Article:
Rønde, HS, Wee, L, Pløen, J et al. (1 more author) (2017) Feasibility of preference-driven radiotherapy dose treatment planning to support shared decision making in anal cancer. Acta Oncologica, 56 (10). pp. 1277-1285. ISSN 0284-186X

https://doi.org/10.1080/0284186X.2017.1315174

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

Running title

Feasibility of preference-driven radiotherapy dose planning for anal cancer

Heidi S Rønde M.Sc.[1,a], Leonard Wee Ph.D.[2,3], John Pløen M.D.[3,4] and Ane L Appelt Ph.D.[3,5]

[1] Department of Medical Physics, Vejle Hospital, Denmark

[2] MAASTRO Clinic, School of Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands

[3] Danish Colorectal Cancer Centre South, Vejle Hospital, and Institute of Regional Health Research, University of Southern Denmark, Denmark

[4] Department of Oncology, Vejle Hospital, Denmark

[5] Leeds Institute of Cancer and Pathology, University of Leeds, and Leeds Cancer Centre, St. James' University Hospital, Leeds, United Kingdom

[a] Corresponding author : heidi.staghoej.roende@rsyd.dk

Disclosure

No potential conflicts of interest.

Acknowledgements

The authors thank RaySearch Laboratories for use of a non-clinical software license and their technical support. The authors acknowledge discussions and feedback about Shared Decision Making from Karina Dahl Steffensen M.D., Ph.D. and on the general clinical concept of anal cancer clinical trials from Lars Henrik Jensen, M.D., Ph.D.

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 trade-offs 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.

Materials and Methods: Retrospective plans were generated for 22 anal cancer patients. Multi-criteria optimisation 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* (60.2Gy tumour boost and 50.4Gy to elective nodes with physician-defined order of priorities), *low dose preference* (53.75Gy tumour boost, 45Gy 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]; $p<0.01$) and for a bowel sparing preference (median change in V_{45Gy} : 281 cm^3; [73;488]; $p<0.01$). 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]; $p<0.01$) and for a bladder sparing preference (median change in V_{35Gy} : 30.3%-points; [12.4;43.1]; $p<0.01$).

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

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 tumour and involved nodes are 54-60Gy as simultaneous integrated boost (SIB) with 45-50Gy to elective nodes, using per fraction doses of 1.8-2.0Gy daily. Meanwhile, most UK centres [2, 3] would prescribe 50.4-53.2Gy to the primary tumour and involved nodes as SIB, with 40Gy 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, 5, 6, 7]. At lower doses, the risk of adverse events may be reduced, presumably at the cost of increased risk of local recurrence. However, tumour 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 personalised treatments. Specifically in radiotherapy treatment

91 planning, preferences are expected to be important when determining the
92 prioritisation of clinical objectives since there are inherent *trade-offs* between
93 competing objectives.
94
95 In a Shared Decision Making (SDM) paradigm [9, 10], a patient and their
96 treating physician *both* bring their individual preferences and desired treatment
97 outcomes directly into a structured consultation, and thus arrive at a treatment
98 decision together. Ideally, SDM consultations should be supported by
99 information about the necessary trade-offs in clinical outcomes pertaining to
100 clinically equipoise choices.
101
102 There is a genuine gap in anal cancer radiotherapy in the range of clinically
103 equipoise tumour doses, such that the joint preferences of the physician and the
104 patient might be used to determine which trade-offs are acceptable when
105 designing an individually customized treatment plan.
106
107 The typical approach of inversely-planned intensity modulated radiotherapy
108 (IMRT) requires a planner to iterate many times through a fixed list of *a priori*
109 clinical objectives, usually defined according to a physician's priorities, until a
110 single clinically acceptable plan found [11].
111
112 Multi-criteria optimisation® (MCO) is a novel dose planning approach [12, 13]
113 that allows dynamically variable (i.e. floating) clinical objectives while always

satisfying fixed clinical constraints, such as a minimum dose to the tumour 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 trade-offs can be interactively visualised.

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

Materials 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).

Radiotherapy treatment planning

The delineations of anal tumour (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 tumour and involved nodes were prescribed 60.2Gy as SIB with 50.4Gy 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 53.75Gy in the anal tumour and involved nodes as SIB and 45Gy 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 - 300cm^3), bowel V_{30Gy} range (0 - 600cm^3), bladder V_{50Gy} range (0 - 20%) and bladder V_{35Gy} range (0 - 75%) [17, 18, 19]. A complete list of objectives is provided (see online Appendix e2, Table e5).

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 over-doses (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) using a pencil-beam approximation for the pre-computation of feasible plans followed by collapsed-cone convolution for the accurate dose. An 8-field 6MV IMRT technique was used assuming treatment on an Elekta Agility delivery system (Elekta AB, Stockholm, Sweden).

