J Vet Intern Med 2012;26:987–995

Intensity-Modulated and Image-Guided Radiation Therapy for Treatment of Genitourinary Carcinomas in Dogs

M.W. Nolan, L. Kogan, L.R. Griffin, J.T. Custis, J.F. Harmon, B.J. Biller, and S.M. LaRue

Background: External beam radiation therapy can be used to treat pelvic tumors in dogs, but its utility is limited by lack of efficacy data and associated late complications.

Hypothesis/Objectives: The objective of this study was to assess local tumor control, overall survival, and toxicosis after intensity-modulated and image-guided radiation therapy (IM/IGRT) for treatment of genitourinary carcinomas (CGUC) in dogs.

Animals: 21 client-owned dogs.

Methods: A retrospective study was performed. Medical records of dogs for which there was intent to treat with a course of definitive-intent IM/IGRT for CGUC between 2008 and 2011 were reviewed. Descriptive and actuarial statistics comprised the data analysis.

Results: Primary tumors were located in the prostate (10), urinary bladder (9), or urethra (2). The total radiation dose ranged from 54–58 Gy, delivered in 20 daily fractions. Grade 1 and 2 acute gastrointestinal toxicoses developed in 33 and 5% of dogs, respectively. Grade 1 and 2 acute genitourinary and grade 1 acute integumentary toxicoses were documented in 5, 5, and 20% of dogs, respectively. Four dogs experienced late grade 3 gastrointestinal or genitourinary toxicosis. The subjective response rate was 60%. The median event-free survival was 317 days; the overall median survival time was 654 days. Neither local tumor control nor overall survival was statistically dependent upon location of the primary tumor.

Conclusions and Clinical Importance: IM/IGRT is generally well-tolerated and provides an effective option for locoregional control of CGUC. As compared with previous reports in the veterinary literature, inclusion of IM/IGRT in multimodal treatment protocols for CGUC can result in superior survival times; controlled prospective evaluation is warranted.

Key words: Bladder; Dog; Genitourinary; IGRT; IMRT; Prostate; Urethra.

Genitourinary carcinomas (CGUC) in dogs, encompassing transitional cell carcinomas, adenocarcinomas, and solid carcinomas of the urinary bladder, urethra, and prostate, are locally aggressive tumors that have a high propensity for regional and distant metastasis. Death is often attributable to partial or complete urethral, ureteral obstruction, or both; 1–2 month survival times are typical when no therapy is pursued.[1] Palliation of clinical signs is often achievable through urinary diversion.[2–8] Such palliative measures can significantly improve quality of life but are not associated with significantly improved survival. The infiltrative nature of genitourinary carcinomas contributes to difficulties in achieving complete histological margins; as a result, tumors often recur within 3–10 months of more aggressive surgical interventions.[9–12] Survival can be extended through the use of nonsteroidal anti-inflammatories (NSAIDs); median survival times of approximately 6 months have been reported in dogs that received NSAID monotherapy for CGUC.[13,14] Such NSAID therapy can also be combined with antineoplastic chemotherapy to improve survival and has been associated with survival times ranging from 4.3 to 11 months.[15–18] In addition, incorporation of external beam radiation therapy (RT) into multimodal treatment protocols is potentially beneficial for locoregional control of CGUC. Intraoperative RT after surgical cytoreduction as well as fractionated external beam RT (FRT) for transitional cell carcinomas of the urinary tract have been associated with median survival times ranging from 4 to 15 months.[19–22]

Despite the potential benefits of RT, the high incidence (39–56%) of severe late radiation-associated

Abbreviations:

CGUC	canine genitourinary carcinoma
CSU-ACC	Colorado State University Animal Cancer Center
CT	computed tomogram
CTV	clinical target volume
DART	dynamic-adaptive radiation therapy
EFS	event-free survival
GTV	gross tumor volume
FRT	fractionated radiation therapy
IGRT	image-guided radiation therapy
IMRT	intensity-modulated radiation therapy
kV-CBCT	kilovoltage cone-beam CT
MIBC	muscle-invasive bladder cancer
MTD	maximally tolerated dose
NSAID	nonsteroidal anti-inflammatory drug
PTV	planning target volume
RT	radiation therapy

From the Department of Environmental and Radiologic Health Sciences (Nolan, Griffin, Custis, LaRue); and the Department of Clinical Sciences (Kogan, Biller), College of Veterinary Medicine and Biomedical Sciences, Fort Collins, CO (Kogan, Biller); and the Bon Secours Cancer Institute, Richmond Radiation Cancer Center, Henrico, VA (Harmon). *A portion of this work was presented as an oral abstract at the Veterinary Cancer Society's annual conference, Albuquerque, New Mexico (November 5, 2011).*

Corresponding author: Dr Michael W Nolan, CSU Animal Cancer Center, Campus Delivery 1620, Fort Collins, CO 80523-1620; e-mail: Michael.Nolan@colostate.edu.

