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Reducing margins for abdominopelvic tumours in dogs: Impact on dose-coverage and normal tissue complication probability

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Abstract

Image-guided, intensity modulated radiation therapy (IG-IMRT) reduces dose to pelvic organs at risk without losing dose coverage to the planning target volume (PTV) and might permit margin reductions potentially resulting in lower toxicity. Appropriate PTV margins have not been established for IG-IMRT in abdominopelvic tumours in dogs, and herein we explore if our usual PTV 5 mm margin can be reduced further. Datasets from dogs that underwent IG-IMRT for non-genitourinary abdominopelvic neoplasia with 5 mm-PTV expansion were included in this retrospective virtual study. The clinical target volumes and organs at risk (OAR) colon, rectum, spinal cord were adapted to each co-registered cone-beam computed tomography (CBCT) used for positioning. New treatment plans were generated and smaller PTV margins of 3 mm and 4 mm evaluated with respect to adequate dose coverage and normal tissue complication probability (NTCP) of OAR. Ten dogs with a total of 70 CBCTs were included. Doses to the OAR of each CBCT deviated mildly from the originally planned doses. In some plans, insufficient build-up of the high dose-area at the body surface was found due to inadequate or missing bolus placement. Overall, the margin reduction to 4 mm or 3 mm did not impair dose coverage and led to significantly lower NTCP in all OAR except for spinal cord delayed myelopathy. However, overall NTCP for spinal cord was very low (<4%). PTV-margins depend on patient immobilization and treatment technique and accuracy. IG-IMRT allows treatment with very small margins in the abdominopelvic region, ensuring appropriate target dose coverage, while minimizing NTCP.

KEYWORDS
anal gland adenocarcinoma, IGRT, IMRT, planning target volume, PTV, radiation therapy

1 | INTRODUCTION

Compared to three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) can reduce dose

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to pelvic organs at risk (OAR) without losing dose coverage to the planning target volume (PTV).[1-3] The precision of IMRT additionally increases with image guidance: Using on-board imaging devices (OBI), high quality orthogonal kV-images or images acquired in an arc rotation (cone-beam computed tomography, CBCT) provide excellent 3D anatomical information and bone- and soft-tissue visibility.[4-7] Such images of the patient's set-up are taken at the beginning of each treatment session and aligned to reference images from the treatment plan. Then, patient's position can immediately be corrected if required. The position is typically adjusted with a couch positional shift, and possible in four degrees of freedom - longitudinal, vertical, horizontal, rotational (yaw) - unless a 6D robotic couch is available allowing for additional pitch and roll corrections.[8] The consequential increase in precision often permits PTV reduction, which could result in lower toxicity and a shift in therapeutic ratio.[9,10] Appropriate PTV margins have not yet been established for IG-IMRT treatment of tumours in the dog's abdominopelvic region and herein we explore if our usual 5 mm margin can be reduced further.

In contrast to PTV margins, organ (at risk) movement has been quantified for the dog's abdominopelvic region with CBCT for image-guided IMRT (IG-IMRT). The extent of displacement is known for the canine bladder in treating urinary bladder cancer,[11] for prostate and urethra intrafraction motion,[12] as well as for interfraction ureteral movement.[13] Earlier, we have computed a PTV expansion margin for dogs with large abdominopelvic tumours treated with simple 3D-CRT or IMRT, without image guidance. We extracted daily treatment position correction data from IG-IMRT treatments and derived a margin according to one of van Herk et al.'s formula: $2.5\Sigma + 0.7\sigma$.[14] The resulting clinical target volume (CTV) to PTV expansion margin was 7x7x18mm (lateral-vertical-longitudinal). This anisotropic margin can be applied where a rigid, well-reproducible positioning device is used without imaging position verification.[15] For IG-IMRT treatments, however, this margin can most likely be smaller. For genitourinary and anal sac tumours a 5 mm PTV margin has been used, but not further tested.[15,16]The purpose for this study was 2fold. Firstly, we wanted to investigate if our currently used 5 mm PTV margin provides appropriate dose coverage to the CTV for IG-IMRT treatment of tumours in dog's abdominopelvic area. A series of pretreatment CBCTs from dogs affected by such tumours were used to investigate the PTV margin, deriving the delivered dose to the effectively treated CTV positions. The aim was to investigate whether or not the CTV-PTV expansion of 5 mm could be reduced while still maintaining coverage of the CTV in the imaging series of each patient. Secondly, the theoretical clinical impact on normal tissue complication probability (NTCP) of the initially planned and effectively delivered doses was calculated for the treatment datasets of formerly treated dogs. These NTCPs calculated for 5 mm PTV were then compared to NTCPs of virtual plans derived for possible smaller margins to investigate a relative change in possible toxicity.

