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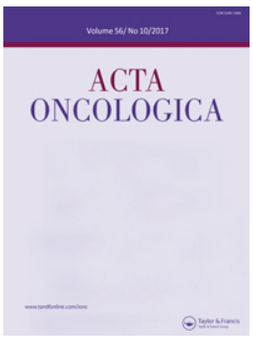

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ORIGINAL ARTICLE

Feasibility of preference-driven radiotherapy dose treatment planning to support shared decision making in anal cancer

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ABSTRACT

Purpose/Objective: Chemo-radiotherapy is an established primary curative treatment for anal cancer, but clinically equal rationale for different target doses exists. If joint preferences (physician and patient) are used to determine acceptable tradeoffs in radiotherapy treatment planning, multiple dose plans must be simultaneously explored. We quantified the degree to which different toxicity priorities might be incorporated into treatment plan selection, to elucidate the feasible decision space for shared decision making in anal cancer radiotherapy.

Material and methods: Retrospective plans were generated for 22 anal cancer patients. Multi-criteria optimization handles dynamically changing priorities between clinical objectives while meeting fixed clinical constraints. Four unique dose distributions were designed to represent a wide span of clinically relevant objectives: high-dose preference (60.2 Gy tumor boost and 50.4 Gy to elective nodes with physician-defined order of priorities), low-dose preference (53.75 Gy tumor boost, 45 Gy to elective nodes, physician-defined priorities), bowel sparing preference (lower dose levels and priority for bowel avoidance) and bladder sparing preference (lower dose levels and priority for bladder avoidance).

Results: Plans satisfied constraints for target coverage. A senior oncologist approved a random subset of plans for quality assurance. Compared to a high-dose preference, bowel sparing was clinically meaningful at the lower prescribed dose [median change in V_{45Gy}: 234 cm^3; inter-quartile range (66; 247); $p < .01$] and for a bowel sparing preference [median change in V_{45Gy}: 281 cm^3; (73; 488); $p < .01$]. Compared to a high-dose preference, bladder sparing was clinically meaningful at the lower prescribed dose [median change in V_{35Gy}: 13.7%-points; (0.3; 30.6); $p < .01$] and for a bladder sparing preference [median change in V_{35Gy}: 30.3%-points; (12.4; 43.1); $p < .01$].

Conclusions: There is decision space available in anal cancer radiotherapy to incorporate preferences, although tradeoffs are highly patient-dependent. This study demonstrates that preference-informed dose planning is feasible for clinical studies utilizing shared decision making.

ARTICLE HISTORY
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Introduction

Chemo-radiotherapy is well-established as the primary curative treatment modality for anal cancer; however, an optimum radiotherapy treatment dose has not yet been established [1]. Scandinavian prescriptions to the primary tumor and involved nodes are 54–60 Gy as simultaneous integrated boost (SIB) with 45–50 Gy to elective nodes, using per fraction doses of 1.8–2.0 Gy daily. Meanwhile, most UK centers [2,3] would prescribe 50.4–53.2 Gy to the primary tumor and involved nodes as SIB, with 40 Gy to the elective nodes, in 28 fractions.

Higher dose levels have not been unequivocally shown to be clinically superior, and adverse radiotherapy-related events are common even when using highly conformal delivery techniques [4–7]. At lower doses, the risk of adverse events may be reduced, presumably at the cost of increased risk of local recurrence. However, tumor control and normal-tissue complication models are currently not of sufficient sophistication for fully radiobiology-based risk assessment [8]. At present, dose–volume metrics continue to be used as one of several key criteria for radiotherapy planning and treatment selection.

When clinically equal rationale for several different treatment approaches exists, it is natural to propose that preferences could have a significant role in designing personalized treatments. Specifically, in radiotherapy treatment planning, preferences are expected to be important when determining the prioritization of clinical objectives since there are inherent tradeoffs between competing objectives.

In a shared decision making (SDM) paradigm [9,10], a patient and their treating physician both bring their individual preferences and desired treatment outcomes directly into a structured consultation, and thus arrive at a treatment decision together. Ideally, SDM consultations should

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Supplemental data for this article can be accessed here.

be supported by information about the necessary tradeoffs in clinical outcomes pertaining to clinically equipoise choices.

There is a genuine gap in anal cancer radiotherapy in the range of clinically equipoise tumor doses, such that the joint preferences of the physician and the patient might be used to determine which tradeoffs are acceptable when designing an individually customized treatment plan.

The typical approach of inversely-planned intensity modulated radiotherapy (IMRT) requires a planner to iterate many times through a fixed list of *a priori* clinical objectives, usually defined according to a physician's priorities, until a single clinically acceptable plan found [11].

Multi-criteria optimization® (MCO) is a novel dose planning approach [12,13] that allows dynamically variable (i.e., floating) clinical objectives while always satisfying fixed clinical constraints, such as a minimum dose to the tumor volume. This process permits a planner to navigate over a large number of pre-computed optimal plans by only adjusting the relative importance among the floating objectives while always satisfying the fixed constraints, and hence the effect of prevailing preferences and their consequential tradeoffs can be interactively visualized.

