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Radiation toxicity grading after chemoradiotherapy of canine urinary tract carcinomas: Comparing VRTOG to VRTOG_v2.0

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Abstract

Radiation toxicities may be underestimated after treatment of transitional cell carcinoma in dogs' lower urinary tract. Assessing acute and late toxicities and differentiating them from progressive disease (PD) impacts further therapeutic approach. We retrospectively assessed dogs treated with definitive-intent chemoradiotherapy (12 × 3.8 Gy, various first-line chemotherapeutics). Local tumour control, radiation toxicities and survival were evaluated. We classified radiation toxicities according to the previously published radiation toxicity scheme "VRTOG" as well as the updated version, "VRTOG_v2.0". Fourteen dogs with transitional cell carcinoma of bladder ± urethra ($n = 8$), +prostate ($n = 3$) or solely urethra ($n = 3$), were included. Median follow-up was 298 days (range 185–1798 days), median overall survival 305 days (95%CI = 209;402) and 28.6% deaths were tumour-progression-related. Acute radiation toxicity was mild and self-limiting with both classification systems: In VRTOG, 5 dogs showed grade 1, and 1 dog grade 2 toxicity. In VRTOG_v2.0, 2 dogs showed grade 1, 3 dogs grade 2, and 3 dogs grade 3 toxicity. Late toxicity was noted in 14.2% of dogs (2/14) with the VRTOG, both with grade 3 toxicity. With VRTOG_v2.0, a larger proportion of 42.9% of dogs (6/14) showed late toxicities: Four dogs grade 3 (persistent incontinence), 2 dogs grade 5 (urethral obstructions without PD resulting in euthanasia). At time of death, 5 dogs underwent further workup and only 3 were confirmed to have PD. With the updated VRTOG_v2.0 classification system, more dogs with probable late toxicity are registered, but it is ultimately difficult to distinguish these from disease progression as restaging remains to be the most robust determinant.

KEYWORDS
bladder tumour, canine urogenital cancer, late toxicity, radiation side effects, radiation therapy, veterinary radiation therapy oncology group

1 | INTRODUCTION

Canine urothelial malignancies are mostly treated systemically with chemotherapy despite macroscopic disease that might be inherently resistant to it.[1] To enhance locoregional control, external beam radiotherapy (RT) was added to definitive-intent treatment protocols and chemoradiotherapy showed promising median survival times.[2,3] Nowadays, these patients profit from highly conformal techniques with image-guided (IG) intensity-modulated radiotherapy (IMRT or volumetric modulated arc therapy (VMAT)), sparing

the organs at risk (OAR) to a high degree. Genitourinary and gastrointestinal complications after definitive-intent (chemo-)radiotherapy may still occur, especially as some of the OAR are of tubular shape (ureter, urethra, intestines) and late toxicity may consist of strictures. Furthermore, often large volumes are treated, if the whole bladder is included.[2–4] Severe radiation effects such as permanent urinary incontinence or stricture/obstruction were suspected in up to 31% of dogs treated for prostate, bladder or urethral cancer at a median of 70 days post irradiation.[2,3] Strictures were presumed to be due to radiation-induced fibrosis based on unremarkable imaging findings, while presenting with persistent clinical signs.[3] These clinical signs can be difficult to distinguish from progressive disease (PD) or tumour-associated complications (bleeding, secondary bacterial infection).[5]

In human genitourinary cancers (mostly prostate, cervical) treated with definitive-intent radiation protocols, late radiation toxicities are well documented. Moderate grade ≥2 late genitourinary and low GI toxicities, graded according to the Radiation Therapy Oncology Group (RTOG), are described in 6%–24% and 1.9%–8% of patients, respectively.[6–10] As advantage in human patients, patient-reported data are complementary and were shown to be superior to physician-reported data, although its collection is more complex.[11]

With new radiation or multimodal treatment protocols, toxicity rates must be closely monitored, as it represents good clinical practice to limit the probability of (potentially untreatable) late toxicity to a low level. While a veterinary radiation toxicity scoring system has been established for monitoring radiation toxicity,[12] the genitourinary and gastrointestinal tract organs are poorly represented in this scheme.

Herein, we retrospectively assessed the presumed early and late toxicities in dogs treated with chemoradiotherapy for transitional cell carcinomas (TCC) of the bladder or urethra. Side effects as recorded and scored according to the Veterinary Radiation Therapy Oncology Group (VRTOG) were re-scored with the newly refined scoring system VRTOG_v2.0.[13] Additionally, adverse events or clinical signs, respectively, were attributed to the attribution standard categories as defined in Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events VCOG-CTCAE_v2.[14] With the updated VRTOG_v2.0 classification system, more dogs with probable late toxicity are registered. Whereas VRTOG_v2.0 identifies more dogs with adverse effects that may be attributed to RT, it remains difficult to determine radiotoxicity from progressive disease. Restaging is the most robust determinant but is also not consistently reliable to distinguish these events.

2 | METHODS

2.1 | Patient and tumour characteristics

Dogs with histologically or cytologically confirmed TCC of the bladder and/or urethra and prostate treated with definitive-intent chemoradiation at the Division of Radiation Oncology, Vetsuisse Faculty, University of Zurich, Switzerland between January 2018 and June 2022 were considered eligible for this retrospective study. Patients were treated with dose-intense chemotherapy and COX-inhibitors prior to treatment with moderately hypofractionated RT (12 × 3.8 Gy). Afterwards, treatment was continued with either another cycle of dose-intense chemotherapy or switched to oral maintenance chemotherapy. Dogs were treated with this protocol with explicit owners' consent.

