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# Treatment planning for patients with low rectal cancer in a multicenter prospective organ preservation study

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ABSTRACT

*Background:* Non-surgical management of rectal cancer relies on (chemo)radiotherapy as the definitive treatment modality. This study reports and evaluates the clinical high dose radiotherapy treatment plans delivered to patients with low resectable rectal cancer in a Danish multicenter trial.
*Methods:* The Danish prospective multicenter phase II Watchful Waiting 2 trial (NCT02438839) investigated definitive chemoradiation for non-surgical management of low rectal cancer. Three Danish centers participated in the trial and committed to protocol-specified treatment planning and delivery requirements. The protocol specified a dose of 50.4 Gy in 28 fractions to the elective volume (CTV-/PTV-E) and a concomitant boost of 62 Gy in 28 fractions to the primary target volume (CTV-/PTV-T).
*Results:* The trial included 108 patients, of which 106 treatment plans were available for retrospective analysis. Dose coverage planning goals for the main target structures were fulfilled for 94% of the treatment plans. However, large intercenter differences in doses to organs-at-risk (OARs) were seen, especially for the intestines. Five patients had a V60Gy>10 $cm^3$ for the intestines and two patients for the bladder.
*Conclusion:* Prescribed planning goals for target coverage were fulfilled for 94% of the treatment plans, however analysis of OAR doses and volumes indicated intercenter variations. Dose escalation to 62 Gy (as a concomitant boost to the primary tumor) introduced no substantial high dose volumes (>60 Gy) to the bladder and intestines. The treatment planning goals may be used for future prospective evaluation of highdose radiotherapy for organ preservation for low rectal cancer.

## 1. Introduction

The standard treatment in Denmark for low (≤6cm from anal verge) resectable T1-T3 rectal tumors is total mesorectal excision (TME)-based surgery (often abdominoperineal resection (APR)), potentially preceded by neo-adjuvant chemoradiation for T3 cancers. Although effective in terms of oncological outcome, these surgical procedures lead to a substantial risk of acute and long-term complications, as well as a permanent stoma [1,2]. Several studies have shown that a significant fraction of patients (12–58 %, strongly dependent on stage) may obtain a complete response after standard chemoradiation (CRT) [3,4], which implies that operative intervention might not be needed for all patients. Therefore, the last decade has seen multiple clinical trials of non-surgical management via so-called Watch & Wait strategies [5,6]. These explore CRT as the definitive treatment modality, with an extensive follow-up scheme, ensuring that patients with sign of tumor progression (immediately following CRT) or regrowth (after an initial complete response) are referred to surgical management.

Standard dose-fractionation regimens for neo-adjuvant CRT in rectal cancer are either 25 Gy in 5 fractions or 45–50.4 Gy in 25–28 fractions, depending on baseline risk factors. It is unclear, however, whether these treatment schedules are optimal when the primary aim is organ

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preservation through non-surgical management. Several studies have investigated long-term tumor control with or without boost to the primary tumor [5–8]; using a variety of boost modalities, including external beam radiotherapy (EBRT), contact (Papillon) X-ray treatment, and endorectal brachytherapy. Very recently, the randomized phase III OPERA trial demonstrated the benefit of a high-dose contact X-ray boost for increasing the rate of organ preservation [9]. A dose–response relationship for local control as function of equivalent dose in 2 Gy per fraction (EQD2) has been estimated from published data by Appelt et al [10], supporting the notion that dose escalation to the tumor volume increases the chance of local control at 2 years for early and locally advanced rectal cancer patients. However, dose escalation to target structures potentially increases the risk of radiation induced acute and late toxicity to organs at risk (OARs). Although there is limited data on dose–response for OARs for rectal cancer radiotherapy (RT), especially in the organ preservation setting, higher dose to normal tissue will likely translate into increased toxicity; as seen for e.g. acute [11] and late [12] bowel toxicity, urinary toxicity, [13] and anorectal function [14]. Therefore, it is important to consider the risk of radiation induced toxicity compared to the advantages of non-surgical management when opting for dose intensification. There are no established plan optimization goals for high-dose RT for organ preservation, however, and creating guidelines for treatment planning for organ preservation studies is challenging, in particular due to the lack of published evidence on OAR dose–response and dose constraints in this setting. Collection of dose data, and correlation with toxicity and functional outcome data from prospective trials will be key to change this status quo.

This study reports and evaluates the clinical high-dose RT treatment plans delivered to patients with low resectable rectal cancer in a Danish prospective multicenter phase 2 clinical trial of non-surgical management (Watchful Waiting 2, NCT02438839). We report the suggested dose planning goals for EBRT treatment plans with a dose escalation to the tumor of 62 Gy as a concomitant boost. The feasibility of reaching these goals and the resulting characteristics of the delivered treatment plans are reported and evaluated.

## 2. Material and methods

### 2.1. Clinical trial design

The Danish prospective multicenter phase 2 clinical trial Watchful Waiting 2 investigated whether radical external high dose chemoradiation for organ preservation of low rectal cancer is feasible, safe and effective in a multicenter study with results comparable to those of single center studies. Patients were enrolled and treated from 2015 to 2019. The primary endpoint of the trial was proportion of patients with locoregional tumor control two years after end of treatment and the main secondary endpoint was rate of long-term side effects. The primary endpoint results were reported at the 2022 ASCO Annual Meeting [15], with 61 % of the patients having tumor control without surgery after 2 years of follow-up. Late toxicity at 2 years was very low (11 % grade 2+) and two thirds of patients reported no or minor low anterior rection syndrome (LARS). Main inclusion criteria were histopathologically verified, primary resectable T1-T3, N0-N1 adenocarcinoma located $\leq 6$ cm from the anal verge with a planned abdominoperineal resection (APR) or ultralow resection (i.e. procedures either resulting in permanent stoma or very low anastomosis, i.e. potential long-term anorectal functional issues). N1 was only allowed for lymph nodes localized to the mesorectum at the level of the tumor. The trial protocol was approved by the Regional Scientific Ethics Committee for Southern Denmark (protocol ID S-2015011), and all patients provided written informed consent. The WW2 trial was registered on ClincalTrials.gov (NCT02438839).