We studied the degree to which individual preferences for toxicity risks might be incorporated into treatment plan selection by changing the relative prioritization of tumor dose and various organs at risk (OARs) (focusing on bowel and bladder), in order to elucidate the feasible decision space for SDM in anal cancer radiotherapy.

Material and methods

Patients

Eleven consecutive men treated with (chemo-)radiotherapy for anal cancer between July 2012 and November 2015 were selected for this study, and 11 women were approximately case-matched to these by the American Joint Committee on Cancer (AJCC) T and N staging. Exclusion criteria were: previous pelvic surgery, focal electron radiation monotherapy and metastatic disease. The 22 patients were representative for anal cancer cohorts as seen in routine clinical practice and as reported in other studies [5,14]; patient summary characteristics are given in Table 1 (and a full list of characteristics are given in Table e1 in the online supplementary materials).

Table 1. Patient characteristics.

Characteristics	Men (n = 11)	Women (n = 11)	Total (n = 22)
T stage (T1/T2/T3/T4)	1/7/3/0	1/6/2/2	2/13/5/2
N stage (N0/N1/N2/N3)	5/1/4/1	6/1/3/1	11/2/7/2
Chemo-radiotherapy[a]		CISPLATIN	
Tumor/organ volumes (cm^3)			
PTV-T	158 (137–231)	130 (116–244)	156
PTV-N	2030 (1900–2257)	1931 (1719–2112)	2014
Bowel	1135 (893–1328)	1557 (1483–1698)	1406
Bladder	168 (114–267)	76 (50–169)	139

PTV: planning target volume; T: tumor; N: elective volume. For all continuous measures, median values are reported with interquartile ranges in brackets. [a]All patients received concurrent chemo-radiotherapy with CISPLATIN. Full list in online supplementary material, Table e1.

Radiotherapy treatment planning

The delineations of anal tumor (PTV-T), involved nodes (PTV-P), elective nodal (PTV-N) planning target volumes and OARs were done by experienced radiation oncologists, in accordance with Danish Anal Cancer Group (DACG) guidelines [15] based on the atlas by Roels et al. [16]. Delineation details are provided in the online Appendix e2 in the supplementary materials.

Using MCO, mathematically feasible treatment plans were pre-computed prior to interactive planning. We navigated to four unique dose distributions that represented a wide span of clinically relevant treatment objectives: (i) a high-dose preference in which the anal tumor and involved nodes were prescribed 60.2 Gy as SIB with 50.4 Gy to elective nodes in 28 fractions, and using a physician-defined order of priorities for OAR sparing; (ii) a low-dose preference that has the same order of priorities as the high-dose preference, but the target dose was reduced to 53.75 Gy in the anal tumor and involved nodes as SIB and 45 Gy to elective nodes in 25 fractions; (iii) a bowel sparing preference with same target dose as for the low-dose preference, but with maximum OAR importance assigned to bowel dose reduction and lastly (iv) a bladder sparing preference with same target dose as for the low-dose preference but with maximum OAR importance assigned to bladder dose reduction. The list of prescriptions is summarized in Table 2. Figure 1 gives examples (in sagittal view) of the above four different dose distributions observed in one female patient. When a dose distribution was found that matched the intended preference, final plan optimization and accurate dose computation was performed.

Fixed clinical constraints were such that the minimum clinical target volume (CTV) dose was at least 95% of the prescribed dose, and more than 98% of the planned target volume (PTV) received at least 95% of the prescribed dose. Floating clinical objectives included: bowel V_{45Gy} range (0–300 cm^3), bowel V_{30Gy} range (0–600 cm^3), bladder V_{50Gy} range (0–20%) and bladder V_{35Gy} range (0–75%) [17–19]. A complete list of objectives is provided (see online Appendix e2, Table e5 in the online supplementary materials).

Within the bowel sparing and the bladder sparing preferences, we used the OAR dose–volume metrics in the high-dose preference as a ceiling limit for the other simulated preferences (bladder and bowel, respectively). OAR overdoses (if any) in the high-dose preference were reviewed and approved by a senior radiation oncologist. Absolute volumes were used for the bowel dose metrics. A dose 'hot spot' was defined as any region exceeding 107% of the prescribed dose to PTV-N that was located outside of PTV-T.

All treatment plans were made in RayStation® v4.7.2 (RaySearch Laboratories, AB, Stockholm, Sweden) using a pencil-beam approximation for the pre-computation of feasible plans followed by collapsed-cone convolution for the accurate dose. An eight-field 6-MV IMRT technique was used assuming treatment on an Elekta Agility delivery system (Elekta AB, Stockholm, Sweden).

Analysis

Cumulative dose–volume histograms (DVH) for each plan were exported to R statistical software (v3.2.3) for analysis.