2 | METHODS

2.1 | Patient and tumour characteristics

We included datasets from dogs undergoing radiation therapy (RT) for non-genitourinary neoplasia in the abdominopelvic region at the Division of Radiation Oncology, Vetsuisse Faculty, University of Zurich, Switzerland in this retrospective study. For treatment planning, a pre- and post-contrast standard computed tomography (CT) scan of the tumour was performed with a 16 MDCT unit (Brilliance CT 16-slice, Philips Health Care Ltd, Best, Netherlands) as previously described.[17] Patients were placed under general anaesthesia and immobilized in sternal recumbency with outstretched hind limbs in an individually shaped vacuum cushion (BlueBag BodyFix, Elekta AB). A tissue-equivalent bolus (Superflab) was placed in a non-standardized manner, usually over scars in the perianal area. Further information retrieved from the records included signalment (age, sex and breed), type, size and location of the primary tumour and metastatic locoregional lymph nodes.

2.2 | Contouring of organs at risk and target volumes

Contouring and computer-based treatment planning was performed with the external beam planning system (Eclipse Planning system, version 15.1 Varian Oncology Systems, Palo Alto, California), using Anisotropic Analytical Algorithm (AAA), version 15.1.51, with heterogeneity correction. Dose calculation was performed on the pre-contrast CT images. As previously described for this region, contouring of OAR as well as tumour-related volumes was performed on co-registered post-contrast CT images in order to increase the accuracy of contouring.[18] The body contour and bones were automatically segmented. OAR contouring included rectum (from the anus until the start of the colon), colon (from the pelvic inlet, the cranial border of the pelvic symphysis until transition into the small intestines or alternatively to the most cranial CT image), spinal cord (cranially from the start of CT dataset to the caudal end of L7), and cauda equina (the intraspinal part of all cauda equina nerves contributing to the lumbosacral plexus was contoured: from the caudal end of L7 to the caudal end of the sacrum). We contoured tubular structures (rectum and colon) as the volume within the outer wall contour, including the contents. Tumour-related volumes were defined as follows: gross tumour volume (GTV), the visible primary tumour as seen on co-registered contrast-enhanced CT images, GTV lymph node including metastatic lymph nodes, clinical target volume (CTV), microscopic disease surrounding the primary tumour (with a 1 cm GTV to CTV expansion margin) and (non-macroscopically involved) locoregional lymph nodes and PTV, accounting for systematic and random uncertainties. The CTV-PTV isotropic expansion margin was 5 mm, as described above, cropped 1 mm inside the body outline. The targets of the reference dataset used for treatment planning were labelled with the suffix "_0".

2.3 | Matching procedure and image selection

For each patient, several kilovolt (kV)-CBCT were acquired as part of routine practice, at the radiation oncologist's discretion. CBCT settings used were 125 kV (x-ray tube voltage), 80 mA (x-ray tube current), 674 mAs (exposure), 16 cm scan length and half fan mode. A full 360° acquisition was used at 180/min. The maximum diameter for reconstruction was 450 mm; 512x512 pixels and a resolution of 0.88 mm. All CBCT images were automatically imported into the Eclipse treatment planning system at their initial setup position, with 2 mm slice spacing. For treatment, the CBCT images were manually matched to the reference planning CT by an experienced radiation therapy radiographer, using soft tissue window level and using the GTV_0/ CTV_0 structures to ensure optimal match. Upon satisfactory match, the isocenter shifts were applied by table movement (four dimensions) and stored in the system. No specific measures were taken to ensure bladder or bowel emptying before treatment, but all patients were treated in the mornings, after their first walk for urination and defecation.

2.4 | Generating the sum of treated CTVs and OAR

CTV_0 was copied from the initial treatment plan, the reference dataset, to each co-registered CBCT. To reflect the daily actual situation and influence of normal organ filling, also the organs at risk were copied from the original reference dataset. Both the (copied, that is, new) CTV and organs at risk were adapted manually on each CBCT by a single investigator (CS). The adapted CTV and OAR structures (labelled with the suffixes "_CBCT_1", "_CBCT_2", etc. for each CBCT) added to the original reference dataset. The sum of the treated CVTs was created with the boolean operator tool, resulting in the structure "CTVbool".