Prior to treatment, dogs underwent our standard staging procedure: clinical examination, haematology, biochemistry profile, urinalysis, urinary bacteriology, thoracic radiographs, abdominal ultrasound, ultrasonographic measurements of tumour size. Tumour stage was classified according to the modified WHO staging system for canine bladder tumours in domestic animals.[15]

2.2 | Chemotherapy

COX-inhibitors were started at presentation. Dogs were administered a first series of dose-intense chemotherapy prior to RT, either Gemcitabine (900 mg/m^2 if >15 kg, 800 mg/m^2 if <15 kg) every 10 days for 4–5 times, Vinblastine with starting dose 2.3 mg/m^2 weekly for 4 times or Mitoxantrone at 5 mg/m^2 every 3 weeks twice. In case of adverse events, chemotherapy was postponed, or dose reduction was performed at discretion of the treating clinician. Haematology was performed before each treatment. Adverse events were classified according to VCOG-CTCAE_v2.[14]

Three weeks after RT, a second chemotherapy series was started. If in stable disease or partial remission, dogs that initially received gemcitabine were treated with 3–4 additional doses of gemcitabine (8 total administrations). In case of tumour progression after gemcitabine, chemotherapy was switched to carboplatin at a dose of 300 mg/kg (dog >10 kg) or 10 mg/kg (dogs <10 kg) every 3 weeks for 4 times. Dogs that received mitoxantrone before RT and showed stable disease or partial remission, were treated with 4 additional doses. Dogs that received vinblastine before RT were switched to metronomic chemotherapy with chlorambucil at a daily dose of 4 mg/m^2 orally. Chlorambucil was offered to all patients after completion of dose-intense chemotherapy as maintenance chemotherapy. In case of disease progression during or after post-RT dose-intense chemotherapy, a rescue protocol was offered based on clinician's preferences and owner decision.

After the first series of the dose-intense chemotherapy, a planning computed tomography (CT) and urogenital ultrasound were performed to assess tumour size. For treatment planning, pre- and post-contrast standard CT scans of the caudal abdomen were performed with a 16 multidetector computed tomography unit (Brilliance CT 16-slice, Philips Health Care Ltd, Best, Netherlands) under general anaesthesia as previously published.[16] Patients were immobilized in sternal recumbency with outstretched hind limbs in an individually shaped vacuum cushion (BlueBag BodyFix, Elektra AB, Stockholm, Sweden).

2.3 | Contouring of target volumes and organs at risk, planning and treatment

Contouring and treatment planning were performed with Eclipse External Beam Planning system version 15.1.51 (Varian Oncology Systems, Palo Alto, USA) with the Anisotropic Analytical Algorithm (AAA) and heterogeneity correction. Co-registered pre- and post-contrast CT images were used to increase accuracy of contouring. OAR were defined according to an anatomy textbook[17] and as previously published.[18] Tumour-related volumes were defined as follows[18]: (a) Primary gross tumour volume (GTVprim): tumour as seen on co-registered contrast-enhanced CT images. (b) Primary clinical target volume (CTVprim): includes GTVprim, extended 2 cm within the urinary tract beyond grossly evident disease to account for microscopic disease burden[19] and the entire urinary bladder. (c) Locoregional lymph node clinical target volume (CTVlnn): lymph nodes (bilateral medial and internal iliac and sacral lymph nodes) as seen on co-registered contrast-enhanced CT images. (e) Primary planning target volume (PTVprim) and locoregional lymph node PTV (PTVlnn): CTVprim/CTVlnn, three-dimensionally extended by 4–5 mm.[20,21] PTVprim and PTVlnn were combined to PTV combined using the Boolean operator tool. Irradiated volumes, mean, minimum and maximum dose were reported as suggested.[21]

In most cases, offline dynamic hybrid adaptive RT (DART) plans were prepared, resulting in multiple plans for different bladder fill states.[22] OARs and GTVs were kept as contoured, but CTV (whole bladder) and PTVs were adjusted. In daily treatment sessions, the best plan of the day was chosen. DART planning was performed either with a new planning CT or by using CBCT images performed on the linear accelerator.

Radiation was delivered under general anaesthesia on a daily schedule over 2.5 consecutive weeks, with a 6 MV linear accelerator (Clinac iX, Varian, Palo Alto, California), equipped with a 5 mm multi-leaf-collimator and on-board imaging. Daily image-guidance (IGRT) was performed using kilovolt kV–kV images in dorsoventral and laterolateral planes for preliminary matching and additional daily cone beam CT (kV-CBCT) for soft tissue matching of the bladder position. Therapy was delivered in a dynamic IMRT or VMAT mode with isocentrically planned beams arranged in a coplanar manner. Quality assurance of linear accelerator and on-board imager was performed as required by institutional and federal guidelines.[23,24]

2.4 | Follow-up

Three weeks post-RT chemotherapy was continued, and early toxicities were graded. Another urogenital ultrasound was performed for evaluation of disease status before continuing chemotherapy.[25] Further ultrasound examinations were performed at the end of the post-RT dose-intense chemotherapy, before starting metronomic chemotherapy and every 3 months thereafter or at any time if clinically indicated. At each visit, radiation toxicity grading was included.

2.5 | Statistical analysis

Data were coded in Excel (Microsoft Excel 2022, Version 16.66.1) and analysed with SPSS (IBM SPSS Statistics, Version 29). Graphical assessment and Shapiro–Wilk normality test was performed on all data and mean ± SD or median and interquartile range was reported, as appropriate. RT toxicities were graded according to the VRTOG and, retrospectively, with the updated VRTOG_v2.0 toxicity criteria and descriptively reported.[12] Radiation toxicities were considered as early from the start of RT until ≤90 days after RT, and as late if >90 days.[26] Overall survival (OS) was defined as interval from the first chemotherapy until death. Time to progression (TTP) was defined as interval between the first chemotherapy until confirmed or clinically suspected progression of disease. In both analyses, dogs were censored if lost to follow-up or euthanized because of reasons unrelated to TCC. Mean OS and mean TTP are reported with the corresponding 95% confidence intervals (95%CI).

3 | RESULTS

3.1 | Patient population

Fourteen dogs were included, patient and tumour characteristics are presented in Table 1 and radiation volumes and absorbed doses are presented in Table 2. The mean age of all dogs was 10.1 years (± 2.0, range 5.3–2.5 years). The mean body weight was 21.2 kg (± 13.1, range 3.1–45.0 kg). One intact female and 6 castrated females, as well as 7 neutered males were included.