We examined dose–volume metrics for the abovementioned target coverage and OAR sparing. A plan conformity index (PCI) was used to quantify how absolute volumes of high dose were affected by changing the relative importance among OARs:

$$PCI = \frac{(volume\ in\ PTV - N\ receiving\ at\ least\ 95\%\ of\ prescribed\ dose)}{(volume\ in\ whole\ body\ receiving\ at\ least\ 95\%\ of\ prescribed\ dose)}$$

Our analysis addresses only the differences between feasible dose distribution arising within the same patient due to applying different preferences. Two-sided non-parametric paired tests of significance of differences were applied to selected DVH metrics. Statistical significance was assumed when $p < .01$, but no additional corrections were applied for multiple hypothesis testing.

Results

For plan quality assurance, a random selection of 25% of final dose distributions were reviewed with a senior radiation oncologist to ensure overall clinical quality and plan consistency. Fixed clinical constraints for target coverage were always met. Our results focused on the tradeoff between DVH metrics of OARs, as well as the PCI. Dose metrics for the four treatment regimens for bowel V_{45Gy}, bladder V_{35Gy} and PCI are listed in Table 3. Further results are summarized in Table e5 in the online supplementary materials.

Figure 2 illustrates an example of the differences in dose distribution for one female patient, shown in the transverse slices intersecting the middle of the bladder (insets a and c) and bowel (insets b and d), respectively. The qualitative differences in the OARs can be quite marked, given the same target volume coverage in all cases. Here, the bowel sparing preference has resulted in a high-dose region that overlaps the least amount of bowel but encompasses much of the bladder. Conversely, the bladder sparing preference allows a 'gap' to be sculpted around the bladder at the expense of more exposure in the bowel.

Figure 3 demonstrates (for two men and two women) that feasible dose distributions can also be created anywhere in between the maximally OAR-sparing preferences. Every data point was a unique dose distribution that originated from the same pre-computed set of feasible plans. The difference arose only from changing the relative importance of the floating objectives. In this example, the data points traced out patient-specific optimality curves (i.e., Pareto fronts) projected onto a simple two-dimensional surface corresponding to the DVH metrics 'bowel V_{45Gy}' and 'bladder V_{35Gy}'. In actuality, the complete set of all feasible plans resides in a highly multi-dimensional space corresponding to the total number of clinical objectives.

The available space for tradeoffs was highly specific to each patient; however, the summary statistics of the cohort also show the consistent trend, as shown in Figure 4. Changing from the high-dose preference to the low-dose preference resulted in a median difference of 37 cm^3 bowel sparing [range (0; 220 cm^3), $p < .01$) at V_{30Gy} and 234 cm^3 [(66; 467 cm^3), $p < .01$] at V_{45Gy}. The median changes from a high-dose preference to a bowel sparing preference were 128 cm^3 [(14; 331 cm^3), $p < .01$) and 281 cm^3 (73; 488 cm^3), $p < .01$], for V_{30Gy} and V_{45Gy}, respectively. The median change in bowel sparing at V_{45Gy} due to the low-dose preference was statistically significant and clinically meaningful, since an objective was to limit the total bowel volume irradiated to 45 Gy below 300 cm^3.

In the bladder, going from the high-dose preference to the low-dose preference resulted in a median difference of 13.7 percentage points [(0.3;30.6), $p < .01$] at V_{35Gy}. The median change from a high-dose preference to a bladder sparing preference was 30.3 percentage points [(12.4; 43.1), $p < .01$]. The median change in bladder sparing at V_{35Gy} due to the bladder sparing preference was statistically significant and clinically meaningful, since an objective was to limit the total bladder irradiated to 35 Gy below 75%. Median differences for bladder V_{50Gy} in the low dose, bowel sparing and bladder spring preferences were an average of 7.9 percentage points lower than the high-dose preference, and were not significant.

To further illustrate that planning tradeoffs generally operate on multiple clinical objectives at the same time, we found that the relative volume of dose 'hotspots' in the PTV-N (but outside the PTV-T) increased in all of the plans with the lower prescription dose. This impacted on the PCI; the median PCI was lowest in the bladder sparing preference [0.68 (0.66; 0.70)] compared to all the others [0.71 (0.69; 0.74)], but this change in PCI was not statistically significant.

Discussion

In this study, we explored multiple simultaneously optimal plans per patient. We thereby simulated the range of possible preferences for competing tradeoffs implicit in radiotherapy dose planning. Specifically, re-distribution of doses and differential OAR sparing was feasible by using MCO to navigate

Table 2. List of prescriptions.