2.5 | Treatment planning and delivery

Treatment plans were calculated as deliverable by the investigator's linear accelerator, with a 6 MV linear accelerator (Clinac iX, Varian, Palo Alto, California). Coplanar photon treatment planning was performed with 5 to 7 fields and additional contouring helper structures to ensure optimal dose homogeneity, target coverage and minimal dose to OAR. Dose was optimized with IMRT using a dynamic 120 multi-leaf collimator. Recommendations for specification of dose were adhered to as proposed by the International Commission on Radiation Units and Measurements (ICRU) report 83 and as recommended for veterinary medicine.[9,19] The dose was normalized adhering to the guidelines: the PTV $D_{near\text{-}min}$ (the minimal dose-coverage of $D_{98\%}$) was required with 95% of total prescribed dose (≥98% of the PTV was covered by the 95% isodose line) and $D_{50\%}$ (median dose) as the value of dose prescription. A moderately hypofractionated dose of 12x3.8Gy was prescribed in this definitive-intent approach.[18] Hence, we set $D_{98\%}$ ($D_{near\text{-}min}$) to ≥43.32 Gy, $D_{2\%}$ ($D_{near\text{-}max}$) to ≤48.79Gy and $D_{50\%}$ to 45.6 Gy.

2.6 | Margin reduction and evaluation procedure

An optimal PTV-extension margin was defined for margins as follows. On average at least 95% of the prescribed dose is delivered to 99% of the CTV.[20] While the original, effectively treated plan was used for PTV5mm ($Plan_{5mm}$), we generated new plans each, for the reduced PTVs (4 mm: $Plan_{4mm}$ and 3 mm: $Plan_{3mm}$): the original plan was copied and the new target (PTV) was assigned. Using at least the prior described constraints, the plans were re-optimized and then re-calculated. The new plans were required to fulfil the prescription criteria as above, with OAR-doses kept as low as possible through optimization.

2.7 | NTCP calculations for the planned dataset vs the delivered treatment

For the fraction to fraction NTCP calculations, the effective dose applied to the OAR was extracted from each contoured CBCT. In-house analysis codes were used to calculate the NTCP from the differential dose-volume histograms (DVH). The NTCPs were then compared to the dose delivered to the OAR during the fractions over the course of treatment, as previously described ($NTCP_{planned}$; $NTCP_{delivered}$).[18] NTCP was also calculated for the OAR in the subsequent plans with PTV4mm and PTV3mm (where the "delivered" doses were only virtually delivered). The parameter sets were retrieved from human data and computations performed as previously published.[18]

2.8 | Statistical analysis

Data was coded in Excel and analysed with a commercial statistical software package (IBM SPSS Statistics, Version 25 (IBM Corp., Armonk, New York). Shapiro-Wilk testing was carried out to assess normality. $D_{98\%}/D_{50\%}/D_{2\%}$ dose distributions were assessed graphically with box-plots and Wilcoxon test was used for paired observations (testing the differences in doses between the plans). Wilcoxon test was further used for paired observations (testing the differences in $NTCP_{planned}$ vs $NTCP_{delivered}$) and to compare organ dose parameters (NTCPs) derived from the DVHs between the three individual two level comparisons (ie, 3 mm vs 4 mm, 3 mm vs 5 mm, 4 mm vs 5 mm). For the comparison of the organ at risk NTCPs under the different PTV margins, Friedman's test (non-parametric, for multiple comparison) was carried out. Differences were considered significant at P values <.05.

3 | RESULTS

3.1 | Patient population

Ten dogs (two neutered males, two intact males, six spayed females) were included into this study. The mean age at diagnosis

TABLE 1 Mean volumes and delivered doses for target volumes

		Mean Volume (mean ± SD) [cm^3]	$D_{2\%}$ (mean ± SD) [%]	$D_{50\%}$ (mean ± SD) [%]	$D_{98\%}$ (mean ± SD) [%]	$D_{99\%}$ (mean ± SD) [%]
$Plan_{5mm}$:	PTV_5mm	237.8 ± 94.6	104.0 ± 1.5	101.5 ± 1.1	92.8 ± 2.9	
	CTV_0_ $plan_{5mm}$	116.6 ± 69.2[a]				90.8 ± 11.5
	CTVbool_$plan_{5mm}$	124.7 ± 65.4[a]				92.6 ± 9.9
$Plan_{4mm}$:	PTV_4mm	214.8 ± 88.5	103.3 ± 1.1	100.5 ± 0.6	95.5 ± 0.5	
	CTV_0_$plan_{4mm}$	116.6 ± 69.2[a]				92.5 ± 8.5
	CTVbool_ $plan_{4mm}$	124.7 ± 65.4[a]				94.9 ± 5.3
$Plan_{3mm}$:	PTV_3mm	191.8 ± 82.7	103.1 ± 1.3	100.3 ± 0.4	95.4 ± 0.4	
	CTV_0_ $plan_{3mm}$	116.6 ± 69.2[a]				91.9 ± 8.8
	CTVbool_ $plan_{3mm}$	124.7 ± 65.4[a]				94.0 ± 5.6