Submitted January 20, 2012; Revised February 24, 2012; Accepted April 17, 2012.

10.1111/j.1939-1676.2012.00946.x

toxicoses (such as chronic colitis, cystitis, rectal perforations and strictures) after pelvico-abdominal radiation has kept definitive RT from inclusion as standard of care therapy in treatment of CGUC. Fraction and field size are known risk factors for development of late complications.[23,24]

In light of these limitations, there have been efforts to create RT protocols that are better tolerated by dogs. Use of laparoscopically implanted tissue expander RT has been reported in 2 dogs; although there was clinically important morbidity associated with the surgically implanted tissue expanders in both dogs, RT was apparently well-tolerated.[25] Helical Tomotherapy allowed for delivery of intensity-modulated and image-guided RT (IM/IGRT). Target localization via image-guidance decreases interfraction variability in the position of the target within the dog, and thus enables employment of smaller treatment fields. Use of IMRT increases the conformity of radiation dose, allowing for rapid fall-off of radiation dose outside of target volumes. The use of smaller fields in combination with so-called "dose-painting" limits dose exposures in normal tissues and accounts for the improved tolerability of pelvico-abdominal IM/IGRT as compared with more traditional forms of FRT.

The goals of the present study were to (1) determine the incidence and severity of both acute and late treatment-associated toxicoses and (2) assess local and locoregional tumor control, as well as overall survival, after completion of IM/IGRT for treatment of CGUC. It was hypothesized that treatment-associated toxicoses would be mild and self-limiting, and that IM/IGRT would improve local tumor control and survival, as compared with historically reported outcomes.

Materials and Methods

A descriptive retrospective analysis of data from dogs for which there was intent to complete IM/IGRT for CGUC at the Animal Cancer Center at Colorado State University (CSU-ACC) between June 2008 and July 2011 was performed. Histologic or cytologic evidence of a carcinoma in the genitourinary tract, as well as complete local and systemic staging (including complete blood count, serum biochemical profile, urinalysis, three-view thoracic radiographs, abdominal ultrasound and computed tomography of the pelvis), were requisite for inclusion.

A medical records review was performed. Information relating to dog demographics, oncologic histories, details of RT plans, response to treatment, local tumor control, compound toxicity, and overall survival was extracted. Timing of follow-up examinations and restaging lacked uniformity; when possible, information about extent and duration of tumor responses, normal tissue toxicoses and overall survival was obtained through review of medical records and verbal follow-up with primary care veterinarians and pet owners.

A standardized and anonymous written questionnaire was administered to owners of dogs in this study, with the intent of determining the impact of RT on pets and pet owners; questions related to challenges and difficulties associated with the logistics of treatment (cost, travel, duration of therapy, etc.), quality of life during and after completion of RT, overall outcomes, and client satisfaction. Institutional Review Board approval for research involving human subjects was obtained before releasing this survey. Surveys were sent to owners whose pets completed RT before June 2011 (18/21 cases); although much of the information gathered through this survey could have been applied to the 3 cases with shorter follow-up times, protocol approval did not allow for prospective data collection. Likewise, the retrospective nature of case identification did not allow for a standard temporal relationship between the time of RT and the time of questionnaire administration.