### 2.2. Participating centers

Three cancer centers (and hence three RT departments) participated in the trial, located in different health care regions of Denmark. Centers 1 and 3 had Varian treatment units (Varian Medical Systems, Palo Alto, CA), with Eclipse™ Treatment Planning System (TPS), and Center 2 had Elekta treatment units (Elekta AB, Stockholm, Sweden) and Raystation® TPS (RaySearch Medical Laboratories AB, Sweden).

### 2.3. Treatment planning guidelines

The trial protocol specified a dose of 50.4 Gy in 28 fractions to the elective volumes (CTV-/PTV-E) and 62 Gy in 28 fractions to the primary target volumes (CTV-/PTV-T) delivered as EBRT with a concomitant boost (see Fig. 1). The trial RT guidelines followed the principles of the ICRU report 83 [16] and included detailed instructions for delineation of all target and OAR volumes (see Appendix A.1) as well as for treatment plan optimisation. The tumor clinical target volume (CTV-T) was defined as the primary tumor (GTV) as well as the rectum circumference at the same level (and any pathological lymph nodes directly adjacent to the primary tumor). The elective clinical target volume (CTV-E) included the mesorectal and presacral nodes and lateral pelvis lymph region (superior rectal, middle rectal, internal iliac, obturator and pudendal lymph nodes). The OARs were the intestines, bladder, sacral bone, femoral heads, testicles and penile bulb.

The centers were required to use inverse plan optimization techniques and daily image-guidance (IGRT). Treatment planning optimization goals for target and OAR structures were provided (Table 1); where, for example, the denotation $V_{95\%}$=100 % for CTV-T means that the whole volume (100 %) of the CTV-T should receive at least 95 % of the prescribed dose. All values for bowels were considered for absolute rather than relative volumes. The optimization goals were to be prioritized in the following order: *CTV-T* > *CTV-E* > *PTV-T* > *PTV-E* > *Intestines* $V_{45Gy}$ > *Bladder* $V_{50Gy}$ > *Intestines* $V_{30Gy}$ > *Bladder* $V_{35Gy}$ > *High dose to PTV-E outside PTV-T* > *Other organs at risk*. Importantly, note that no planning goals were regarded as mandatory or critical; i.e. non-compliance was not considered a protocol deviation, and it was expected that OAR goals in particular would not be achievable for some patients. Instead, these were regarded as goals to guide plan optimisation to ensure as low as possible dose to OAR, in a setting where no definitive data exist on OAR dose tolerances.

A suggestion for CTV-to-PTV margin (cranio-caudal 10 mm, lateral 10 mm, posterior 7 mm and anterior 13 mm for both the PTV-E and PTV-T) construction was also provided, but not mandatory, as centers were encouraged to establish PTV margins appropriate to their local IGRT procedures and treatment pathway uncertainties.

### 2.4. Treatment plan analysis

All treatment plans (planning CT scans, structure sets, dose distributions) were retrospectively uploaded to a Danish national RT treatment plan databank (DcmCollab), which facilitates direct and easy access to data and statistics from all the treatment plans from each center [17]. From DcmCollab, the treatment plan data were extracted and analysed using Matlab (MATLAB version: 9.8.0.1380330 (R2020a) Update 2, Natick, Massachusetts: The MathWorks Inc.; 2022.). Data for all dose metrics for planning goals were extracted for analysis. In addition, data for $V_{60Gy}$ for the intestines and bladder were analysed: Since standard fractionation schemes for neoadjuvant long course RT of locally advanced rectal cancer are around 45–50.4 Gy, escalating dose to the tumor volume might introduce high dose areas (>60 Gy). At the time of trial initiation, no data were available to guide high dose OAR planning goals. Therefore, high dose OAR volumes were not considered for the prospective treatment planning goals, but were deemed of interest for the retrospective evaluation.