[a]The volumes of the CTVs remain the same in all plans.
Abbreviations: CTV, clinical target volume; PTV, planning target volume.

was 9.6 ± 2.9 years (range 6.2-12.8 years), and the mean body weight was 20.6 ± 8.0 kg (range 12.5-40.7 kg). Four dogs were of mixed breed, there were two Border Collies and one of each of the following pure breeds: Golden Retriever, Cocker Spaniel, Field Spaniel and Cavalier King Charles Spaniel. Nine dogs were treated for lymph node-metastatic anal gland adenocarcinoma (macroscopic disease or microscopic primary and macroscopic lymph nodes) and one dog had a pelvic histiocytic sarcoma with locoregional lymph node involvement.

3.2 | Planned and delivered doses

A mean of 7 (± 3.4) CBCTs were performed (range 3-12) (median 6) per dog. OAR (rectum, colon, spinal cord, and cauda equina) were adapted manually in all 70 CBCTs.

The mean doses to target volumes were within the prescribed range, displayed in Table 1. Except for one plan with 5 mm margins, all plans had adequate PTV coverage of D98/95. In some cases, PTVs had to be cropped 1 mm inside of the body surface: in the 5 mm plans in 7/10, in the 4 mm plans in 4/10 and in the 3 mm plans in 2/10 dogs. Regarding the PTV $D_{98\%}$, the sign test showed differences: 4 mm-plans had higher $D_{98\%}$ than the 5 mm-plans (P = 0.018), with no differences between 5 mm-plans vs 3 mm plans (P = 0.050) and the 4- and 3 mm-plans (P = 0.279). This observation reflects insufficient build-up of the high dose-area in areas close to the body surface or areas that were not covered sufficiently with bolus for dose-build-up. Insufficient dose-build-up is corroborated by a margin-independent lack of CTV-bool coverage (which was *not* cropped inside the body surface), where in the 5- and 3 mm plans 6/10 patients had a $D_{99\%}$ in 95% of volume coverage in all fractions, and 7/10 patients in the 4 mm plan. The initially planned CTV coverage was lower than $D_{99\%}$ in 95% of volume in 3/10 patients with all PTV-margins. Due to surface cropping the PTV margins were smaller than intended in some areas, resulting in underdosing CTVs close to the body surface in bulging primary tumours.

3.3 | NTCP calculations of planned dataset vs delivered treatment

The (relative) NTCP-values from the planned vs delivered or virtually delivered doses generally showed systematic differences, an example of which is shown in Figure 1A. The NTCP values as planned were mostly lower than the values of the actually delivered doses.

For the different margins, the NTCPs of the delivered or virtually delivered doses were significantly different for all NTCP parameter-value assumptions published, as summarized in Tables 2 and 3. The individual 2-level comparisons show that smaller margins yield lower NTCPs (Figure 1B). The effect of smaller margins yielding lower NTCPs was not seen for spinal cord delayed myelopathy. But for spinal cord the overall risk was very low (<4%) and the spinal cord was often sufficiently distant from the target. The risk of late toxicity spinal cord necrosis was again significantly dependent on margin size, albeit very low as well (<2%).

Given the lack of parameter data for the calculation of NTCP values for the cauda equina, D_{mean}, D_{median} and D_{max} for the delivered and virtually delivered (4- and 3 mm-margin; mean of all fractions) "radiation doses" to this OAR are presented in Table 4.

4 | DISCUSSION

The aim was to investigate if our currently used 5 mm PTV margin provides appropriate dose coverage to the CTV for IG-IMRT in treating tumours in the dog's abdominopelvic area, or if this margin could even be reduced. While a lack in dose-coverage on the patient's surface was identified in some cases, appropriate bolus-placement will mitigate this loss of surface dose and ensure appropriate dose coverage for PTV extension margins as small as 3 mm, when delivered with IG-IMRT. Doses to organs at risk were found to deviate slightly from the predicted doses and normal tissue complication probabilities for all organs but spinal cord myelopathy decreasing significantly for the margin reductions.

