. Rectum and bladder were used as so-called influencers i.e., a set of system-defined structures that influence the deformation of the targets. The CTVs were propagated from the ref-CT to the CBCT through elastic or structure-guided deformation per system default, but rigid propagation was optional. Three structure sets were generated per session:

- ss_{def} with unedited deformed CTVs
- ss_{rig} with unedited rigidly propagated CTVs
- ss_{clin} with both deformed and rigidly propagated CTVs, in accordance with an expected clinical oART workflow. Manual edits and rigid shifts were performed when necessary. The deformed CTV was selected if it agreed with CBCT anatomy (for CTVs visible on CBCT) or reference delineations (for CTVs not visible on CBCT). Rigid propagation was selected if the need for manual edit was reduced compared to when choosing the deformed CTV.

The three structure sets included identical structures of bowel bag, bladder, femoral heads and body. OARs of priority 3 (Table 2) were excluded due to technical limitations.

For the oART sessions, the oART reference plan was re-optimized on ss_{clin} in Ethos TPS v1.0. For the non-ART sessions, the non-ART reference plan was re-calculated on ss_{clin} in Eclipse TPS v15.6. CBCT and ref-CT were registered based on a bony-match in three degrees-of-freedom according to clinical non-ART routine.

The preferred target propagation method in ss_{clin} was noted and dice similarity coefficients (DSC) between CTVs in ss_{def} and ss_{clin} were calculated. Bowel bag V_{30Gy} and V_{45Gy}, and bladder V_{35Gy} and V_{50Gy} were evaluated and compared between non-ART and oART sessions. CTV coverage ($V_{95\%}$) was evaluated for non-ART sessions.

To investigate the effect of selecting ss_{def} instead of ss_{clin} on target coverage, the oART reference plans were re-optimized on ss_{def}, and thereafter re-calculated on ss_{clin}. The target coverage in the re-calculated plans were evaluated based on constraints (Table 2) and dose distribution.

Clinical treatments

Clinical oART treatments were delivered using Ethos treatment management system v2.1, with bladder and rectum as influencers, and targets and OARs re-generated at each fraction. During the oART treatments, the system generated two plans with the same field geometry as the reference plan: the scheduled plan (the reference plan re-calculated on the daily anatomy) and the adapted plan (the reference plan re-optimized to the daily anatomy). The most optimal plan regarding constraints (Table 2) and dose distribution was selected for treatment. Plan-specific quality assurance (QA) was conducted for reference and adapted plans prior to treatment using an integrated independent dose calculation software (Mobius3D and MobiusAdapt v3.1, VMS).

To verify target coverage, a CBCT was acquired after the oART procedure but before treatment delivery at the first two oART fractions and thereafter on a weekly basis and whenever indicated (e.g., due to patient movement as observed on a monitor, prolonged oART procedure or when considerable rectal/bowel gas was observed on the CBCT acquired prior to the oART procedure). If necessary, to ensure CTV coverage, the treatment couch was shifted and/or gas cavities were removed through flatulence or use of catheter before treatment delivery.

The choice of target propagation method and treatment plan was recorded, together with the oART procedure time measured from CBCT acquisition to completion of plan review and QA.

Table 2
Priorities and constraints for targets and OARs.

Priority	Structure	Constraint
1	CTV-T, CTV-N	$V_{95\%} = 100\%$
1	CTV-E	$V_{95\%} = 100\%$
1	PTV-T, PTV-N	$V_{95\%} \geq 99\%$
1	PTV-T, PTV-N	$V_{90\%} = 100\%$
1	PTV-T, PTV-N	$V_{105\%} \leq 1\%$
1	PTV-E	$V_{95\%} \geq 98\%$
1	PTV-E	$V_{90\%} = 100\%$
1	PTV-E excl. (PTV-T + 5 mm margin)	$99\% \leq D_{mean} \leq 100\%$
1	PTV-E excl. (PTV-T + 5 mm margin)	$V_{107\%} < 3\%$
1	GTV-T, GTV-N	$99\% \leq D_{mean} \leq 102\%$
1	CTV-T, CTV-N	$99\% \leq D_{mean} \leq 102\%$
2	Bowel bag	$V_{45Gy} < 300$ cc
2	Bowel bag	$V_{30Gy} < 600$ cc
2	Bladder	$V_{50Gy} < 20\%$
2	Bladder	$V_{35Gy} < 75\%$
2	Femoral heads	$V_{52Gy} = 0\%$
3	Sacrum	$V_{50Gy} = 0\%$
3	Penile bulb	$V_{50Gy} < 20\%$
3	Vagina	*As low as possible*
3	Testis	*As low as possible*
3	Sacroiliac joint	$V_{30Gy} < 50\%$