For a subset of patients some of the mandatory structures were not

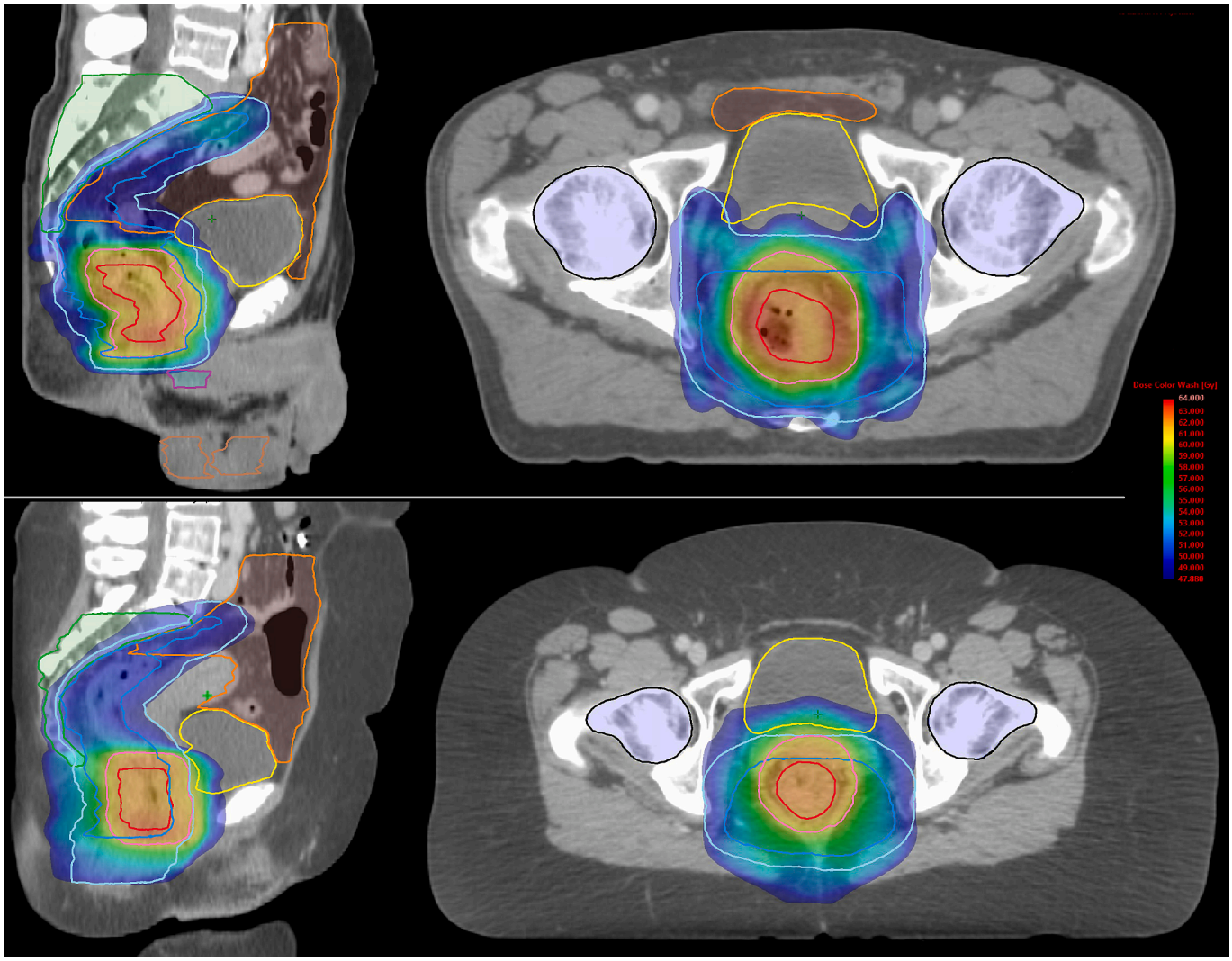


**Fig. 1.** Sagittal and transversal views of two dose distributions showing 95 % of 50.4 Gy to the elective target volumes CTV-/PTV-E (blue/cyan contour) and boost volume for primary target volumes CTV-/PTV-T (red/pink contour). Intestines, delineated as the bowel cavity, is contoured in orange, bladder in yellow, sacral bone in green, femoral heads in black, penile bulb in purple and testicles in brown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

prospectively delineated (in violation of the trial RT guidelines). Therefore, these structures were retrospectively delineated on the planning CT scans by an experienced therapeutic radiographer as part of the centralized data analysis.

### 2.5. Statistical analysis

Non-parametric Kruskal-Wallis tests [18] were used for intercenter comparison of median doses and volumes of targets and OARs. For correlation analysis Spearman's rho [19] was used, reported as the value of $\rho^2$, which measures the strength of correlation on a scale of 0 to 1 (from none to completely correlated).

## 3. Results

The trial enrolled 108 patients, of which 107 patients started the RT treatment and 104 received the full RT course. One patient was planned outside of the trial guidelines, without concomitant boost, and therefore excluded from this report. This resulted in a total of 106 treatment plans available for retrospective analysis. General patient characteristics can be seen in Table 2. The patient cohort was unevenly distributed between the centers with 27 (Center 1), 67 (Center 2) and 12 (Center 3) participants. This was due to differences in date of opening for trial enrollment and local inclusion rates. Table A.2 (appendix) shows the preparation, treatment planning and IGRT details for each center. All patients were treated in supine position, with similar fixation equipment. A variety of treatment planning systems (Eclipse / Oncentra MasterPlan/ RayStation) were used to deliver IMRT or VMAT. Most notably was the use of three different bladder filling protocols; empty (Center 1), none (Center 2) and comfortably full (Center 3).

For 24 treatment plans, not all mandatory OAR structures were prospectively delineated. Most predominant was the lack of delineations for the testicles and penile bulb. For Center 1 the testicles were not delineated for 12 patients (67 % of male patients) and for Center 3 the testicles were not delineated for 8 patients (89 % of male patients) and the penile bulb for 6 patients (67 % of male patients). The full overview and distribution of the missing structures can be seen in the Appendix A.3.

Target volumes and doses are reported in Table 3 for the full cohort as well as for the three centers separately. The primary clinical target volume, CTV-T, had a median volume of 38.4 $cm^3$, and the PTV-T a median volume of 143.9 $cm^3$. Center 3 had the largest median volumes of CTV-T and PTV-T. No intercenter volume difference were observed for the elective target volume, CTV-E, with a median volume of 584.7

**Table 1**
Treatment planning goals and prioritization for elective volumes (CTV-/PTV-E), target volumes (CTV-/PTV-T) and organs-at-risk as proposed in trial RT guidelines. For CTV-/PTV-E the prescribes dose was 50.4 Gy and for CTV-/PTV-T the prescribed dose was 62 Gy. All values for bowels related to absolute rather than relative volumes. The denotation e.g., V95%=100 % means that the whole volume (100 %) of the structure should receive at least 95 % of the prescribed dose. For organs-at-risk the denotation e.g., V30Gy $<$ 600 $cm^3$ means the no more than 600 $cm^3$ should receive more than 30 Gy. PTV-E − (PTV-T + 5 mm) is PTV-E with (PTV-T plus a 5 mm margin) subtracted.