	High dose	Low dose		
		Low dose	Low-dose bladder sparing	Bowel sparing
PTV-T dose	60.20 Gy		53.75 Gy	
PTV-N dose	50.40 Gy		45.00 Gy	
Fractions	28		25	
Plan priority	High tumor dose and target coverage	General sparing of OAR	Spare the bladder as far as possible	Spare the bowel as far as possible
Expected outcomes	Tumor control	Tumor control	Tumor control	Tumor control
	Generally higher toxicity	Generally lower toxicity	Lower bladder toxicity	Lower bowel toxicity

PTV: planning target volume; T: tumor; N: elective volume.

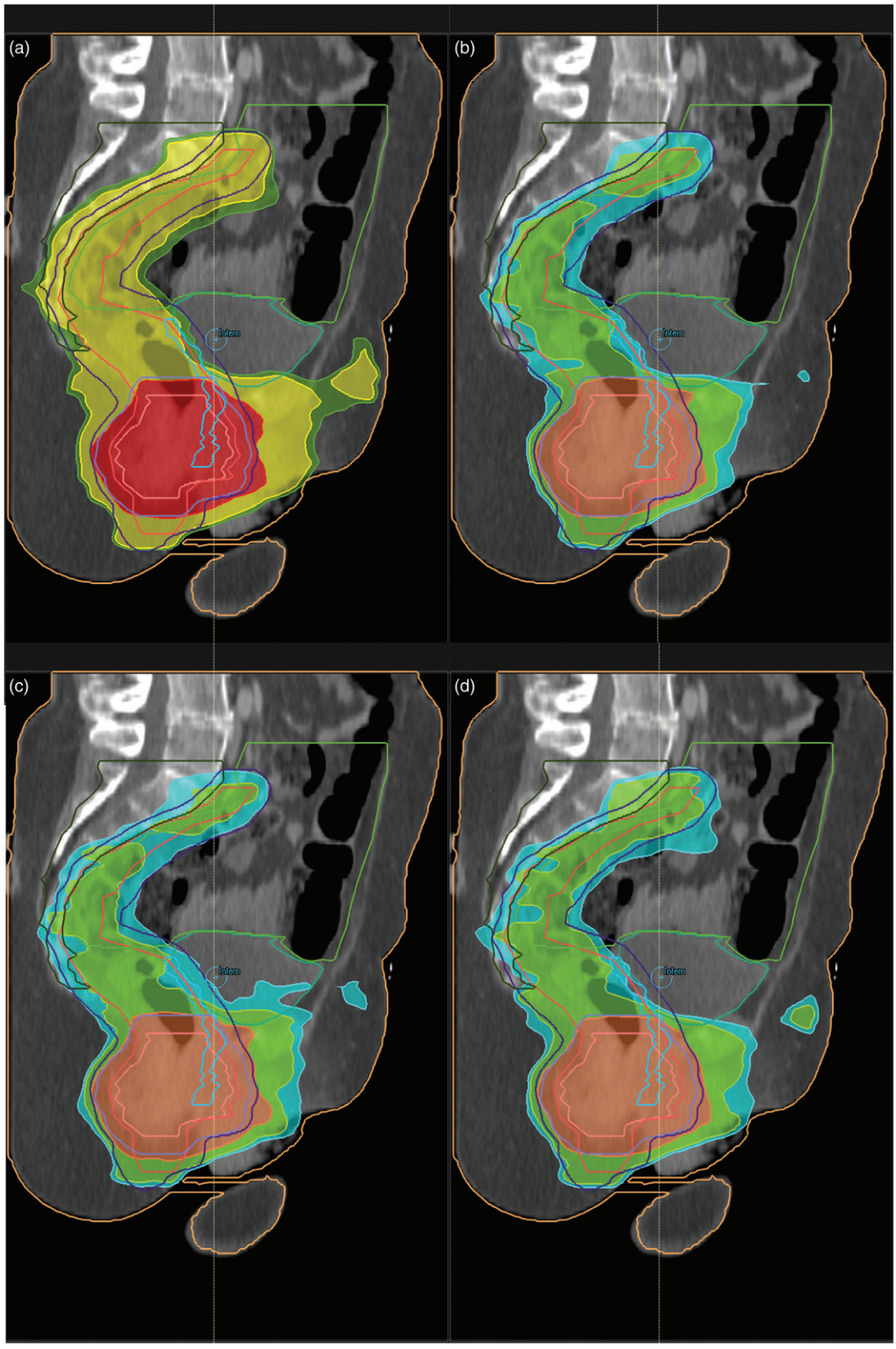

Figure 1. Dose distribution for one female patient in sagittal view for four regimens: (a) high dose, (b) low dose, (c) bowel sparing and (d) bladder sparing. Dose color wash shows the two dose levels and the 45 Gy isodose (bowel optimization objective). Red: (95% of 60.2 Gy). Yellow: (95% of 50.4 Gy). Green: 45 Gy. Orange: (95% of 53.75 Gy). Turquoise: (95% of 45 Gy).

Table 3. Dose metrics for the four treatment regimens.