Statistical analyses

Statistical analyses were carried out in Matlab (R2019a, The MathWorks, Inc.). The difference in dose to bowel bag and bladder between non-ART and oART in the planning study was assessed using non-parametric tests (Wilcoxon signed-rank tests), at a Bonferroni adjusted significance level of 1.25% (=5%/4).

Results

In the pre-implementation planning study, all non-ART and oART reference plans included 12 IMRT fields, except one non-ART plan with 9 IMRT fields. Bowel bag V_{30Gy} and V_{45Gy} were in median (interquartile range, IQR) reduced by 6.4 (3.8;8.5) % ($p < 0.001$) and 11.4 (9.7;14.0) % ($p < 0.001$), respectively, with oART compared to non-ART (Fig. 1). This corresponds to 39.4 (17.9;80.2) cc and 48.5 (35.6;61.3) cc, respectively. The median (IQR) relative reduction in bladder V_{35Gy} and V_{50Gy} were 16.1 (5.9;21.8) % ($p < 0.001$) and 6.9 (1.3;28.6) % ($p < 0.01$), corresponding to 8.8 (3.5;13.7) percentage points and 0.6 (0.1;1.6) percentage points, respectively (Fig. 2).

Patient 3, 4, 6, 8, and 19 were randomly selected in the pre-implementation session simulation study. Comparing oART to non-ART over all sessions, the median (IQR) reduction in bowel bag V_{30Gy} and V_{45Gy} were 6.2 (2.1;13.7) % and 7.5 (5.1;11.8) %, respectively, corresponding to 38.0 (12.0;91.0) cc and 28.6 (15.7;48.4) cc. Bladder V_{35Gy} and V_{50Gy} were reduced by 27.1 (13.5;36.4) % and 35.4 (-4.8;70.6) %, respectively, which equals to 13.5 (7.2;17.5) percentage points and 0.7 (-0.1;2.0) percentage points (Fig. 1). The study revealed good coverage of CTVs in ss_{clin} for the non-ART sessions (Table A1 in Supplementary material).

In the simulated sessions, the deformed CTV was preferred for 35% of all CTV's, while the remaining 65% were rigidly propagated (Fig. 3). The system managed inter-fractional variations in rectum well but had challenges deforming CTV-E inguinal when the bladder changed. As CTV-T was not visible on CBCT, rigid propagation was chosen if any difference from the reference CTV-T was observed. Comparing ss_{clin} and ss_{def}, DSC > 0.85 for all CTVs.

Re-optimizing oART reference plans on ss_{def} and thereafter re-calculating them on ss_{clin} resulted in plans with lacking target coverage ($V_{95\%}$ below the constraint of Table 2) of CTV-T in 4/30 sessions (range, 99.7–100.0%), PTV-T in 29/30 (range, 90.3–100.0%), CTV-E in 16/30 (range, 98.7–100.0%), PTV-E in 4/30 (range, 96.6–100.0%), CTV-N in 2/12 (range, 99.1–100.0%), and PTV-N in 11/12 (range, 79.3–100%) (Table A1 in Supplementary material). None of the dose distributions were clinically acceptable, primarily due to lack of coverage in medial and anterior parts of CTV-E and PTV-E inguinal and iliac.