| Structure | Planning goal | Priority |
|---|---|---|
| CTV-T, CTV-E | $V_{95\%} = 100$ % | 1 |
| PTV-T | Mean dose = 99 % − 102 %<br>$V_{95\%} \geq 99$ %<br>$V_{90\%} = 100$ %<br>$V_{105\%} \leq 1$ % | 2 |
| PTV-E | $V_{95\%} \geq 98$ %<br>$V_{90\%} = 100$ % | 3 |
| PTV-E − (PTV-T + 5 mm) | Mean dose = 99 % − 102 %<br>$V_{90\%} = 100$ %<br>$V_{107\%} \leq 3$ % | 8 |
| Intestines | $V_{30Gy} < 600$ $cm^3$<br>$V_{45Gy} < 300$ $cm^3$ | 6<br>4 |
| Bladder | $V_{50Gy} < 20$ %<br>$V_{35Gy} < 75$ % | 5<br>7 |
| Sacral bone | $V_{50Gy}$ as low as possible | 9 |
| Penile bulb | $V_{50Gy} < 20$ %<br>$V_{50Gy}$ as low as possible | 9 |
| Femoral heads | $V_{50Gy} < 5$ %<br>$V_{50Gy}$ as low as possible | 9 |
| Testicles | Mean dose $<$ 15 Gy<br>$V_{50Gy}$ as low as possible | 9 |
| External body contour | $V_{105\%} < 3$ $cm^3$ outside PTV | 9 |

**Table 2**
Patient characteristics for full cohort and separate centers. cT: clinically staged T category. cN: clinically staged N category. IQR: interquartile range. Tumor height is defined as distance measured on magnetic resonance imaging scan (MRI) from anal verge to lowest part of tumor.

| | | All | Center 1 | Center 2 | Center 3 |
|---|---|---|---|---|---|
| Number of patients | | 106 | 27 | 67 | 12 |
| cT category | T1 | 16 | 2 | 13 | 1 |
| | T2 | 56 | 15 | 34 | 7 |
| | T3 | 34 | 10 | 20 | 4 |
| cN category | N0 | 75 | 17 | 46 | 12 |
| | N1 | 31 | 10 | 21 | 0 |
| Age | Median | 71 years | 67 years | 72 years | 74 years |
| Sex | Female | 39 | 9 | 27 | 3 |
| | Male | 67 | 18 | 40 | 9 |
| Tumor height on MRI (mm) | Median | 45 | 41 | 48 | 35 |
| | IQR | 35–55 | 38–58 | 35–55 | 30–40 |
| Tumor length on MRI (mm) | Median | 34 | 30 | 35 | 34 |
| | IQR | 23–40 | 25–42 | 30–40 | 25–40 |

$cm^3$. For the planning target volumes, the suggested protocol specified margins were applied for 98 of the 106 of the treatment plans. However, whilst Center 2 was consistent in use of these margins, Centers 1 and 3 used alternative margins for a subset of patients, either based on the standard national guidelines for rectal cancer radiotherapy or individually adjusted margins. For 8 patients, smaller margins (lateral, craniocaudal and posterior: 3–5 mm, anterior: 10–13 mm) were used for the elective volume and for 6 patients slightly larger margins (up to 2 mm larger) were used for the tumor boost volume. Intercenter volume differences were observed with Center 2 having the largest median volume for the PTV-E. Mean dose for the target volumes were different across the centers, however these were all within protocol specifications.

The intestines and bladder showed significant intercenter volume differences ($p < 0.001$), see Fig. 2. For the intestines, the largest volume was seen in Center 1 (median 2079 $cm^3$, interquartile range: 1507 $cm^3$ − 2868 $cm^3$) and the smallest in Center 3 (median volume 868 $cm^3$, interquartile range: 606 $cm^3$ − 1405 $cm^3$). For the bladder, the largest volume was seen in Center 3 (median 222 $cm^3$, interquartile range: 167 $cm^3$ − 310 $cm^3$) and smallest in Center 1 (median 101 $cm^3$, interquartile range: 71 $cm^3$ – 154 $cm^3$).

The planning goals to the target structures and OARs are illustrated in Figs. 3 and 4, with tolerances shown as green and red. For the majority of treatment plans, the target and OAR planning goals were achieved.

To quantify the applicability of the planning goals when used in the clinic, the number of treatment plans fulfilling each planning goal are shown in Table 4. Each planning goal was evaluated with a tolerance of ± 0.5 %, to discard decimal rounding effects. All planning goals were fulfilled for 100 of 106 plans with regards to dose coverage of the target structures, except for V107% $<$ 3 % for the PTV-E-(PTV-T + 5 mm), which 83 plans fulfilled.

For the bladder, femoral heads and testicles, at least 90 treatment plans fulfilled the respective planning goals. However, for the intestines only 71 treatment plans fulfilled both planning goals. For Centers 1 and 2, 52 %–74 % of the plans (depending on the specific goal) fulfilled the goals, whereas Center 3 fulfilled both planning goals for all treatment plans. For the penile bulb Center 3 exceeded the planning goal for 56 % of treatment plans.

To test if the planning goals for the intestines affect the achievability of the goals for the bladder and vice versa, a scatterplot (Appendix A.4) and correlation analysis was performed for the low dose planning goals (bladder $V_{35Gy}$ vs intestines $V_{30Gy}$) and high dose planning goals (bladder $V_{50Gy}$ vs intestines $V_{45Gy}$). For the high dose goals no statistically significant correlation was found ($\rho^2 = 0.02$, $p = 0.17$), and for the low dose only a weak correlation was found ($\rho^2 = 0.05$, $p = 0.02$).