Plan regimens	Bowel V_{45Gy} (cm^3)	Bladder V_{35Gy} (%)	PCI[a]
High dose	482 (409–633)	73.8 (68.5–78.8)	0.71 (0.69–0.74)
Low dose	248 (195–315)	63.6 (50.9–69.9)	0.71 (0.69–0.73)
Δ from high dose[b]	**−234**	**−13.7**	−0.01
Bladder sparing	285 (220–351)	44.6 (32.5–56.3)	0.68 (0.66–0.70)
Δ from high dose[b]	**−193**	**−30.3**	**−0.03**
Δ from low dose[b]	26	−13.6	**−0.03**
Bowel sparing	229 (159–269)	72.2 (63.4–81.9)	0.71 (0.69–0.74)
Δ from high dose[b]	**−281**	−1.7	0.0
Δ from low dose[b]	**−32**	**10.8**	0.0
Δ from bladder sparing[b]	**−71**	**28.3**	**0.04**

All values are medians, numbers in parenthesis are first and third interquartile ranges. [a]Plan conformity index (PCI) for PTV-N (see text for definition). [b]A negative value means that the metric in question (in percentages or cubic centimetres) is lower compared to the regimen mentioned. Bold text: significance at the 1% level ($p < .01$) using paired rank tests.

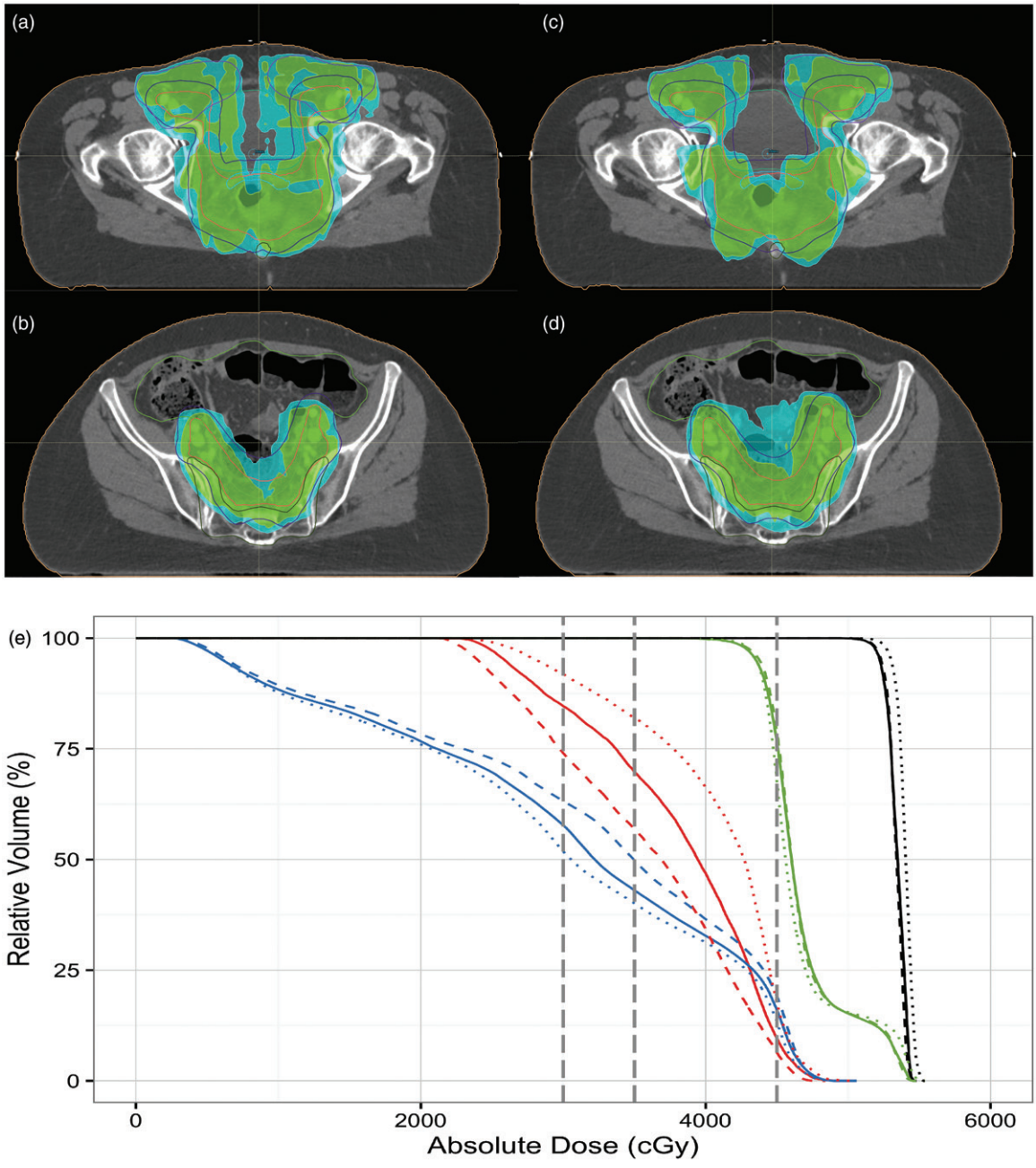