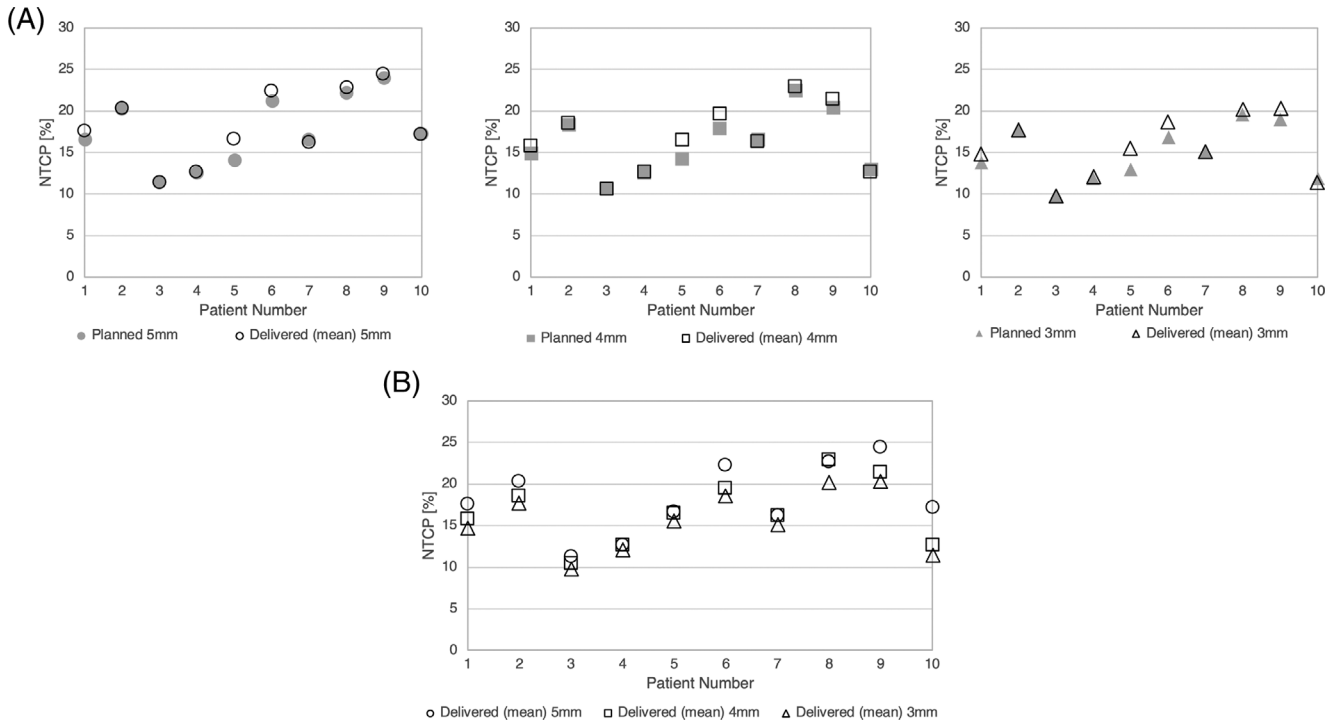

FIGURE 1 Normal tissue complication probability (NTCP) values for early rectal radiation toxicity[21] in all 10 dogs: A, Planned (filled symbols) vs delivered or virtually delivered (in the 4- and 3 mm- margin plans) "radiation doses" for each patient, expressed by the NTCP as risk surrogate. B, Example of lower NTCP from the plans with smaller PTV margins: original 5 mm margin (circles) vs 4 mm (squares) and 3 mm (triangles)

As described above, the effect of smaller margins yielding lower NTCPs was not seen for spinal cord delayed myelopathy, most probably because the spinal cord was far away from the target and therefore the overall risk for spinal cord was very low (<4%). Another explanation would be that during the patient positioning process, the best match was performed in the region of the spinal cord as organ at risk with most detrimental late toxicity - if it occurs.