Radiation Therapy

Computerized three-dimensional treatment planning was utilized in all cases. Simulation CT scans were obtained before and after intravenous administration of iodinated contrast medium, with dogs positioned in lateral, dorsal, or sternal recumbency. The current preference is to immobilize dogs in a moldable cushion,[a] while positioned in lateral recumbency, with another cushion[b] between their pelvic limbs to minimize interfraction variability of target tissue localization and maximize separation between the urinary and gastrointestinal tracts.[26] Dogs were positioned in right lateral recumbency in 68% of these cases. Grossly evident tumor was delineated using the CT scan and defined as the gross tumor volume (GTV). Radiation fields were extended 2 cm in all directions, but confined to the urogenital tract to encompass potential microscopic extension of local disease (clinical target volume, CTV). A final uniform field expansion of 0.5 cm comprised the planning target volume (PTV) and accounted for possible intra- and interfraction variations in target position, shape, and size. A second target within the IMRT field was created to include lymph nodes (plus a margin of 1 cm) when there was clinical or tomographic suspicion of lymph node metastasis (14/22 cases, confirmed by cytology or histopathology in 4/22); one dog's lymph nodes were irradiated prophylactically. Inverse planning was performed at a treatment planning workstation[c]. Prescriptions for initial courses of IM/IGRT ranged from 54–58 Gy delivered in 20 daily fractions on a Monday to Friday basis (2.7–2.85 Gy per fraction administered over 28–31 days); lymph node prescriptions ranged from 28–54 Gy in 20 fractions. Institutional standards for radiation prescriptions in IMRT plans were applied; the prescribed isodose was normalized such that it covered at least 95% of the PTV, with the maximum global dose being 110% of the prescribed dose. Treatment plans typically involved 6–9 isocentrically placed coplanar 6 or 10 MV X-ray beams which were shaped by means of dynamic multileaf collimation in a sliding-window fashion to achieve intensity-modulation. Plans were constructed by iterative inverse-planning with heterogeneity corrections to meet specified goals for both tumor/target volumes and organs at risk (OAR). The OAR included colon, urethra, ureters, and urinary bladder. Dose constraints varied during the development of our institutional IM/IGRT program, but generally adhered to our current standard, which is to constrain all OAR lying within the PTV to a maximum dose of 57 Gy, with no more than 54 Gy delivered to the colon lying outside of the PTV. Data regarding treatment volumes, prescriptions and normal tissue exposures are summarized in Tables 1 and 2, and Fig 1. A conformity index (CI) was calculated as follows: $CI = \frac{TV^2_{PIV}}{TV * PIV}$, where TV_{PIV} is volume of the target (PTV) covered by the prescription isodose, TV is 95% of the target volume and PIV is the prescription isodose volume. This index expresses the relationship between a fraction of the tumor volume covered by the prescription isodose and the volume delineated by that isodose, thereby quantifying both coverage of the delineated target volumes and the dose gradient outside that volume. Thus, the conformity index provides an absolute score; this score is complementary to dose-volume histogram and

Table 1. Absorbed dose within the target volumes.

	GTV		CTV		PTV		Lymph Nodes	
	Vol (mL)	D_{99}	Vol (mL)	D_{99}	Vol (mL)	D_{95}	Vol (mL)	D_{95}
Min.	2.3	49.6	4.7	49.8	18.1	48.3	4.4	29.1
Max.	130.4	57.9	130.4	57.9	339.4	56.6	30.5	53.8
Median	16.6	54.9	23.6	55.6	60	54.1	43.3	40.9
Mean	25.1	54.7	31.6	54.7	83.9	53.9	39.7	40.2
SD	29.5	2.6	27.7	2.5	71.3	1.7	17.3	8.3

Average size of and dose delivered to treatment volumes are detailed above. D_x refers to the radiation dose (in Gray) delivered to X% of the respective treatment volume.

Table 2. Absorbed dose within organs at risk.

	Colon	Urethra	Ureters
D_{max} (Gy)			
Median	58.2	56.8	56.4
Mean	58.2	56.8	47.1
SD	1.5	2.1	17.1
$D_{X\ mL}$ (Gy)			
Median	52.3	54.9	41.5
Mean	51.4	52.2	37.5
SD	1.5	10.7	20.2
$V_{54\ Gy}$ (mL)			
Median	2.9	0.7	0.1
Mean	3.4	1.8	0.3
SD	2.7	2.5	0.4

Average values of the maximum dose (D_{max}) delivered to an organ at risk, minimum dose delivered to the X cubic centimeters of an organ at risk which are receiving the highest dose (D_x), and volume of an organ at risk exceeding 54 Gy (V_{54}). X = 4 mL for rectum, 0.5 mL for urethra, 0.25 mL for ureters.

dose-distribution data and adds to the armamentarium upon which overall RT plan quality can be judged, but should not be used alone for plan evaluation.[27,28] The mean value of the conformity index was 0.77 ± 0.13 (range: 0.54–1.05). Individual treatment plan review was performed by an American College of Veterinary Radiology board-certified veterinary radiation oncologist and an American Board of Radiology certified therapeutic medical physicist. Dog-specific plan quality assurance was performed for each field comprising the treatment plan by gamma analysis comparing treatment plan data to that measured with the Varian portal dosimetry system. A minimum of 95% gamma for a 3-mm distance to agreement and a 3% absolute dose difference was defined as a passing QA score.