For the clinical treatments, 274/300 fractions were delivered as oART with oART margins, and remaining fractions were delivered as non-ART with non-ART margins because of downtime due to maintenance or public holidays (limited number of trained staff).

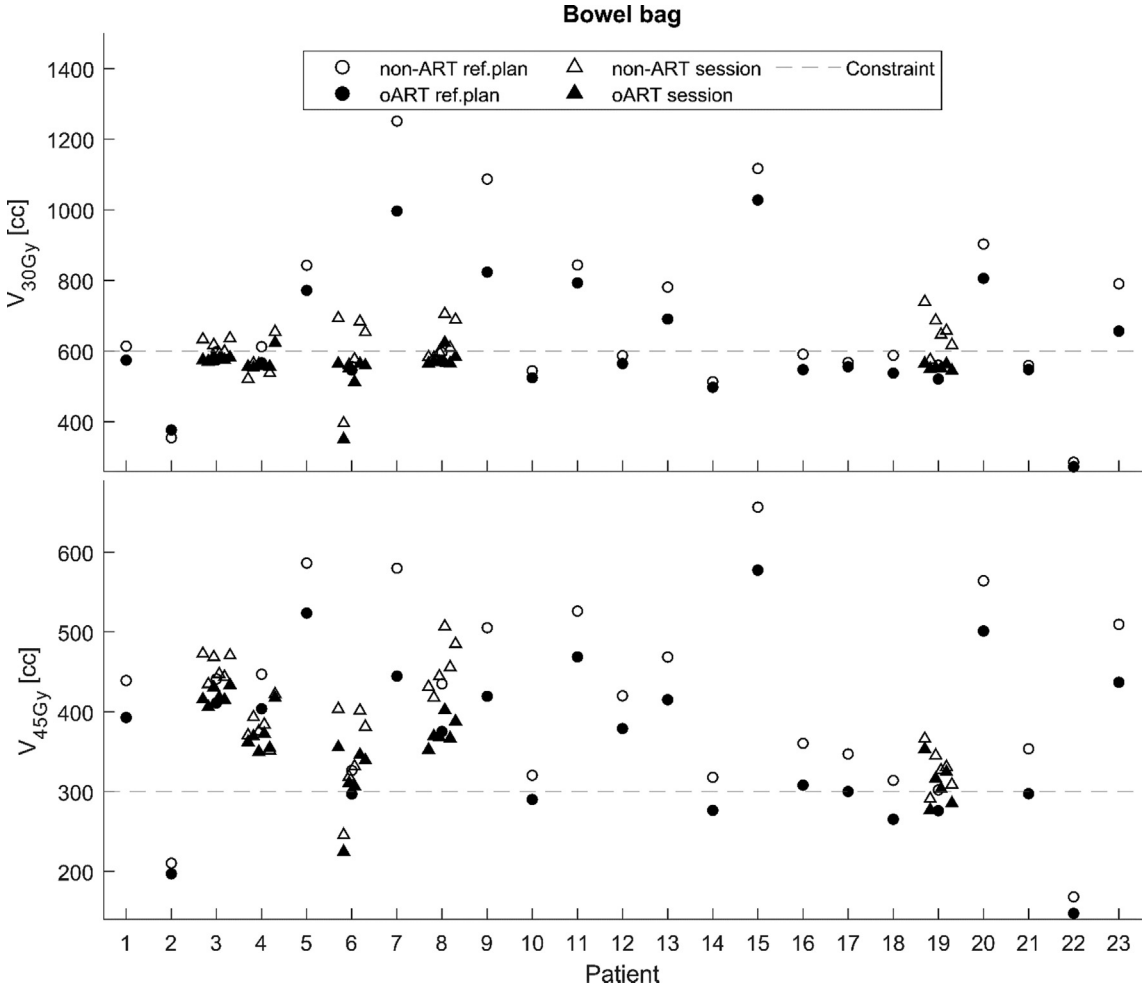

Fig. 1. Bowel bag V_{30Gy} (top) and V_{45Gy} (bottom) in non-ART reference plans (circles), oART reference plans (filled circles), non-ART sessions (triangles), and oART sessions (filled triangles) for patients included in the pre-implementation studies. The sessions are chronologically separated on the x-axis, and the dashed line represents the clinical constraint.