In veterinary radiation therapy, margin guidelines often neither exist nor can be extracted from older publications. Earlier treatments were applied with simpler dose calculations (2D or 3D-CRT), without daily online image guidance. For example, margins of 3 cm were used in the postoperative setting (treated with Cobalt-teletherapy)[22] or 2 cm margins surrounding CTV for a treatment planning study.[23] In the latter example, these large margins still yielded inaccurate treatments, with non-graphic (two-dimensional) treatment plans found to underdose CTVs between 0.6 and 50% (median 16%)![23] After evaluating daily online corrections with a rigid positioning device, we described a smaller margin of $7 \times 7 \times 18$mm for a correspondingly positioned unguided approach and 3D-CRT treatment planning.[15]

A commonly accepted CTV-PTV expansion margin does not exist for IG-IMRT radiation treatments in abdominopelvic tumours such as anal sac, urinary bladder, prostate in dogs. The 5 mm was chosen as a uniform CTV-PTV expansion to account for intra- and interfraction variations in a series of genitourinary or anal sac tumours treated with IG-IMRT.[15,16] This margin can most likely be justified, as the online correction of the pre-treatment CBCT eliminates the largest part of the interfractional uncertainties (systematic errors). After correcting for the systematic error with a couch shift, residual inaccuracy resulting from respiratory movement, organ filling state and motion influences the target's location. The dosimetric impact of this inaccuracy can be evaluated by checking the dose coverage in targets and OAR at or even during the individual fractions. Adamson et al. (2010) monitored prostate intrafractional motion in human prostate-cancer patients treated with hypofractionated RT. By using kV fluoroscopy during treatment, they found the probability of a 5 mm intrafraction prostate displacement being very patient-specific and ranging from 0.0% to 58.8% of the time *during* a treatment session. The probability of motion increased with treatment duration.[24] In terms of target dose coverage in these prostate patients, the investigators determined right-left, anterior-posterior, and superior-inferior margins of 2, 3, and 4 mm to be sufficient to account for translational errors while limiting the CTV $D_{99\%}$ reduction to 1%.[25] Hence, in 29/30 of the prostate tumour patients the reduction in CTV $D_{99\%}$ was ≤5% when 3 mm uniform margins were used.[25] In line with these findings, prostate-PTV margins of ≥2 mm achieved the minimum dose coverage of 95% of the prescription dose (based on mean, SD, and motion amplitudes) even for patients with the largest motion.[26] These findings are commensurate with our results: a reduction to 4 mm or 3 mm PTV margins does not decrease CTV $D_{99\%}$ to a relevant degree in most dogs (Table 1). This is surprising as we used a boolean CTV - a worst-case scenario approach. This approach, however, could lead to a marked PTV extension in other parts of the body such as the thorax area under respiratory movement. However, the result of similar $CTV_{D99\%}$ might be patient-specific and the planned PTV dose coverage could

TABLE 2 NTCPs for different OAR, calculated along published parameter sets

	Parameter sets (Reference)	$NTCP_{planned}$ 5 mm (mean ± SD) [%]	$NTCP_{delivered}$ 5 mm (mean ± SD) [%]	$NTCP_{planned}$ 4 mm (mean ± SD) [%]	$NTCP_{delivered}$ 4 mm (mean ± SD) [%]	$NTCP_{planned}$ 3 mm (mean ± SD) [%]	$NTCP_{delivered}$ 3 mm (mean ± SD) [%]
Acute rectal toxicity							
any	Rancati et al. (2005)	17.6 ± 4.2	18.6 ± 4.5	16.1 ± 3.7	17.0 ± 4.0	14.9 ± 3.3	15.9 ± 3.8
≥ grade 2 RTOG	Strigari et al. (2009)	1.2 ± 0.6	1.4 ± 0.7	1.0 ± 0.4	1.1 ± 0.5	0.8 ± 0.4	1.0 ± 0.5
severe proctitis	Burman et al. (1991)	1.1 ± 0.8	1.4 ± 1.0	0.7 ± 0.5	0.9 ± 0.6	0.6 ± 0.4	0.8 ± 0.5
Late rectal toxicity							
rectal bleeding grade 2/3 within 18 months	Rancati et al. (2004)	3.1 ± 2.2	3.9 ± 2.6	2.3 ± 1.6	2.8 ± 1.8	1.7 ± 1.1	2.2 ± 1.4
rectal bleeding ≥ grade 2 at 2 years	Cheung et al. (2004)	7.0 ± 12.5	12.3 ± 17.5	2.7 ± 6.5	4.3 ± 7.6	0.4 ± 0.8	1.4 ± 2.5
≥ grade 2 RTOG after 120 days	Tucker et al. (2007)	1.3 ± 0.8	1.6 ± 1.0	1.0 ± 0.5	1.2 ± 0.7	0.8 ± 0.4	1.0 ± 0.6
Late spinal cord toxicity							
myelopathy	Schultheiss et al. (2008)	2.8 ± 5.0	3.3 ± 5.9	2.6 ± 4.4	3.9 ± 6.1	1.8 ± 2.7	2.4 ± 4.0
necrosis	Burman et al. (1991)	1.6 ± 1.9	2.0 ± 2.2	1.5 ± 1.6	2.0 ± 2.0	1.2 ± 1.5	1.4 ± 1.7