In Appendix A.5 median values for all planning goals for OARs are listed. The median volume of intestine or bladder receiving over 60 Gy were very close to zero for both organs (Appendix A.6); only 5 patients had a $V_{60Gy} > 10$ $cm^3$ for the intestines and just 2 patients for the bladder.

## 4. Discussion

This is the first study to report dose planning goals for long-course EBRT with concomitant boost to 62 Gy to the primary tumor, and the feasibility of using these goals in a multi-center setting. Although other studies have looked at boost regimes for rectal cancer RT for organ preservation, these have either been to a substantially lower dose (median 54 Gy) [20] or using a different treatment modality (contact- or brachy-therapy) [9,21]. No previous reports have provided dose planning results for high-dose RT for organ preservation in a prospective trial setting.

The differences in CTV-T volumes in this study are relatively small and expected in a patient cohort of this size, especially considering the uneven distribution of accrued number of patients. The CTV-E volumes, however, are consistent across centers, indicating uniform outlining of elective volumes. The observed variation in PTV-E volumes may reflect that Centers 1 and 3 where not consistent in using the suggested protocol specified CTV-to-PTV margins. Although these CTV-to-PTV margins were not mandatory, this could potentially affect dose to OARs. Dose coverage planning goals for the target structures were met for 100 of the 106 treatment plans.

The primary and highest prioritized OARs in rectal cancer RT plan optimisation are the intestines and bladder. We observed large intercenter differences in doses to these OARs, especially for the intestines. This may be related to differences in treatment planning prioritization, intercenter differences in CTV-to-PTV margins, or differences in bladder filling protocol (as a full bladder may displace bowel out of the irradiated volume). However, intercenter differences were also seen in the contoured volume of the intestines. This could also be due to the difference in bladder filling protocol (as seen in Appendix A.2) or indicate

**Table 3**
Median and interquartile range (IQR) for volume and mean doses of elective volumes (CTV-/PTV-E) and target volumes (CTV-/PTV-T). P-value from Kruskal-Wallis test for intercenter difference.

| | | | All | Center 1 | Center 2 | Center 3 | p-value |
|---|---|---|---|---|---|---|---|
| CTV-T | Volume ($cm^3$) | Median | 38.4 | 31.9 | 39.2 | 49.2 | <0.001 |
| | | (IQR) | (26.8–54.1) | (21.4–38.3) | (27.7–54.2) | (45.7–80.2) | |
| | Mean dose (Gy) | Median | 62.9 | 62.0 | 63.1 | 62.0 | <0.001 |
| | | (IQR) | (62.0–63.4) | (62.0–62.0) | (62.9–63.5) | (61.8–62.2) | |
| CTV-E | Volume ($cm^3$) | Median | 584.7 | 579.8 | 580.0 | 594.5 | 0.831 |
| | | (IQR) | (536.5–652.0) | (520.6–685.6) | (536.5–653.5) | (539.5–634.4) | |
| | Mean dose (Gy) | Median | 54.1 | 53.6 | 54.3 | 54.6 | <0.001 |
| | | (IQR) | (53.6–54.7) | (53.2–53.9) | (53.9–54.9) | (54.2–54.9) | |
| PTV-T | Volume ($cm^3$) | Median | 143.9 | 124.1 | 146.1 | 202.5 | <0.001 |
| | | (IQR) | (118.4–182.7) | (104.7–144.1) | (121.2–182.5) | (166.9–313.4) | |
| | Mean dose (Gy) | Median | 62.3 | 61.9 | 62.4 | 62.0 | <0.001 |
| | | (IQR) | (62.0–62.6) | (61.5–62.0) | (62.3–62.7) | (61.6–62.0) | |
| PTV-E | Volume ($cm^3$) | Median | 1279.4 | 1116.4 | 1292.2 | 1169.7 | <0.001 |
| | | (IQR) | (1117.5–1396.1) | (1039.9–1306.3) | (1217.3–1435.6) | (1080.7–1367.2) | |
| | Mean dose (Gy) | Median | 52.9 | 52.6 | 53.0 | 53.2 | <0.001 |
| | | (IQR) | (52.6–53.3) | (52.4–52.7) | (52.7–53.4) | (52.7–53.8) | |

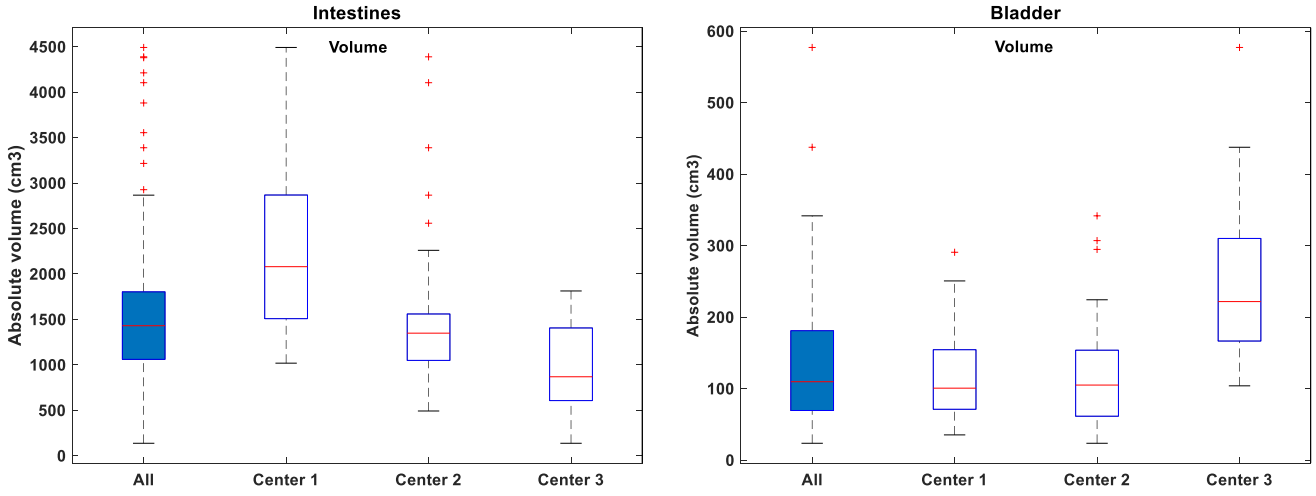


**Fig 2.** Absolute volumes for intestines and bladder for the full patient cohort (blue) and individual centers (white). Center 1 has a significantly higher volume for the intestines and Center 3 has a significantly higher bladder volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