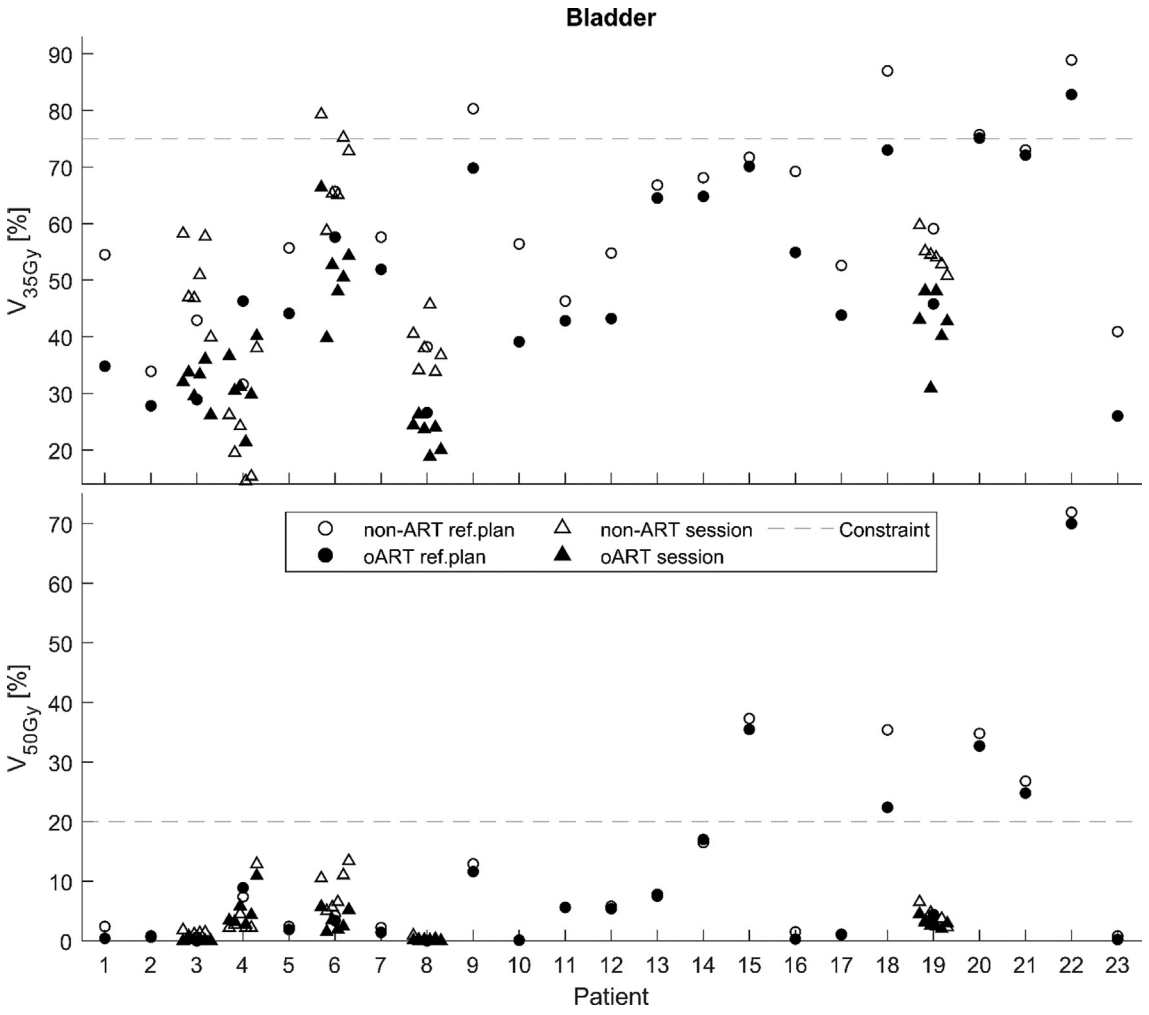

Fig. 2. Bladder V_{35Gy} (top) and V_{50Gy} (bottom) in non-ART reference plans (circles), oART reference plans (filled circles), non-ART sessions (triangles), and oART sessions (filled triangles) for patients included in the pre-implementation studies. The sessions are chronologically separated on the x-axis, and the dashed line represents the clinical constraint.