Figure 2. Dose distribution for a female patient in transversal view. Bowel sparing regimen at the planes of the bladder (a) and the bowel (b). Bladder sparing regimen at the planes of the bladder (c) and the bowel (d). Dose color wash, Green: 45 Gy (bowel optimization objective). Turquoise: (95% of 45 Gy). Also shown are the CTV-N, PTV-N, vagina, femoral heads, bowel and bladder. (e) DVH for the same patient, illustrating the dose to the bowel and bladder for the different low-dose plan regimens. Black is PTV-T, green is PTV-N, red is bladder and blue is bowel. Full line: low-dose regimen plan; dashed line: bladder sparing regimen plan; dotted line: bowel sparing regimen plan.

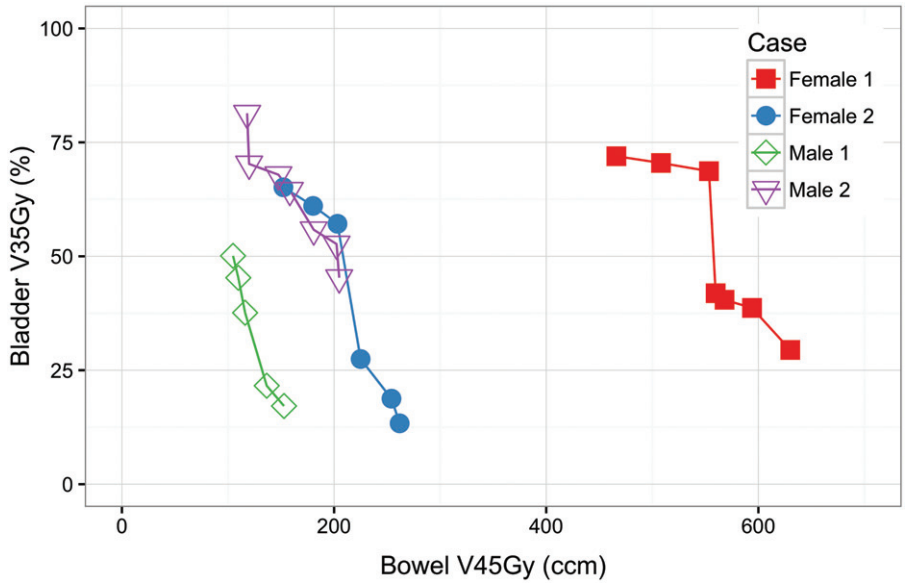

Figure 3. Pareto fronts for two male patients and two female patients; each connected set of points represents a set of dose plans for a single patient. Each data point corresponds to one dose plan, with the position of the point determined by the bowel V_{45Gy} and bladder V_{35Gy} for that specific plan.