an intercenter variation in contouring procedures, despite outlining following provided delineation guidelines. Differences in delineation procedures could be quantified be re-delineating all volumes at the same center but was outside the scope of this study. The differences in bladder volume, however, are most likely due to differences in patient preparation. Despite the significant intercenter bladder volume variations, the participating centers fulfilled the planning goals for 83 %–95 % of the treatment plans, depending on center and planning goal, by minimizing the dose to the bladder. In general, planning on a full bladder may minimize overall dose to the bladder and intestinal volumes on the treatment planning CT, but it may be questioned whether this is reproducible throughout the treatment course.

For the femoral heads (which are amongst the lowest priority goals), the boxplots in Fig. 4 as well as the fact that nearly all treatment plans fulfilled the planning goal (Table 4) all indicate that there might, for most treatment plans, be further room to shift the dose distribution away from the anterior OARs. In other words, a more laterally focused dose fluence may potentially further spare the bladder and intestines. Future dose planning guidelines may include this in planning recommendations.

For the relative volume of the penile bulb, Center 3 had a substantially higher dose. This clearly demonstrates that if an OAR is not specifically delineated for treatment planning, it may potentially receive unnecessary high dose. In this study only male genitalia were delineated and considered for treatment planning. However, future work should include delineation of female genitalia, as these are equally radiosensitive [22]. Furthermore, additional organs not usually considered for rectal cancer treatment planning, could be relevant to consider in the organ preservation setting, especially when considering dose intensification schemes. This may include OARs potentially related to long term anorectal function, such as the anorectal sphincter complex. Planning goals and constraints for OARs should preferably be informed by evidence on normal tissue dose–response in the organ preservation setting. This, however, demands that the relevant data is accumulated, to support the establishment of valid dose–response relationships.

Although large intercenter differences were found in this study, these are within an acceptable range: Considering the entire patient cohort, the majority of treatment plans fulfilled the proposed planning goals, except for the intestines and penile bulb. Although intercenter differences are expected for a multi-center setup, with e.g., different treatment planning systems and local routines [23], mandatory standardization of bowel and rectal preparation could minimize the differences. Additionally, we would recommend continuous on-trial treatment plan reviews, to ensure site trial implementation is