3.2 | Clinical presentation

Dogs most frequently presented with pollakiuria ($n = 9$) and stranguria ($n = 7$); tenesmus and a history of recurrent UTIs was present in 3 dogs each. Three dogs also presented with hematuria. In only 1 dog the tumour diagnosis was an incidental finding. In 2 dogs, additional abdominal pain was noted. No dogs presented with hydronephrosis or hydroureters. Median duration of symptoms prior to diagnosis was 40 days (IQR 35), ranging between 10 and 180 days. Eleven dogs were started on piroxicam and 2 with meloxicam. No dogs experienced adverse effects from the medication. The medication was continued for the patients' lifetime.

3.3 | Tumour staging

All dogs enrolled had TCC of the urogenital tract, with varying locations as shown in Table 1. Tumour diagnosis was confirmed by cytology (traumatic catheterization) in 12 dogs and by histopathology in 2 dogs. Testing for BRAF was performed in 6 dogs: 4 tested positive for the BRAF mutation, 2 negative. In 1 of those 2 dogs additional histology was performed to verify diagnosis.

TABLE 1 Dog and tumour characteristics, chemotherapy, highest grade of toxicity and survival.

No.	Age (years)	Weight (kg)	Sex	Breed	Tumour stage (location)	ChTx pre-RT (1st series)	ChTx post RT (2nd series)	Highest grade of late toxicity (VRTOG)	Highest grade of late toxicity (VRTOG_v2)	OS (days)[a]	Cause of death
1	12.2	20.6	F, s	Gos d'Atura Catala	T2N0M0 (trigone)	Gemcitabine[b]	Gemcitabine[b]	0	Grade 3 UT @3Mo @6Mo	442	Other tumour
2	10.6	29.0	M, c	Australian Shepherd	T3N0M0 (trigone)	Gemcitabine[b]	Carboplatin[c]	0	0	298	Other tumour
3	9.0	11.2	M, c	Cairn Terrier	T2N0M0 (trigone)	Gemcitabine[b]	Gemcitabine[b]	0	Grade 3 UT @18Mo	1790	Tumour progression
4	11.0	23.6	F	Border Collie	T3N0M0 (cranial pole of bladder)	Mitoxantrone[f]	Mitoxantrone[f]	0	0	278	Unknown
5	7.8	4.2	M, c	Toy Poodle	T3N0M0 (trigone & urethra)	Gemcitabine[b]	Gemcitabine[b]	0	Grade 3 UT @3Mo @6Mo	287	Tumour progression
6	9.0	15.0	M, c	Mixed	T3N0M0 (trigone & urethra)	Gemcitabine[b]	Gemcitabine[b]	Grade 3 bladder @6Mo	Grade 3 colon @6Mo; Grade 5 UT @6Mo	175	Late toxicity versus tumour progression
7	9.8	45.0	M, c	American Staffordshire Terrier	T2N0M0 (prostate)	Gemcitabine[b]	Gemcitabine[b]	0	0	1075	Other tumour
8	11.7	17.7	F, s	Portuguese Waterdog	T3N0M0 (trigone)	Gemcitabine[b]	Gemcitabine[b]	Grade 3 bladder @6Mo	Grade 1skin @3Mo; Grade 2–3 colon @3Mo @6Mo Grade 5 UT @6Mo	361	Late toxicity versus tumour progression
9	5.3	44.6	F, s	Bernese Mountain dog	T3N0M0 (trigone & urethra)	Vinblastine[d]	—	0	0	510	Other tumour
10	8.3	26.8	F, s	Australian Shepherd	T3N0M0 (urethra)	Gemcitabine[b]	Chlorambucil[e]	0	0	260[a]	
11	11.5	21.8	M, c	Mixed	T2N1M0 (body of bladder)	Vinblastine[d]	—	0	0	251	Septic abdomen
12	11.4	27.7	F, s	Labrador Retriever	T3N0M0 (urethra)	Vinblastine[d]	—	0	0	209	Tumour progression
13	12.5	6.6	M, c	Jack Russell Terrier	T3N0M0 (trigone, prostate & urethra)	Gemcitabine[b]	—	0	0	283	Suspected distant metastasis (bone)
14	11.6	3.1	F, s	Chihuahua	T3N0M0 (cranial pole of bladder & urethra)	Vinblastine[d]	—	0	Grade 3 UT @3Mo @6Mo	280[a]	

Abbreviations: C, castrated; ChTx, chemotherapy; F, female, M, male, s, spayed; UT, urinary tract.

[a]Dog still alive.

[b]Gemcitabine Kabi 38 mg/mL, Fresenius Kabi Deutschland GmbH, Germany at 800–900 mg/m^2.

[c]Carboplatin-Teva liquid 450 mg/45 mL, Teva Pharmaceuticals, Israel at 300 mg/m^2.

[d]Velbe 10 mg, Spiring Healthcare AG, Switzerland at starting dose of 2.3 mg/m^2 with continued dose escalation up to 2.7 mg/m^2.

[e]Leukeran Aspen Pharmacare, Australia at 4 mg/m^2 rounded to the next whole 2 mg tablet.

[f]Product unknown, with starting dose 5 mg/m^2.

TABLE 2 Target volumes: mean volumes and absolute absorbed doses.

	Total ($n = 14$)	D_{max} ($D_{2\%}$) (mean ± SD) [Gy]	D_{mean} ($D_{50\%}$) (mean ± SD) [Gy]	D_{min} ($D_{98\%}$) (mean ± SD) [Gy]
GTV mean volume ± SD (cm^3)	7.5 (± 6.5)			
CTV mean volume ± SD (cm^3)	57.3 (± 43.1)			
PTV mean volume ± SD (cm^3)	128.0 (± 73.9)	46.5 (± 0.2)	45.7 (± 0.1)	43.9 (± 0.3)

Abbreviations: CTV, clinical target volume; D_{max}, maximum dose; D_{mean}, mean dose; D_{min}, minimum dose; GTV, gross tumour volume; Gy, Grey; PTV, planning target volume.

Two dogs had enlarged lymph nodes on imaging without subsequent cytological examination. In 1 dog, early pulmonary metastasis could not be ruled out. None of the other dogs had signs of distant metastasis. In total, 3 dogs were staged as T2N0M0, one dog as T2N1M0, one dogs as T3N1M0 and 9 dogs as T3N0M0.

3.4 | Chemotherapy

Nine dogs were treated with Gemcitabine (Table 1). Dose reductions and adverse events are provided in the Table S1. Four dogs received Vinblastine and one dog received 2 doses of Mitoxantrone prior to RT.