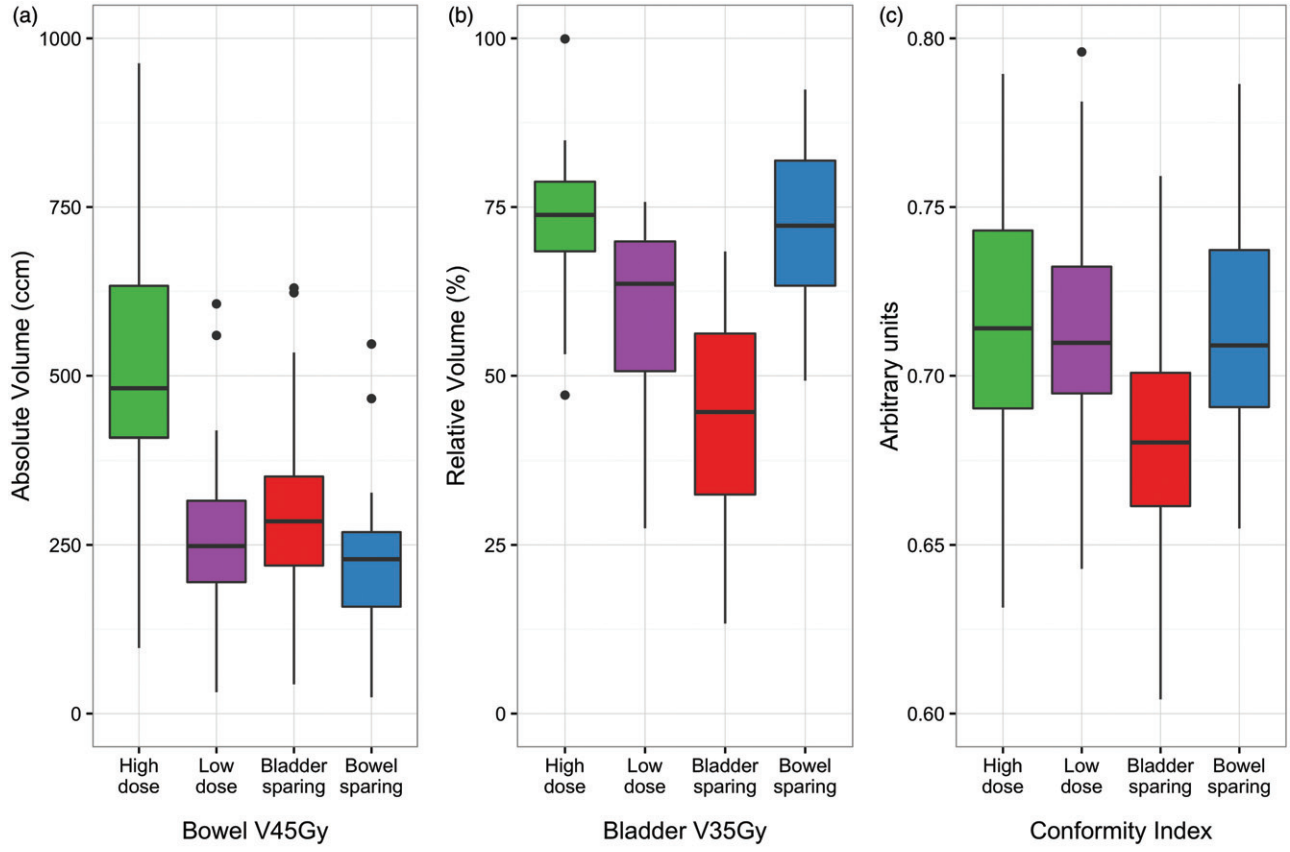

Figure 4. Box–Whisker plots for (a) Bowel V_{45Gy}, (b) Bladder V_{35Gy} and (c) PCI. Outliers are indicated by individual dots.

over a large set of pre-computed plans. This study investigated the impact of changing the total prescribed dose on OARs, and the further impact of prioritizing the sparing of OARs (specifically bowel and bladder). Differential sparing of other OARs (reproductive organs, pelvic bones) were considered but has not been comprehensively quantified.

To date, there is no clinical evidence that conclusively points out a single-dose level as being clinically superior for anal cancer. Guidelines and clinical trials addressed a wide range of prescribed doses and fractionations [1]. The low-dose preference we have simulated here is close to the upper limit of prescribed doses used elsewhere [2,20,21]. We estimated from published models [22] that the lower dose prescription might reduce the 2-year tumor control probability by $<1\%$ for early-stage tumors, and $\sim 5\%$ for late-stage tumors. A limitation associated with this model-based

estimate is that control outcomes are assumed to depend on tumor size, but not on other aspects of tumor biology.

All of the abovementioned chemo-radiotherapy prescribed doses has been associated with significant pelvic toxicity. While it is currently not possible to quantitatively predict which impact our observed changes in dose distribution might have on the absolute risks for acute and late toxicities, there is growing clinical evidence from cohort studies (anal cancer as well as other pelvic cancers) that irradiation of the bowel and the bladder in the range of 30–50 Gy indeed correlates with acute and late treatment-related morbidity [17–19,23].

The above conditions suggest that anal cancer radiotherapy is a natural setting for SDM, where physicians and patients would incorporate their joint preferences into radiotherapy dose planning, and thereby arrive at a more individually personalized treatment plan. For example, they may opt for a low-dose preference to reduce the likelihood of experiencing the most severe pelvic toxicities while accepting an increased chance of disease progression as a tradeoff. However, a different patient–physician pair may opt for the higher dose level to maximize the chance of tumor control while viewing an increased chance of severe pelvic toxicities as an acceptable compromise.

In this context, it would be unduly restrictive to consider only one radiotherapy treatment plan based on a static list of *a priori* clinical objectives. This is because a static list does not elegantly manage preferences that may vary between physicians, between patients, and even change over a course of treatment as different circumstances either arise or recede. The ability to redistribute dose between OARs is essential for incorporating preferences about certain types of toxicity [24], and further studies are required to quantify the clinical impact of modifying dose–volume metrics. Therefore our MCO planning study is an essential adjunct to current and planned clinical trials (see, e.g., ClinicalTrials.gov ID NCT02785263).

To examine the feasibility of redistributing dose between OARs in the pelvic area, we simulated additional OAR-sparing preferences at the lower dose level.

Multiple OARs were considered, including reproductive organs and pelvic bones, but we focused on the dominant tradeoffs that involved the bowel and bladder. This is reasonable given these are the largest OARs at closest proximity to the treated volumes. Our study has mainly focused on the effect of different guiding preferences on the tradeoff between dose–volume metrics in these two OARs. We found that there is potential to spare clinically significant bowel and bladder volumes irradiated up to 45 Gy and 35 Gy, respectively.

The intended clinical objective of 15 Gy average dose to whole testes was met for all but one. Opportunities for dose manipulation in MCO were extremely limited in general, because the testes were generally outside the limits of the IMRT fields and therefore mean doses were well under 15 Gy.