Abbreviations: NTCP, normal tissue complication probability; OARs, organs at risk; RTOG, radiation therapy oncology group.

not be reached in one patient with a very large, bulging primary tumour close to the surface. In this and six other patients the PTVs had to be cropped 1 mm inside the body outline for planning purposes, resulting in a smaller margin in this area (and mostly remaining insufficient dose-buildup). The surface dose loss is also reflected in the *increasing* overall PTV dose coverage from the smaller 4 mm vs the 5 mm plan. In consequence, some patients (even with sufficient PTV coverage in the planned version) had a margin-independent lack of CTV-bool $D_{99\%}$ coverage. The planned CTV_0 $D_{99\%}$ coverage, however, was lower than the delivered (CTV-bool $D_{99\%}$) dose to the CTV, showing that the delivered dose can actually be higher than initially planned, if patient's shift is away from underdosed surface. Here, the daily position error was in favour of dose coverage and "corrected" for the physical loss of dose at the surface. Appropriate bolus-placement, however, can very likely mitigate this loss of surface dose and ensure appropriate CTV coverage for PTV extension margins of as small as 3 mm.

As found for doses to organs at risk in the treated dogs, a randomized assessment of standard or reduced margins for human prostate cancer resulted in significantly lower organ at risk dose (rectum and urinary bladder) with smaller margins.[27] Clinically however, the improved rectal dosimetry did not translate into a statistically significant benefit in acute or late toxicity. This may relate to the low level of theoretical side effects in this trial, most comparable to the low risk for severe acute or late toxicity predicted for the herein used protocol.[15] Smaller margins can still be of interest, especially when increasing the total dose or decreasing fraction number of the treatment in the abdominopelvic region.

The position of the rectum at the time of the treatment-planning CT scan is not fully representative of the position during treatment because of patient motion, inter- or intrafraction variations in rectal filling, intestinal gas, and urinary bladder filling.[28] In human patients, the probability of motion (tumour and organs at risk) increases with treatment duration.[24] By treating animal patients under general anaesthesia, we limit the movement during radiation therapy to respiratory and physiological organ movement and filling state. Mean intrafraction movement for prostate and urethra was found to be small, at ≤0.14 and ≤ 0.22 mm, with maximum intrafraction movements being ≤1.4 and ≤ 1.5 mm, respectively.[12] Intrafraction movement of the canine prostate in enema and rectal balloon prepared dogs could be limited to ≤2 mm 95% of the time in any directions.[12] Prostate gland motion, however, cannot directly be interpolated for other abdominopelvic tumours: anal sac adenocarcinomas for example are less influenced by urinary bladder filling status and less mobile. On the other hand, caudal-dorsal pelvic tumours

TABLE 3 Changes in NTCPs for different OARs, calculated along published parameter sets

		3 related sets[a]	2-level comparisons[b]		
	Parameter sets (Reference)	$NTCP_{delivered}$ 5 mm vs 4 mm vs 3 mm	$NTCP_{delivered}$ 5 mm vs 4 mm	$NTCP_{delivered}$ 5 mm vs 3 mm	$NTCP_{delivered}$ 4 mm vs 3 mm
Acute rectal toxicity					
any	Rancati et al. (2005)	$P < .001$	$P < .05$	$P < .01$	$P < .01$
≥ grade 2 RTOG	Strigari et al. (2009)	$P < .001$	$P < .01$	$P < .01$	$P < .01$
severe proctitis	Burman et al. (1991)	$P < .001$	$P < .01$	$P < .01$	$P < .01$
Late rectal toxicity					
rectal bleeding grade 2/3 within 18 months	Rancati et al. (2004)	$P < .001$	$P < .01$	$P < .01$	$P < .01$
rectal bleeding ≥ grade 2 at 2 years	Cheung et al. (2004)	$P = .003$	$P = .10$	$P < .01$	$P < .01$
≥ grade 2 RTOG after 120 days	Tucker et al. (2007)	$P < .001$	$P < .01$	$P < .01$	$P < .01$
Late spinal cord toxicity					
myelopathy	Schultheiss et al. (2008)	$P = .407$	n.s.	n.s.	n.s.
necrosis	Burman et al. (1991)	$P = .025$	n.s.	$P = .05$	$P < .05$

Abbreviations: NTCP, normal tissue complication probability; OARs, organs at risk; RTOG, radiation therapy oncology group.
[a]Friedman, non-parametric test.
[b]Wilcoxon test for paired numbers.