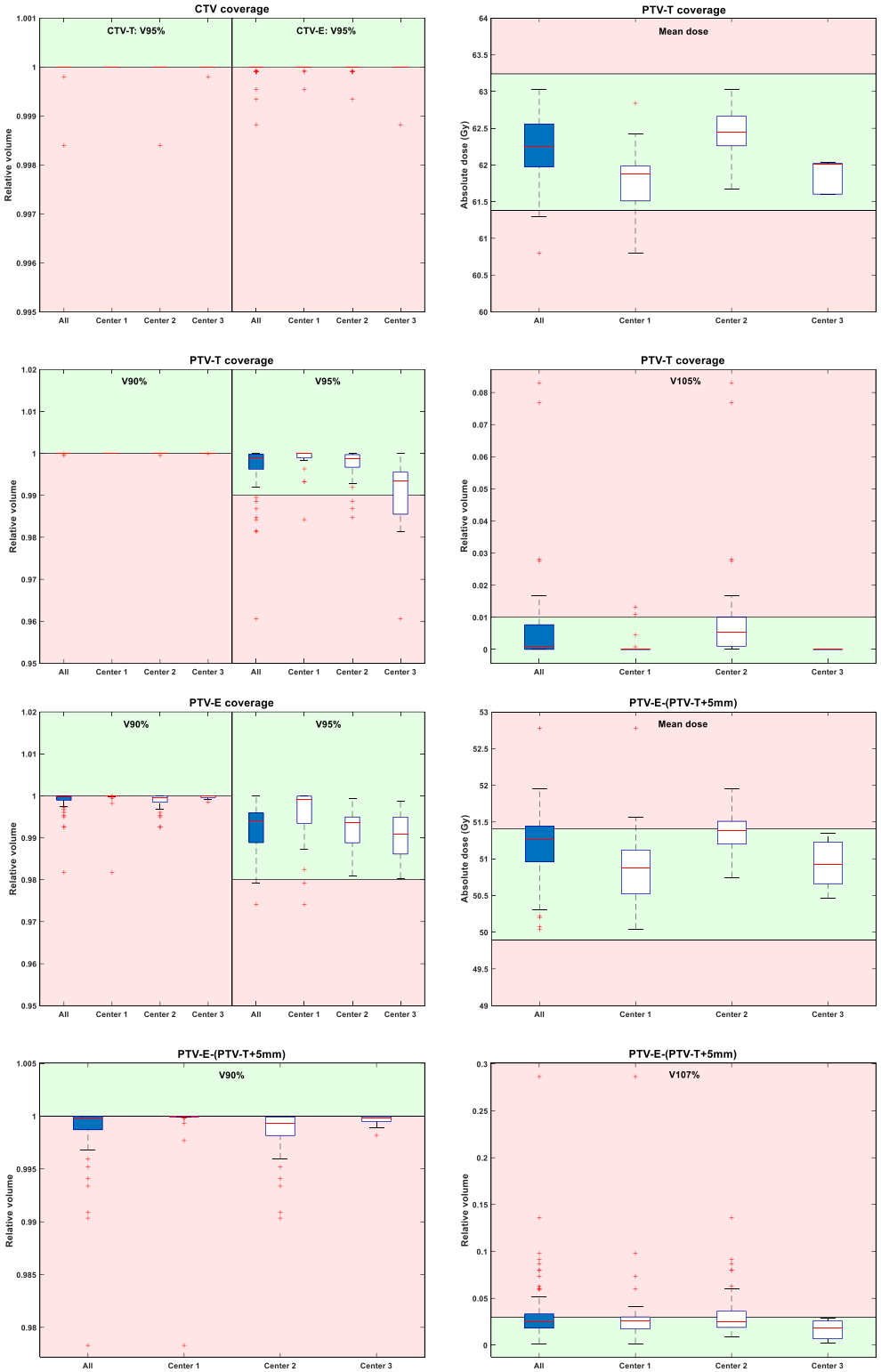


**Fig. 3.** All specified planning goals for target structures for patient cohort (blue) and center-specific treatment plans (white). The border between the green and red area represents planning goals as specified in the trial radiotherapy guidelines. The denotation e.g., V95% means 95% of the volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

successful (such as correct delineation of all structures during the full enrollment period). It is important to state that fulfilling the planning goals were not a hard trial requirement nor an assurance for an optimal treatment planning. However, studies have shown that non-adherence to RT protocol could impact primary study endpoints [23,24]. Furthermore, ensuring consistency in treatment planning across centers makes correlation with patient cohort treatment outcomes more robust, especially in a trial setting where RT is a part of the definitive treatment strategy.

The fact that even though no specific planning goals were provided

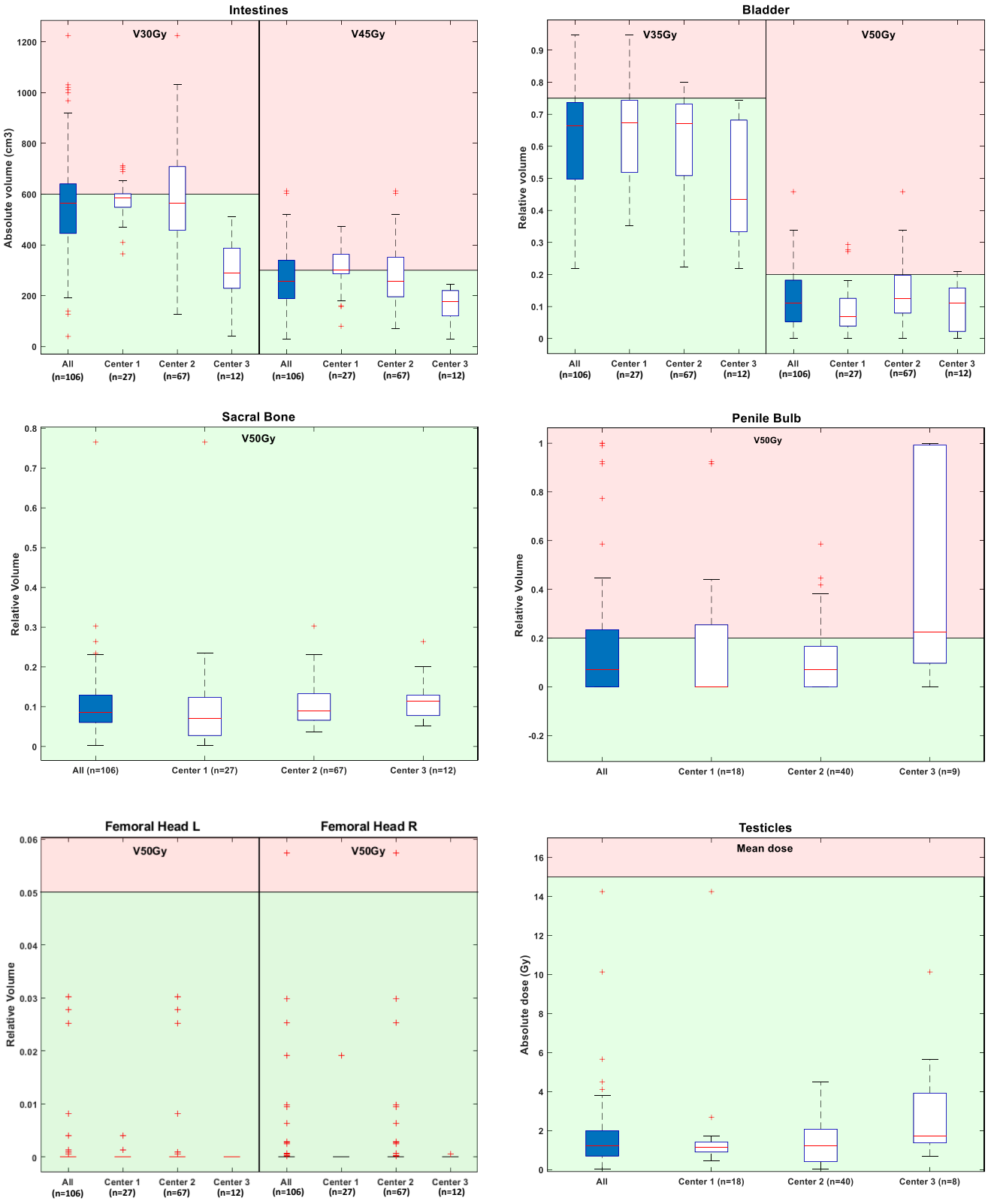


**Fig. 4.** Planning goals for organs-at-risk for patient cohort (blue) and center-specific treatment plans (white). The border between the green and red area represents planning goals as specified in the trial radiotherapy guidelines. The denotation e.g., V30Gy means the relative or absolute volume receiving 30 Gy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 4**
Distribution of number (and percentage) of treatment plans fulfilling optimization goals for elective volumes (CTV-/PTV-E), target volumes (CTV-/PTV-T) and organs-at-risk. Each planning goal was evaluated with a tolerance of ± 0.5 %, to discard decimal rounding effects.