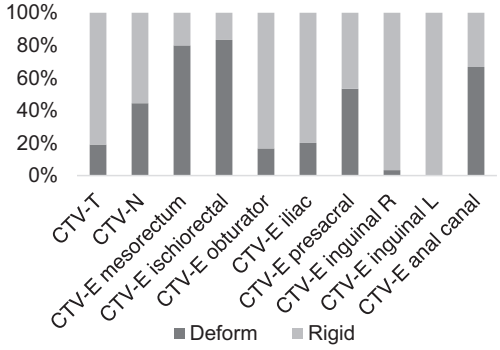

Fig. 3. Distribution of preferred target propagation method (deform or rigid) for the different CTVs in the pre-implementation session simulation study.

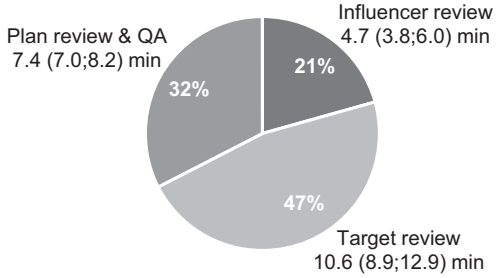

Fig. 4. Median (IQR) duration of the different steps in the oART procedure and the distribution between them, for the clinical treatments.

The time slots were 40 minutes per oART session and 20 minutes per non-ART session, and the median (IQR) oART procedure time was 23.4 (21.4;26.7) min (Fig. 4). CTV-T and CTV-E pre-sacral, iliac, obturator, and inguinal were rigidly propagated at each oART fraction, while CTV-E mesorectum, anal canal and ischiorectal space were usually deformed. The propagation method for CTV-N depended on its location and was the same as the surrounding CTV-E. All clinical oART treatment plans were 12-field IMRT, except one with 9 IMRT fields. The adapted plan was selected in 97.1% of the oART fractions, due to target coverage and/or dose to OARs, and the scheduled plan was selected in the remaining 2.9%. All plan-specific QA resulted in gamma passing rates (3%/3mm, global gamma, 20% dose threshold) above the clinical tolerance of 95%, with differences in dose-volume parameters within 3%.

An oART experienced physicist (LMÅ) and a senior radiation oncologist (ESH) conducted the first 10 oART fractions. The remaining oART fractions were conducted by radiotherapy technicians

trained in CBCT-guided oART, with a physicist (LMÅ) and a physician (ESH, KSS) present at the first 133 fractions, and thereafter only at the first fraction for each patient.

Discussion

This study demonstrates that an online adaptive approach can reduce the dose to critical OARs in radiotherapy of anal cancer, motivating the initiation of a phase II trial to evaluate the clinical effects of CBCT-guided oART. The pre-implementation planning study showed that the reduction in PTV margin that oART allows for, results in significant reductions in bowel bag V_{45Gy}, a dose-volume metric strongly associated with bowel toxicity [23,24]. In similarity with the introduction of IMRT, where Kachnic et al. [10] showed reductions in acute grade 3 + gastrointestinal toxicity from 37% to 21% when comparing CRT and IMRT, these reductions indicate promising reductions in toxicity. oART resulted in more plans fulfilling the clinical constraints for both bowel bag and bladder compared to non-ART. However, for one patient (patient 2), bowel bag V_{30Gy} was slightly higher in the oART reference plan than in the non-ART plan. For another patient (patient 4), bladder V_{35Gy} was higher when comparing oART to non-ART reference plans. This may be explained by a stochasticity in the automatic plan generation in the TPS version used, and the fact that the obtained values were well below the constraints. Values on bowel bag V_{30Gy} similar to that reported for patient 2 could not be reproduced when re-optimizing the oART reference plan.