TABLE 4 Mean, median and maximum delivered and virtually delivered (4- and 3 mm-margin) radiation doses to the cauda equina

		D_{mean} (mean ± SD) [Gy]	D_{median} (mean ± SD) [Gy]	D_{max} (mean ± SD) [Gy]
Cauda equina $Plan_{5mm}$:	planned	20.7 ± 9.6	20.8 ± 10.7	31.0 ± 8.4
	delivered (mean)	21.1 ± 9.6	21.4 ± 10.9	31.4 ± 8.0
Cauda equina $Plan_{4mm}$:	planned	20.8 ± 8.9	20.6 ± 10.1	31.7 ± 7.0
	delivered (mean)	21.3 ± 8.8	21.5 ± 10.0	31.9 ± 6.9
Cauda equina $Plan_{3mm}$:	planned	19.2 ± 8.3	19.0 ± 9.4	30.3 ± 6.5
	delivered (mean)	19.5 ± 8.1	19.6 ± 9.3	30.2 ± 6.5

could be more susceptible for pitch and roll deviations, which are less likely to occur in the centrally located, often roundish prostate. Due to their strong volume fluctuance, urinary bladder tumours can be highly variable in position, and treatment with an adaptive strategy is recommended.[11,29]

A strength of this study includes the assessment of margin volumes, relative to former point, for example, isocentric shift assessments.[11-13,29] Our CTVbool, however, represents a worst-case scenario: by "boolean-combining" the CTVs we assigned the same weight to all shifts, even if a shift only took place once in one direction during the whole treatment. In addition, pitch and roll errors had to be incorporated, due to a lack of a six-dimensional couch. Still, we have found 3 mm PTV expansion margins to provide sufficient dose coverage in most of our cases, given appropriate surface build-up. Surface dose-build up is usually improved when treating with multi-directional treatment field arrangements (as used in static or rotational IMRT and tomotherapy). Simple and proactive bolus placement, however, is still warranted in selected cases, as it supports physical dose-build-up even in the modern era of radiation therapy. We agree with several other authors, however, in cautioning against reducing PTV margins to less than 3 mm.[30-33]

We acknowledge the limitations of our findings: (a) The comparison of NTCP is made with human tolerance data.[21,34-38] This approach was chosen under the premises of the lack of structured data of radiation toxicity in canine rectal and spinal cord tissue. While one could argue that the NTCP value assumptions cannot be extrapolated from human to dog, NTCP values serve as relative values in this evaluation, rather than absolute. (b) An additional inherent potential error in this type of study occurs in the comparison of dose delivered to OAR contoured on

CBCT: as the soft tissue resolution is lower and artefact susceptibility (gas) is higher on CBCT relative to the better quality of the diagnostic CT used for planning, the derived doses could thereby be slightly skewed. Moreover, no contrast agent was used for CBCTs. (c) Changes in body contour were not considered. Marked weight loss during radiation therapy associated with possible body contour changes was rare according to a recent study.[39] However, body contour changes are still possible despite stable weight and can for example happen in the region of movable skin folds in the inguinal and/or abdomen region according to personal experience. If this is in the order of several centimetres and happens to occur in the path of an incident radiation beam this could indeed change radiation dose and distribution.

Any proposed CTV PTV expansion margin is institution dependent. The margin can vary with the patient immobilization devices used, the actual recumbency (and maybe even size) of the animal, type and accuracy of the image-guidance (kV- vs MV-CBCT). Further, it also depends on the experience of the staff with the imaging matching process. In-depth knowledge of inherent uncertainties of an institution's own set-up and radiation techniques is therefore advised.

In conclusion, while PTV-margins depend on patient immobilization and on the institution's treatment technique and accuracy, daily CBCT-IG-IMRT allows treatment with very small margins in the dog's abdominopelvic area. Routine image-guidance helps to ensure appropriate target dose coverage while minimizing normal tissue complication probability when treating with the smallest possible margins.

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CONFLICT OF INTEREST

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Harvard Dataverse at https://doi.org/10.7910/DVN/PZ3KRM, reference number UNF:6:jFeUw3HReC7bcmjDmmP5oA== [fileUNF].

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