After RT completion, Gemcitabine ($n = 6$) or Carboplatin ($n = 1$, with PD) were administered in 7 dogs receiving gemcitabine before RT. One dog that received mitoxantrone prior to RT received 4 additional doses of after RT. This dog was then switched to a rescue protocol with Carboplatin due to PD. Ten dogs (71.4%) were started on maintenance chemotherapy with Chlorambucil directly after RT ($n = 4$) or after completing the post-RT dose-intense chemotherapy ($n = 6$). Dose-intense chemotherapy was generally well tolerated, although dose reduction was required in 6 dogs (43%). Adverse events (AE) reported were frequent but mild and self-limiting with supportive care (Table S1). Only 2 dogs (14.2%) experienced no AE. No AE were registered in patients receiving chlorambucil.

3.5 | Radiation therapy treatment delivery

RT was commonly started 2 weeks after the last administration of the first series of chemotherapy. Owners were advised to ensure their dogs to have had sufficient time to urinate prior to treatment for smallest possible bladder volume. In 6 dogs, treatment was carried out with DART, with 4 dogs having 3 treatment plans according to different bladder volumes and 2 dogs having 2 treatment plans to cover a variance of fill states. In all but one dog the medium bladder size plan was used with highest frequency throughout the treatment. Locoregional lymph nodes were included into the treatment plan in all patients, regardless of tomographical abnormality or suspected metastasis.

3.6 | Acute radiation toxicity

Overall, acute radiation toxicities were mild and self-limiting within 3 weeks post radiotherapy. Radiation toxicities are displayed according to the VRTOG (Figure 1, top) and the VRTOG_v2.0 (Figure 1, bottom). Acute radiation effects according to the VRTOG were noted in 6 patients (42.9%), and in 7 patients (50%) in the updated VRTOG_v2.0. According to the VRTOG, acute toxicity was only noted in female patients with urethral tumour involvement. Four dogs (28.6%) showed grade 1 side effects on the skin around the vulva. One of those females (7.1%) showed moist desquamation (grade 2) within 3 weeks post RT. In total, 4 dogs (28.6%) showed grade 1 genitourinary side effects entailing polyuria. One dog (7.1%) showed increased frequency in urination and defecation. Another dog (7.1%) showed potential rectal discomfort with scooting classified as grade 1 lower GI side effects. One male dog (7.1%) showed solely an increased frequency of urination post RT. Acute side effects occurred as frequently according to the updated VRTOG_v2.0, but at a different intensity. One dog (7.1%) developed intermittent, self-limiting incontinence within the post treatment period. Three dogs (21.4%) showed grade 1–3 (grade 1 $n = 1$, grade 2 $n = 1$, grade 3 $n = 1$) pain during the post treatment period of 3 weeks. No dogs lost weight between the start of RT to 3 weeks post treatment. All acute toxicities resolved between 3 and 4 weeks after RT (Figure 1).

3.7 | Late radiation toxicity

According to the VRTOG scoring system, late radiation toxicities were noted in 2 dogs (14.2%) (Figure 2, top). These two patients were incapable to void their bladder 3 and 8 months after RT without sonographic and/or fluoroscopic evidence of PD. In both dogs, tumours were mainly located in the urethra and the prostate in one dog, and both were in partial remission with no obstruction noted at examination and had shown normal urination beforehand. Because already a small increase in tumour volume in a partially obstructed urethra could have led to voiding incapability, however, PD cannot completely be ruled out. Medical treatment was unsuccessful and both dogs were euthanized. According to the VRTOG_v2.0, late toxicity occurrence was higher (Figure 2, bottom): Six dogs (42.8%) were classified to have late radiation toxicity. Five of these dogs developed chronic incontinence at a mean of 8.5 months (256 days ± 329; range 39–973 days) post RT. All patients were restaged at reoccurrence of clinical signs to exclude PD and had no evidence thereof. Two patients (14.2%) were graded to have Grade 5 toxicity due to incapability of voiding coupled with incontinence as priorly described. Those two patients were