Analysis

Cumulative dose-volume histograms 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 $p < 0.01$, 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 focussed on the trade-off 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 2 men and 2 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 2-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 trade-offs 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], $p<0.01$) at V_{30Gy} and 234 cm^3 ([66;467 cm^3], $p<0.01$) at V_{45Gy}. The median changes from a high dose preference to a bowel sparing preference were 128 cm^3 ([14;331 cm^3], $p<0.01$) and 281 cm^3 ([73;488 cm^3], $p<0.01$), 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 45Gy below 300cm^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], $p<0.01$) 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], $p<0.01$). The median *change* in bladder sparing at V_{45Gy} due to the bladder sparing preference was

statistically significant and clinically meaningful, since an objective was to limit the *total* bladder irradiated to 35Gy 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 trade-offs 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 trade-offs implicit in radiotherapy dose planning. Specifically, re-distribution of doses and differential OAR sparing was feasible by using MCO to navigate 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 prioritising 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 tumour control probability by less than 1% for early stage tumours, and approximately 5% for late stage tumours. A limitation associated with this model-based estimate is that control outcomes are assumed to depend on tumour size, but not on other aspects of tumour 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 30-50Gy indeed correlates with acute and late treatment-related morbidity [17, 18, 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 personalised 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 trade-off. However, a different patient-physician pair may opt for the higher dose level to maximise the chance of tumour 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, for example, *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 focussed on the dominant trade-offs 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 focussed on the effect of different guiding preferences on the trade-off 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 45Gy and 35Gy, respectively.

The intended clinical objective of 15Gy 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 15Gy.

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], $p > 0.01$). We also considered the feasibility to shift dose away from the penile bulb. However, the trade-off 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

365 the expense of another. The trade-offs between OARs were also observed to
366 impact on dose uniformity and dose conformality (PCI). The sensitivity of the
367 PCI to bladder sparing preference was presumed to be due to the bladder being
368 tightly confined on almost all sides by the PTV-N.
369
370 At present, we do not have a method for predicting (before commencing
371 treatment planning) the space in which trade-offs would be possible for any
372 given patient. However, the cohort statistics suggests that we should expect
373 some degree of freedom to prioritise certain clinical objectives in most patients.
374 As a study of 22 representative anal cancer patients with a broad range of
375 disease stages, we expect that the overarching conclusions of our analysis to be
376 robust.
377
378 While we do not yet know the exact proportion, characteristics or anatomical
379 complexities of patients who might participate in a study of SDM in anal cancer,
380 studies have shown that prostate cancer patients have a high level of preference
381 for active participation in decision making [26] and, more pertinently, they may
382 have marked prioritisation for higher quality of life rather than potential gains
383 in survival [27]. It is currently unclear whether the same preferences appear
384 among anal cancer patients, but we only know of one SDM clinical study in anal
385 cancer to date that is actively recruiting (PC-Anal-01, NCT02785263).
386

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 trade-offs 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 trade-offs (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 visualise the inherent trade-offs 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 hours 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 hour per additional plan.

Conclusion

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 trade-off in the dose distributions resulting from prioritization of one clinical objective above others. The dominant trade-off in these IMRT plans involved the bowel and the bladder. Although trade-offs 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 tumour control and normal tissue toxicity, further investigations of dose prescription and dose re-distribution in the pelvic region are required.

References

1. Spithoff K, Cummings B, Jonker D, et al. Chemoradiotherapy for Squamous Cell Cancer of the Anal Canal: A Systematic Review. Clinical Oncology 2014;26(8):473-487.
2. R. Muirhead R, Drinkwater K, O'Cathail SM, et al. Initial Results from the Royal College of Radiologists' UK National Audit of Anal Cancer Radiotherapy 2015. Clinical Oncology 2014;29(3):188-197.
3. Hoskin P (ed.), Radiotherapy dose fractionation, 2nd ed. The Royal College of Radiologists, 2012. Chapter 1: Anal Cancer; 10-12
4. Han K, Cummings BJ, Lindsay P, et al. Prospective Evaluation of Acute Toxicity and Quality of Life After IMRT and Concurrent Chemotherapy for Anal Canal and Perianal Cancer. Int J Radiat Oncol Biol Phys. 2014;90(3):587–594.
5. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal. Int J Radiat Oncol Biol Phys. 2013;86(1):27-33.
6. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). Br J Cancer. 2010;102(7):1123–1128.

7. Fakhrian K, Sauer T, Dinkel A, et al. Chronic adverse events and quality of life after radiochemotherapy in anal cancer patients. Strahlenther Onkol. 2013;189:486-494.
8. Fiorinoa C, Valdagnib R, Rancatib T, et al. Dose–volume effects for normal tissues in external radiotherapy: Pelvis. Radiother Oncol. 2009;93(2):153-167.
9. Barry MJ, Edgman-Levitan S. Shared decision making - pinnacle of patient-centered care. N Engl J Med. 2012;366(9):780-781.
10. Stiggelbout AM, Pieterse AH, De Haes JCJM. Shared decision making: Concepts, evidence, and practice. Patient Educ Couns. 2015;98(10):1172-1179.
11. Bortfeld T. I MRT: a review and preview. Phys. Med. Biol. 2006;51:363-379.
12. McGarry CK, Bokrantz R, O'Sullivan JM, et al. Advantages and limitations of navigation-based multicriteria optimization (MCO) for localized prostate cancer IMRT planning. Med Dosim. 2014;39(3):205–211.
13. Monz M, Küfer KH, Bortfeld TR, et al. Pareto navigation: algorithmic foundation of interactive multi-criteria IMRT planning. Phys Med Biol. 2008;53(4):985-98.
14. Call AJ, Prendergast BM, Jensen LG, et al. Intensity-modulated Radiation Therapy for Anal Cancer. Results From a Multi-Institutional Retrospective Cohort Study. Am J Clin Oncol. 2016;39(1):8-12.
15. Danish Anal Cancer Group (DACG): http://www.dccg.dk/03_Publikation/ret_analcancer.pdfhttp://www.dccg.dk/03_Publikation/ret_analcancer.pdf