The intended clinical objective of $V_{50Gy} < 50\%$ to the penile bulb was also satisfied for every plan except one with a high-dose preference. Changing from a high-dose preference to a low-dose preference reduced V_{50Gy} by a median of 21.6 percentage points [(13.8; 25.0), $p > .01$]. We also considered the feasibility to shift dose away from the penile bulb. However, the tradeoff for penile bulb sparing appeared to be higher dose to the bowel and very much higher doses to the bladder.

The vagina was not delineated at the time of the original treatment planning and delivery. In cases where the vagina was retrospectively delineated, the upper and middle parts of the vagina were consistently located adjacent to the internal iliac nodes that had been included in the CTV-T. Therefore, sparing of the vagina was not feasible without violating the fixed clinical constraints on the CTV. Sparing of the vagina might require the use of temporary prosthetic inserts to displace the vagina away from the CTV [25].

There was only very limited possibility of manipulating the dose in the femoral heads; this was because the unwanted exposure of these OARs was low to begin with. In the high-dose preference, the median V_{50Gy} volumes in the femoral heads were 0.29% (0.02; 0.95) on the right side and 0.14% (0.05; 0.65) on the left side. These reduced to a median value of 0% in all of the low-dose preferences.

The median V_{50Gy} relative volume in the sacral bone was 12.7% in the high-dose preference plans, which was reduced to 0% for all plans at the low-dose prescription. The median V_{45Gy} was also reduced from 45.3 to 20.0%, respectively. The sacral bone was always located immediately adjacent to the posterior boundary of the nodal CTV. It is presently unclear whether the irradiation of the sacral bone could be reduced further, with the IMRT approach, without excessive dose penalty to bowel and bladder.

We observed that the available space for differential OAR sparing was highly patient-dependent. In some patients, it proved impossible to spare one OAR at the expense of another. The tradeoffs between OARs were also observed to impact on dose uniformity and dose conformality (PCI). The sensitivity of the PCI to bladder sparing preference was presumed to be due to the bladder being tightly confined on almost all sides by the PTV-N.

At present, we do not have a method for predicting (before commencing treatment planning) the space in which tradeoffs would be possible for any given patient. However, the cohort statistics suggests that we should expect some degree of freedom to prioritize certain clinical objectives in most patients. As a study of 22 representative anal cancer patients with a broad range of disease stages, we expect that the overarching conclusions of our analysis to be robust.

While we do not yet know the exact proportion, characteristics or anatomical complexities of patients who might participate in a study of SDM in anal cancer, studies have shown that prostate cancer patients have a high level of preference for active participation in decision making [26] and, more pertinently, they may have marked prioritization for higher quality of life rather than potential gains in survival [27]. It is currently unclear whether the same preferences appear among anal cancer patients, but we only know of one SDM clinical study in anal cancer to date that is actively recruiting (PC-Anal-01, NCT02785263).

One study [28] found that anal cancer patients experience the least involvement in decisions regarding their treatment

compared to other patient groups, therefore further work is required to facilitate clinical investigations in this area. In current clinical consultations, a report by Kunneman et al. [29] shows that physicians do not discuss treatment options with their patients. Concerns about SDM persist, such as a patient's ability to comprehend tradeoffs or abandoning a patient to make the final decision on their own [30]. Other studies highlight the need for specific interventions [31] that address understanding of preference-sensitive treatment choices, effective management of difficult emotions and active listening to elucidate preferences. The literature on patient regret after participating in an active treatment decision is presently inconclusive, but van Tol-Geerding et al. [32] shows that providing clear information about potential tradeoffs (such as a decision aid) may actually lower the level of decision regret, even in patients experiencing severe side effects.

In regards to practical logistics for treatment planning, we found that the MCO-based approach was an efficient method to explore and visualize the inherent tradeoffs between competing clinical objectives. The MCO module provided an intuitive user interface to design dose distributions according to shifting relative importance between clinical objectives. Derivation of an initial plan typically required 3–4 h of intensive planning time per patient. The pre-computation of all feasible plans, final optimization of a preferred plan and accurate dose computation required 1–1.5 h per additional plan.

Conclusions

For 22 representative patients with various stages of anal cancer suitable for chemo-radiotherapy treatment, we have shown that incorporating preferences into the treatment plan is feasible while maintaining clinically acceptable constraints. A central theme in our results was the inherent tradeoff in the dose distributions resulting from prioritization of one clinical objective above others. The dominant tradeoff in these IMRT plans involved the bowel and the bladder. Although tradeoffs were highly patient-specific, we were nonetheless able to efficiently create preference-informed dose distributions that would support a shared decision-making approach in anal cancer treatment. However, in view of the knowledge gaps remaining in regards tumor control and normal tissue toxicity, further investigations of dose prescription and dose re-distribution in the pelvic region are required.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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