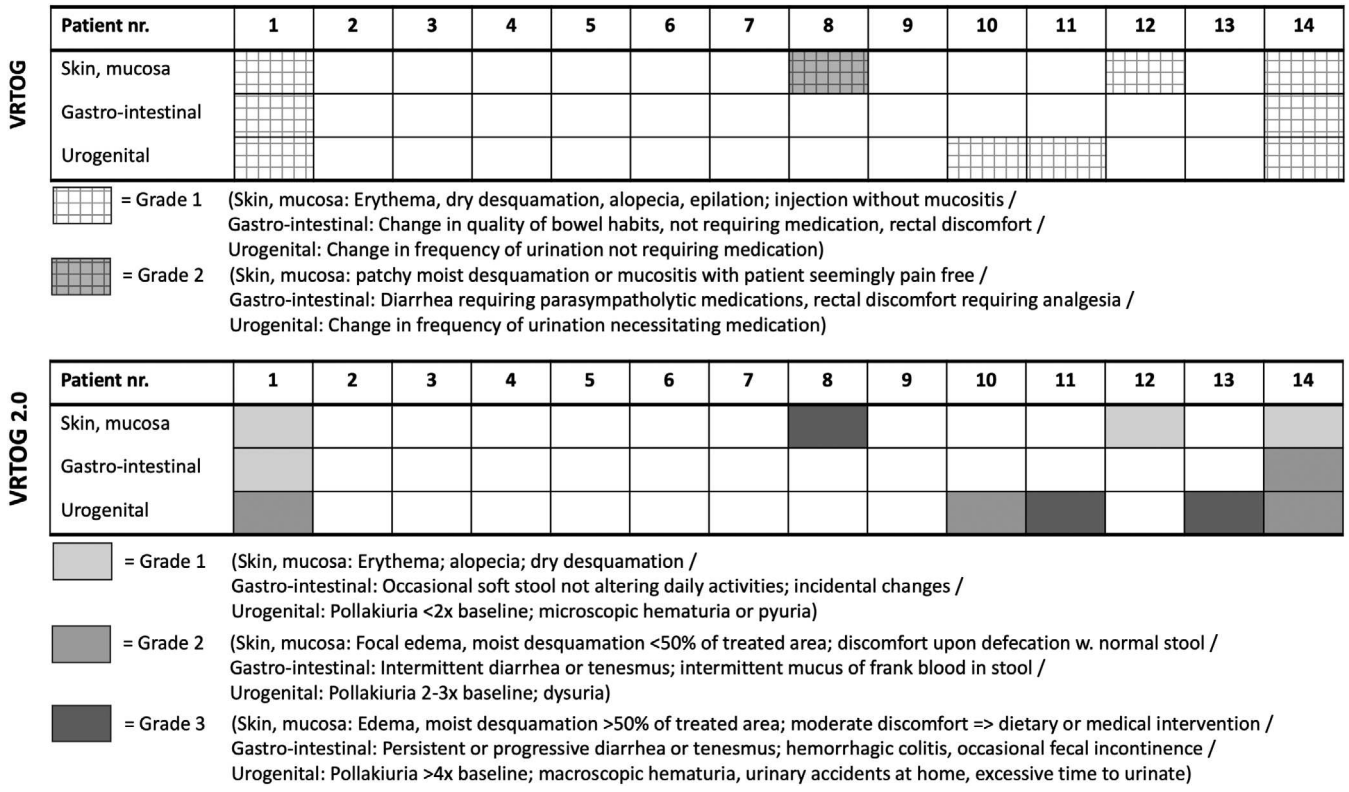

FIGURE 1 Scoring of acute toxicity in all 14 patients within 3 weeks post radiotherapy: Toxicity in skin & mucosa, gastro-intestinal and urogenital systems, along the two scoring systems (VRTOG, top; VRTOG_v2.0, bottom).

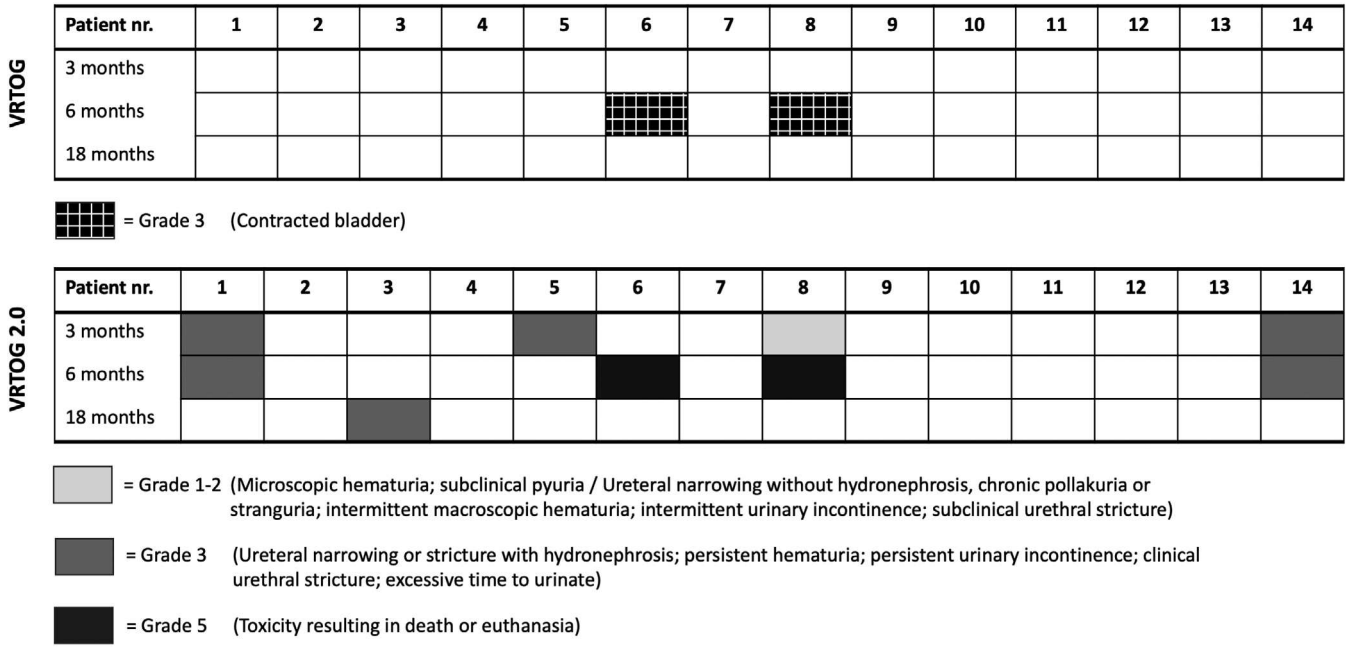

FIGURE 2 Scoring of urogenital toxicity in all 14 patients at 3, 6, 18 months along the two scoring systems (VRTOG, top; VRTOG_v2.0, bottom).

euthanized, which automatically leads to classification in Grade 5 toxicity. According to the attribution standards the toxicity is probable, meaning it being likely to be related to RT. (Figure 2) Temporary placement of a cystotomy tube was performed in one dog, but discontinued due to lack of improvement of symptoms, none of the dogs was urethrally stented.

3.8 | Supportive medical treatment of urinary disorders

Symptoms of incontinence did not resolve within the patients' lifetime. Four of 5 patients were started on a variety of medications to manage symptoms, including flavoxathydrochloride, tamsulosin hydrochloride and phenylpropanolamine. All medications were inefficient and discontinued eventually.

3.9 | Survival analysis and follow-up

Median follow-up time for all dogs was 298 days (range, 185–1798), and for the dogs still alive ($n = 2$) 260 and 280 days. No dog was lost to follow-up. At the time of writing, 12 patients (85.7%) were dead. Four dogs (28.6%) were euthanized due to PD, with one of these dogs in addition having had a suspected bone metastasis in the femur. Four dogs were euthanized due to an additional tumour including multicentric lymphoma ($n = 2$), acute leukaemia ($n = 1$) and a splenic mass ($n = 1$). In four dogs (28.4%) cause of death was unknown (Table 1).

Median TTP after diagnosis for all dogs was 308 days (95%CI: 268;349), and median TTP after start of RT was 237 days (95% CI: 206;269). Median OS after diagnosis for all dogs was 369 days (95%CI: 271;468), and median OS after start of RT was 305 days (95%CI: 209;402).