| Structure | Planning goal (±0.5 %) | All | | Center 1 | | Center 2 | | Center 3 | |
|---|---|---|---|---|---|---|---|---|---|
| | | [n, (%)] | | [n, (%)] | | [n, (%)] | | [n, (%)] | |
| CTV-T | $V_{95\%} = 100$ % | 106 | (100 %) | 27 | (100 %) | 67 | (100 %) | 12 | (100 %) |
| CTV-E | $V_{95\%} = 100$ % | 105 | (99 %) | 26 | (96 %) | 67 | (100 %) | 12 | (100 %) |
| PTV-T | Mean dose = 99 % – 102 % | 106 | (100 %) | 27 | (100 %) | 67 | (100 %) | 12 | (100 %) |
| PTV-T | $V_{95\%} \geq 99$ % | 101 | (95 %) | 26 | (96 %) | 66 | (99 %) | 9 | (75 %) |
| PTV-T | $V_{90\%} = 100$ % | 106 | (100 %) | 27 | (100 %) | 67 | (100 %) | 12 | (100 %) |
| PTV-T | $V_{105\%} \leq 1$ % | 100 | (94 %) | 27 | (100 %) | 61 | (91 %) | 12 | (100 %) |
| PTV-E | $V_{95\%} \geq 98$ % | 105 | (99 %) | 26 | (96 %) | 67 | (100 %) | 12 | (100 %) |
| PTV-E | $V_{90\%} = 100$ % | 102 | (96 %) | 26 | (96 %) | 64 | (96 %) | 12 | (100 %) |
| PTV-E – (PTV-T + 5 mm) | Mean dose = 99 % – 102 % | 106 | (100 %) | 27 | (100 %) | 67 | (100 %) | 12 | (100 %) |
| PTV-E – (PTV-T + 5 mm) | $V_{90\%} = 100$ % | 101 | (95 %) | 26 | (96 %) | 63 | (94 %) | 12 | (100 %) |
| PTV-E – (PTV-T + 5 mm) | $V_{107\%} \leq 3$ % | 83 | (78 %) | 21 | (78 %) | 50 | (75 %) | 12 | (100 %) |
| Intestines | $V_{30Gy} < 600$ cm$^3$ | 72 | (68 %) | 20 | (74 %) | 40 | (60 %) | 12 | (100 %) |
| Intestines | $V_{45Gy} < 300$ cm$^3$ | 71 | (67 %) | 14 | (52 %) | 45 | (67 %) | 12 | (100 %) |
| Bladder | $V_{50Gy} < 20$ % | 90 | (85 %) | 24 | (89 %) | 56 | (84 %) | 10 | (83 %) |
| Bladder | $V_{35Gy} < 75$ % | 97 | (92 %) | 25 | (93 %) | 60 | (90 %) | 12 | (100 %) |
| Penile bulb | $V_{50Gy} < 20$ % | 48 | (72 %) | 13 | (72 %) | 30 | (75 %) | 4 | (44 %) |
| Femoral head L | $V_{50Gy} < 5$ % | 106 | (100 %) | 27 | (100 %) | 67 | (100 %) | 12 | (100 %) |
| Femoral head R | $V_{50Gy} < 5$ % | 105 | (99 %) | 27 | (100 %) | 66 | (99 %) | 12 | (100 %) |
| Testicles | Mean dose < 15 Gy | 67 | (100 %) | 18 | (100 %) | 40 | (100 %) | 9 | (100 %) |

for high dose OAR volumes, the volumes receiving 60 Gy to the bladder and intestines were low, shows that dose escalation to 62 Gy does not introduce substantial high dose volumes to the critical OARs when following the proposed RT treatment planning guidelines. This could potentially allow for even higher dose intensification to the tumor; keeping in mind that the current study did not evaluate dose to non-standard OARs (such as the anorectal sphincter and female genitalia).

Finally, it is important to note that the analysed treatment plans do not fully represent the delivered dose to the patients due to e.g. inter-fraction organ motion. Future studies could account for this by calculating the treatment plan on each daily cone-beam CT (CBCT) if available.

Ongoing studies are currently investigating the effect of dose escalation to the tumor using EBRT in a randomized setting [Watchful Waiting III (NCT04095299)] and with smaller treatment volumes [APHRODITE (ISRCTN16158514)].

## 5. Conclusion

This multicenter study reported homogeneous target coverage for the patient cohort across the participating centers. Prescribed planning goals for target coverage were fulfilled for 100 of the 106 treatment plans. However, doses and volumes of the OARs indicated intercenter variations, especially for the intestines. Standardization of patient preparation and on-trial treatment plan reviews could minimize these differences and are recommended for future trials. Dose escalation to 62 Gy (as a concomitant boost to the primary tumor) introduced no substantial high dose volumes (>60 Gy) to the bladder and intestines. Given the overall trial results [15], which reported 61 % of the patients having tumor control without surgery after 2 years of follow-up, these treatment planning goals may be used for future prospective evaluation of high-dose radiotherapy for organ preservation for low rectal cancer.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2023.103206.

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