16. Roels S, Duthoy W, Haustermans K, et al. Definition and delineation of the clinical target volume for rectal cancer. Int J Radiat Oncol Biol Phys. 2006;65:1129-1142.
17. DeFoe SG, Kabolizadeh P, Heron DE, et al. Dosimetric Parameters Predictive of Acute Gastrointestinal Toxicity in Patients with Anal Carcinoma Treated with Concurrent Chemotherapy and Intensity-Modulated Radiation Therapy. Oncology 2013;85(1):1-7.
18. Appelt AL, Bentzen SM, Jakobsen A, et al. Dose-response of acute urinary toxicity of long-course preoperative chemoradiotherapy for rectal cancer. Acta Oncol. 2015;52(2):179-186.
19. Viswanathan AN, Yorke ED, Marks LB, et al. Radiation dose-volume effects of the urinary bladder. Int J Radiat Oncol Biol Phys. 2010;1;76(3 Suppl):116-122.
20. Franco P, Arcadipane F, Ragona R, et al. Locally Advanced (T3-T4 or N+) Anal Cancer Treated with Simultaneous Integrated Boost Radiotherapy and Concurrent Chemotherapy. Anticancer Res. 2016;36(4):2027-2032.
21. Franco P, Arcadipane F, Ragona R, et al. Early-stage Node-negative (T1-T2N0) Anal Cancer Treated with Simultaneous Integrated Boost Radiotherapy and Concurrent Chemotherapy. Anticancer Res. 2016;36(4):1943-1948.
22. Muirhead R, Partridge M, Hawkins MA, et al. A tumor control probability model for anal squamous cell carcinoma. Radiother Oncol 2015;116(2):192–196.

501 23. Julie DA, Oh JH, Apte AP, et al. Predictors of acute toxicities during
502 definitive chemoradiation using intensity-modulated radiotherapy for anal
503 squamous cell carcinoma. Acta Oncol. 2016;55(2):208-216.
504 24. Smith WP, Kim M, Holdsworth C, et al. Personalized treatment planning
505 with a model of radiation therapy outcomes for use in multiobjective
506 optimization of IMRT plans for prostate cancer. Radiat Oncol.
507 2016;11;11(1):38.
508 25. Briere TM, Crane CH, Beddar S. et al. Reproducibility and genital sparing
509 with a vaginal dilator used for female anal cancer patients. Radiother Oncol.
510 2012;104:161-166.
511 26. Stalmeier PF, van Tol-Geerdink JJ, van Lin EN, et al. Doctors' and Patients'
512 Preferences for Participation and Treatment in Curative Prostate Cancer
513 Radiotherapy. J Clin Oncol. 2007;25(21):3096-3100.
514 27. van Tol-Geerdink JJ, Stalmeier PF, van Lin EN, et al. Do Patients With
515 Localized Prostate Cancer Treatment Really Want More Aggressive
516 Treatment? J Clin Oncol. 2006;24(28):4581-4586.
517 28. Turabi AE, Abel GA, Roland M, et al. Variation in reported experience of
518 involvement in cancer treatment decision making: evidence from the National
519 Cancer Patient Experience Survey. Br J Cancer. 2013;109:780-787.
520 29. Kunneman M, Engelhardt EG, Ten Hove FL, et al. Deciding about (neo-
521)adjuvant rectal and breast cancer treatment: Missed opportunities for shared
522 decision making. Acta Oncol. 2016;55(2):134–139.
523 30. Glimelius B, Cavalli-Björkman. Does shared decision making exist in
524 oncologic practice? Acta Oncol. 2016;55(2):125–128.

31. Bernabeo E, Holmboe ES. Patients, providers, and systems need to acquire a specific set of competencies to achieve truly patient-centered care. Health Aff. 2013;32(2):250-8.
32. van Tol-Geerdink JJ, Leer JW, Wijburg CJ, et al. Does a decision aid for prostate cancer affect different aspects of decisional regret, assessed with new regret scales? A randomized, controlled trial. Health Expect. 2016;19(2):459-470.

Figure legends.

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).

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 Clinical Target Volume (CTV-N), Planning Target Volume (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) Plan Conformity Index. Outliers are indicated by individual dots.