4 | DISCUSSION

The VRTOG_v2.0 grading scheme applied to dogs treated with definitive-intent chemoradiation for urothelial TCC conferred a clinically more congruent assessment of toxicity compared to the VRTOG grading scheme. Acute and late toxicities after chemoradiation of the urogenital tract might have been underestimated in the past,[2,3] as they were not itemized in the initial scoring system.[12] Toxicity scoring along VRTOG_v2.0 revealed a high amount of quality-of-life-relevant clinical signs after combined chemoradiation, indicating that the protocol or the extent of irradiated volumes are likely too toxic. Our study is the first to retrospectively compare toxicities of the initial VRTOG scoring system with the revised version, VRTOG_v2.0.

The multimodal treatment approach to canine urothelial TCC including RT is currently seen as beneficial,[2,3] but often accompanied by clinical signs that may be attributed either to PD or chemoradiation toxicity.[2,27,28] In earlier studies (VRTOG-graded), mostly mild early and sometimes overlapping radiation-associated complications were noted, with dermal/ integumental signs in 19%[3]–22%,[2] gastrointestinal signs in 38%[3]–47%,[2] and in 10%[3] and 16%[2] genitourinary signs such as hematuria and stranguria. However, comparable to our 14% (VRTOG-graded), 6%[2] and 19%[3] of dogs developed late severe grade 3 toxicities at 4–20 months after RT, consisting of urethral functional obstruction or stricture and gastrointestinal strictures, respectively. While no comments were made on urinary continence or the lack thereof (not itemized in VRTOG), the owner questionnaire in Nolan et al. (2012)[3] reported worse or unchanged quality of life in 40% of dogs after RT. In addition, a second study specifically reported permanent urinary incontinence (not present before RT) in 31% (14/45) of dogs with long-term follow-up, with a median time to incontinence of 70 days.[2] With the more detailed VRTOG_v2.0 grading as used herein, 43% of the dogs treated in our study developed chronic incontinence at a mean of 8.5 months post RT.

Urogenital tract side effects can often be difficult to distinguish from PD, tumour-associated bleeding or secondary bacterial infection[5] and imaging-based tumour assessment may vary due to variable bladder fill states or interobserver variability.[29] Using imaging modalities such as fluoroscopy or MRI at baseline and subsequently for follow up may deliver additional information for differentiation between PD and toxicity. Overall, patients' declining physical condition and death is often attributed to local PD and due to partial or complete urethral and/or ureteral obstruction.[1]

The evaluation of 14 patients according to the new VRTOG_v2.0 has shown that 43% of dogs (6/14) presented with symptoms such as persistent, treatment-refractory incontinence without imaging-based evidence of PD. In addition to the 6%–19% severe grade 3 VRTOG grade 3 toxicities found by other authors,[2,3] such high grades of late toxicity are in general not acceptable. "The optimum radiation dose in curative radiotherapy is defined at the dose, which is associated with a certain, low – usually ≤5% – incidence of sequelae of a defined severity in cured patients ('complication-free healing')".[30] Although appearance of symptoms varied in patients among the dog patients described herein, in Nolan et al. (2012) and Clerc-Renaud et al. (2021), most suffered late effects quite early, within 8.5 months after RT. Such an early occurrence indicates a lack of tolerance of the irradiated tissue (bladder urothelium) to the chosen radiation dose and/or treated volume.

In humans, radiation-cystitis is a well-known late toxicity after RT of genitourinary cancers occurring within 3–6 months after RT in 5%–10% of patients.[31] The prevalence of late effects has remained stable throughout the past years despite continuous advances in treatment techniques.[32] Radiation-induced cystitis is a not entirely understood phenomenon: RT damages the submucosal vascularity and leads to fibrosis of the vascular intima, resulting in vessel obliteration and subsequent submucosal and/or vascular fibrosis. The consequence is urothelial atrophy due to hypoxia, ischemia and hypovascularization of the bladder urothelial lining, which leads to recurring perforations and in severe cases fistulization.[30,32,33] Another possible explanation of the high radiosensitivity of the bladder epithelium is related to the damage to intermediate and basal urothelial cells, occurring within 3 months of radiation exposure.[34] Early changes are thought to clearly correlate with chronic sequelae, which illustrates a consequential component[30]: The normal proteoglycan layer may be lost in the consequence, destroying the barrier between urine and bladder tissue, which may be causative for the recurring irritative lower urinary tract symptoms occurring within months to years of radiation exposure.[35]

Chemotherapy is unlikely considered as a primary trigger for observed symptoms, especially with drugs and doses used in our patients.[28,36,37] Nonetheless, gemcitabine induced radiation recall

has been reported rarely in humans and cannot be ruled out completely.[38,39]

To treat urothelial tumours in dogs, definitive-intent protocols with 57 Gy in 20 fractions (2.85 Gy per fraction)[2] and 54–58 Gy in 20 fractions (2.7–2.9 Gy per fraction)[3] have been used. In our study, dogs were treated with 45.6 Gy in 12 fractions, a more hypofractionated approach, prior described for abdominopelvic tumours.[18,40–42] In general, larger doses per fraction yield a higher risk for (late) normal tissue complication as normal pelvic OARs commonly has a low alpha/beta ratio, around 3.[43] When anti-tumour efficacy of protocols is compared by assuming an alpha/beta ratio of 10, our protocol seems less effective: $EQD_{2alpha/beta=10}$ (equivalent dose of 2 Gy fractions with alpha/beta ratio of 10) of the protocols with 20 fractions varies between 57.2 and 61.0 Gy in comparison to our protocol with equivalent dose 52.4 Gy. When evaluating late toxicity, on the other hand, $EQD_{2alpha/beta=3}$ is comparable with 61.6–68.4 Gy for the protocols with 20 fractions and 62.0 Gy for our protocol. Regarding organ tolerance in the abdominopelvic area, hypofractionated treatment in 12 fractions protocol has been found safe regarding early and late toxicity when irradiating dogs with abdominopelvic tumours.[18,40,44] Because those were mainly anal sac tumours ± lymph node metastases, however, the treated volume only included a small part of the urinary bladder, but sometimes a large part of the urethra. In human medicine, even with only partial irradiation of the bladder, the occurrence of early and late radiation effects in tumours of the pelvic area are connected to irradiated volume of the bladder and increases if total dose exceeds 45 Gy.[45] This is stated in the QUANTEC report where irradiating more than 65% of the bladder volume with >50% of dose (e.g., 30–35 Gy) leads to a higher risk of grade 3+ toxicity, whereas irradiating 80% of bladder volume with only 15% of dose (e.g., 9.75–10.5 Gy) already leads to grade 3+ toxicity.[46] In our and prior studies, the whole bladder was treated, to address the risk of possible intravesicular seeding as seeding after surgery or biopsy has been reported. As intravesicular seeding is not commonly reported, irradiation of the entire bladder may not be necessary.[2]