The dosimetric superiority of oART was observed also in the simulated sessions, but with varying effect among the patients. Inter-fractional anatomical variations and patient selection may explain the reduced dosimetric sparing in the sessions compared to the reference plans; a larger number of patients would decrease the effect of single patients. Nevertheless, simulating 30 sessions gave important experience on target propagation for anal cancer. Using Ethos treatment management system v2.1, rigid target propagation was necessary to reduce the need for manual editing, and manual editing was necessary to ensure adequate target coverage. Even though DSC > 0.85 when comparing CTVs in ss_{def} and ss_{clin}, recalculating oART reference plans previously optimized for ss_{def} on ss_{clin} demonstrated that none of the plans were clinically acceptable when using unedited deformed targets.

In the clinical treatments, rigid propagation was used as standard for some CTVs to control the propagation and avoid unwanted deformation and manual edit, as these CTVs were either not visible on CBCT (CTV-T) or non-mobile relative to bones (CTV-E presacral, iliac, obturator and inguinal). However, the choice of rigid propagation was time consuming, not only due to the action itself but also because it prolonged the calculation time of scheduled and adapted plans. All targets were per system default deformed, and when choosing to rigidly propagate or manually edit any of them, the system re-started the generation of treatment plans that was automatically initiated when accepting the influencers. Having the possibility to set the default propagation method for different targets could potentially reduce the time spent on target review, which was the most time-consuming step of the oART procedure (Fig. 4). Alternatively, MR-guided oART with superior soft-tissue contrast could probably enhance target delineation and further motivate a reduction of the PTV-T margin. However, such a procedure would possibly be more time consuming with the current available MR-based systems [18,19] and might thus not be feasible for normo-fractionated regimes. Further investigation of this is needed but beyond the scope of this study.

To our knowledge, this is the first study reporting on anal cancer patients treated with adaptive radiotherapy, either offline or online, MR- or CBCT-guided. The patients were treated as planned, with the adapted plan selected in nearly all fractions, but oART was both time and resource demanding. While CTV coverage was verified through extra CBCTs acquired after the oART procedure, intra-fractional anatomical changes of various degree were noted among the patients. The longer treatment time for oART compared to non-ART may thus influence the estimated dosimetric benefit of oART. Timings on the oART procedure as well as target review are comparable to that reported for CBCT-guided oART of rectum cancer. De Jong et al. [18] report an average time of 20 min for the oART procedure and 9 min for target review when deformed targets were edited. While we rigidly propagated and edited targets at each fraction, de Jong edited the CTVs in 50% of the fractions. Compared to CBCT-guided oART of prostate [14] and bladder cancer [12], where unedited deformed targets were used for all patients, we report longer time on target review as well as plan review and QA. Besides difference in target handling, this may be explained by the larger number of targets and OARs for anal cancer. However, despite these challenges, oART of anal cancer was considered feasible, with a procedure conducted independently by RTTs and promising normal tissue sparing.

Conclusions

Margin reductions enabled by CBCT-guided oART resulted in reduced dose to bowel bag and bladder, indicating potentially reduced toxicity for patients with anal cancer. Rigid propagation of targets was necessary to reduce the need for manual edit and ensure target coverage. Treating the first 10 patients demonstrated a feasible, but time-consuming, procedure for anal cancer.

Conflict of Interest

Varian Medical Systems (VMS) provided support during the project reported on here. The authors provided feedback to VMS on suggestions for improvements and usability of the system. Several research projects, including Ethos-related projects at the Department of Oncology, Herlev & Gentofte Hospital, are sponsored by VMS. None of the authors have any affiliation with VMS.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.09.015.

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