Survival time with a median of 1 year was comparable to previous studies using multimodality treatment,[2,3] and only marginally longer than the median overall survival times of ~10 months in dogs treated chemotherapy in combination with anti-inflammatory drugs without RT.[28,36,47] Given the high risk of quality-of-life-impairing toxicities and costs, a possible benefit of combined (concurrent) chemoradiation in dogs with TCC of the bladder is not discernible.

We acknowledge limitations to this study: (1) While VRTOG-grading was performed in a timely prospective manner, the VRTOG_v2.0-grading was derived retrospectively from the medical records. (2) The RT protocol was standardized, but chemotherapies varied. This was in part due to the attending oncologist's preference, but also due to financial constraints of the owners. (3) The tumours included into this cohort were of various sizes and locations and might have led to clinical signs themselves, impossible to distinguish from radiation toxicities.

In conclusion, the incidence of late effects of the currently used, definitive-intent radiation protocols for canine urothelial cancer is well above the tolerated 5% accepted in our institution. A higher incidence of late radiation effects may be an acceptable trade-off, if the possible outcome with the combined therapy is vastly better, which is currently not the case in canine urothelial cancer. As the multifocal occurrence of carcinomas within the bladder or intra-organ seeding is possible, but rare (and should be inhibited with chemotherapy), it may be a sensible suggestion to limit the irradiation volume to the GTV with small margins aggressively sparing the rest of the bladder volume from radiation. In addition, RT could be saved as a rescue therapy once chemotherapy has failed. Overall, we perceived the updated grading scheme of VRTOG_v2.0 to be clinically useful, being more precise and delivering valuable additional information for decision-making and expectation of treatment results. This can be stated as a proof of principle as it not only captures acute and late radiation effects in bladder cancers to a higher extent, but also asks the clinicians to attribute clinical signs according to attribution standard categories as defined in VCOG-CTCAE_v2.[14]

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Fulkerson CM, Knapp DW. Management of transitional cell carcinoma of the urinary bladder in dogs: a review. *Vet J*. 2015;205(2):217-225.
2. Clerc-Renaud B, Gieger TL, LaRue SM, Nolan MW. Treatment of genitourinary carcinoma in dogs using nonsteroidal anti-inflammatory drugs, mitoxantrone, and radiation therapy: a retrospective study. *J Vet Intern Med*. 2021;35(2):1052-1061.
3. Nolan MW, Kogan L, Griffin LR, et al. Intensity-modulated and image-guided radiation therapy for treatment of genitourinary carcinomas in dogs. *J Vet Intern Med*. 2012;26(4):987-995.
4. Choy K, Fidel J. Tolerability and tumor response of a novel low-dose palliative radiation therapy protocol in dogs with transitional cell carcinoma of the bladder and urethra. *Vet Radiol Ultrasound*. 2016;57(3):341-351.
5. Budreckis DM, Byrne BA, Pollard RE, Rebhun RB, Rodriguez CO Jr, Skorupski KA. Bacterial urinary tract infections associated with transitional cell carcinoma in dogs. *J Vet Intern Med*. 2015;29(3):828-833.
6. Akthar AS, Liao C, Eggener SE, Liauw SL. Patient-reported outcomes and late toxicity after postprostatectomy intensity-modulated radiation therapy. *Eur Urol*. 2019;76(5):686-692.
7. Chennupati SK, Pelizzari CA, Kunnavakkam R, Liauw SL. Late toxicity and quality of life after definitive treatment of prostate cancer: redefining optimal rectal sparing constraints for intensity-modulated radiation therapy. *Cancer Med*. 2014;3(4):954-961.

8. Efstathiou JA, Bae K, Shipley WU, et al. Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89-03, 95-06, 97-06, 99-06. *J Clin Oncol*. 2009;27(25):4055-4061.
9. Hoffman KE, Voong KR, Pugh TJ, et al. Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. *Int J Radiat Oncol Biol Phys*. 2014;88(5):1074-1084.
10. Pederson AW, Fricano J, Correa D, Pelizzari CA, Liauw SL. Late toxicity after intensity-modulated radiation therapy for localized prostate cancer: an exploration of dose-volume histogram parameters to limit genitourinary and gastrointestinal toxicity. *Int J Radiat Oncol Biol Phys*. 2012;82(1):235-241.
11. Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys*. 2010;76(3 Suppl):S116-S122.
12. Ladue T, Klein MK, Veterinary Radiation Therapy Oncology G. Toxicity criteria of the veterinary radiation therapy oncology group. *Vet Radiol Ultrasound*. 2001;42(5):475-476.
13. Poirier VJ, Keyerleber M, Gordon IK, et al. ACVR and ECVDI consensus statement: reporting elements for toxicity criteria of the veterinary radiation therapy oncology group v2.0. *Vet Radiol Ultrasound*. 2023;64(5):789-797.
14. LeBlanc AK, Atherton M, Bentley RT, et al. Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) following investigational therapy in dogs and cats. *Vet Comp Oncol*. 2021;19(2):311-352.
15. Owen LN. TNM classification of tumours in domestic animals. *World Health Organization*. 1980;1(Geneva):32-35.
16. Rossi F, Körner M, Suárez J, et al. Computed tomographic-lymphography as a complementary technique for lymph node staging in dogs with malignant tumors of various sites. *Vet Radiol Ultrasound*. 2018;59(2):155-162.
17. Evans H, Lahunta AD. *Miller's Anatomy of the Dog*. 4th ed. Saunders; 2012.
18. Meier V, Besserer J, Roos M, Rohrer Bley C. A complication probability study for a definitive-intent, moderately hypofractionated image-guided intensity-modulated radiotherapy protocol for anal sac adenocarcinoma in dogs. *Vet Comp Oncol*. 2019;17(1):21-31.
19. Nolan MW, Gieger TL, Vaden SL. Management of transitional cell carcinoma of the urinary bladder in dogs: important challenges to consider. *Vet J*. 2015;205(2):126-127.
20. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;47(4):1121-1135.
21. Rohrer Bley C, Meier V, Robotka J, Schneider U. Image-guided radiation therapy in the palliative management of large abdomino-pelvic tumors. ESVONC Congress, Vienna, Austria. 2014.
22. Nieset JR, Harmon JF, Johnson TE, Larue SM. Comparison of adaptive radiotherapy techniques for external radiation therapy of canine bladder cancer. *Vet Radiol Ultrasound*. 2014;55(6):644-650.
23. Quality control for intensity-modulated radiation therapy. Swiss Society for Radiobiology and Medical Physics. 2007 Report No. 15. http://www.ssrpm.ch/old/recrep-m.htm#rec
24. Quality assurance of gantry-mounted image-guided radiotherapy systems. Swiss Society of Radiobiology and Medical Physics. 2010 Report No. 16. http://www.ssrpm.ch/old/recrep-m.htm#rec
25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
26. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Inte J Radiat Oncol Biol Phys*. 1995;31(5):1341-1346.
27. Poirier VJ, Forrest LJ, Adams WM, Vail DM. Piroxicam, mitoxantrone, and coarse fraction radiotherapy for the treatment of transitional cell carcinoma of the bladder in 10 dogs: a pilot study. *J Am Anim Hosp Assoc*. 2004;40(2):131-136.
28. Arnold EJ, Childress MO, Fourez LM, et al. Clinical trial of vinblastine in dogs with transitional cell carcinoma of the urinary bladder. *J Vet Intern Med*. 2011;25(6):1385-1390.
29. Hume C, Seiler G, Porat-Mosenco Y, Caceres A, Shofer F, Sorenmo K. Cystosonographic measurements of canine bladder tumours. *Vet Comp Oncol*. 2010;8(2):122-126.
30. Doerr W. Pathogenesis of normal tissue side effects. In: Joiner MC, van der Kogel AJ, eds. *Basic Clinical Radiobiology*. 5th ed. CRC Press, Taylor & Francis Group; 2019:152-170.
31. Denton AS, Clarke NW, Maher EJ. Non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database Syst Rev*. 2002;2002(3):Cd001773.
32. Helissey C, Cavallero S, Brossard C, Dusaud M, Chargari C, François S. Chronic inflammation and radiation-induced cystitis: molecular background and therapeutic perspectives. *Cells*. 2020;10(1):21.
33. Jaal J, Dorr W. Radiation induced late damage to the barrier function of small blood vessels in mouse bladder. *J Urol*. 2006;176(6 Pt 1):2696-2700.
34. Jaal J, Dorr W. Radiation-induced damage to mouse urothelial barrier. *Radiother Oncol*. 2006;80(2):250-256.
35. Smit SG, Heyns CF. Management of radiation cystitis. *Nat Rev Urol*. 2010;7(4):206-214.
36. Boria PA, Glickman NW, Schmidt BR, et al. Carboplatin and piroxicam therapy in 31 dogs with transitional cell carcinoma of the urinary bladder. *Vet Comp Oncol*. 2005;3(2):73-80.
37. Schrempp DR, Childress MO, Stewart JC, et al. Metronomic administration of chlorambucil for treatment of dogs with urinary bladder transitional cell carcinoma. *J Am Vet Med Assoc*. 2013;242(11):1534-1538.
38. Biswas J, Dutta S, Sharma S, Choudhury KB. Gemcitabine-induced radiation recall phenomenon in a post-operative and post-radiotherapy case of peri-ampullary carcinoma during adjuvant chemotherapy. *J Cancer Res Ther*. 2012;8(3):439-441.
39. Jeter MD, Jänne PA, Brooks S, et al. Gemcitabine-induced radiation recall. *Int J Radiat Oncol Biol Phys*. 2002;53(2):394-400.
40. Körner M, Staudinger C, Meier V, Rohrer Bley C. Retrospective assessment of radiation toxicity from a definitive-intent, moderately hypofractionated image-guided intensity-modulated protocol for anal sac adenocarcinoma in dogs. *Vet Comp Oncol*. 2022;20(1):8-19.
41. Meier V, Staudinger C, Radonic S, et al. Reducing margins for abdominopelvic tumours in dogs: impact on dose-coverage and normal tissue complication probability. *Vet Comp Oncol*. 2021;19(2):266-274.
42. Rohrer Bley C, Czichon F, Korner M, Staudinger C, Meier VS. Radiation therapy for the treatment of macroscopic canine anal gland tumors - a retrospective study. *Schweiz Arch Tierheilkd*. 2022;164(11):789-799.
43. Fiorino C, Cozzarini C, Rancati T, et al. Modelling the impact of fractionation on late urinary toxicity after postprostatectomy radiation therapy. *Int J Radiat Oncol Biol Phys*. 2014;90(5):1250-1257.
44. Meier V, Polton G, Cancedda S, et al. Outcome in dogs with advanced (Stage 3b) anal sac gland carcinoma treated with surgery or hypofractionated radiation therapy. *Vet Comp Oncol*. 2017;15(3):1073-1086.
45. D'Amico MJ, Foss H, Uhr A, Rudnick B, Kloniecke E, Gomella LG. Hemorrhagic cystitis: a review of the literature and treatment options. *Can J Urol*. 2022;29(5):11276-11283.
46. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys*. 2010;76(3 Suppl):S10-S19.

47. Greene SN, Lucroy MD, Greenberg CB, Bonney PL, Knapp DW. Evaluation of cisplatin administered with piroxicam in dogs with transitional cell carcinoma of the urinary bladder. *J Am Vet Med Assoc*. 2007;231(7):1056-1060.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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