All dogs were anesthetized for treatment; protocols varied, but generally included opioid premedications, followed by intravenous propofol and benzodiazepine induction and inhaled isoflurane maintenance. Daily image-guided dog position verification was performed with an on-board kilovoltage cone-beam CT (kV-CBCT, Fig 2). Aside from lateral positioning, additional measures were employed to minimize interfraction variations in the size and shape of target tissues (especially important when treatment fields include all or part of the urinary bladder), which enabled conformity to the standard established by the 0.5-cm PTV expansion. These measures included adherence to rigid dietary habits (meal size and times were as consistent as possible) and standardization of urination and defecation habits (dogs were taken for a walk at a specific time each day, and then confined to a small living space or cage until anesthetic induction and RT, which occurred at approximately the same time each day). Diet but not urinary habits were typically instituted before CT simulation. In dogs with adequate cardiovascular function,

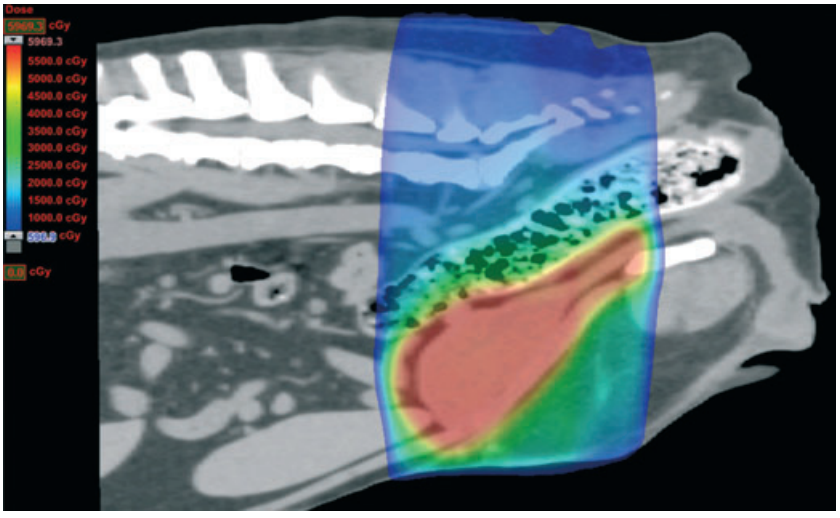

Fig 1. Typical dose distribution for IM/IGRT, depicted as a color-wash superimposed over the simulation CT. A steep dose gradient between target volumes and organs at risk is shown with areas of relatively high dose in red and orange, and lower doses in yellow, green, and blue.

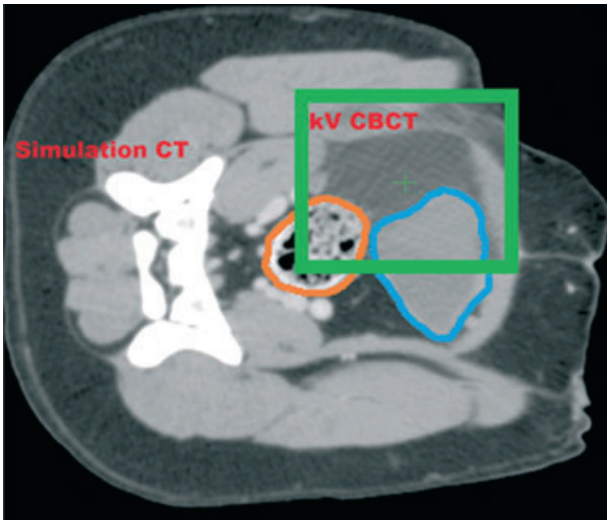

Fig 2. The larger image is derived from a simulation CT scan; the smaller image (within the green box) is a representative example of a daily kV-CBCT for this dog. The colon (orange) and bladder (blue) are outlined. This demonstrates the high level of target and normal tissue reproducibility which is possible when employing three-dimensional image-guidance.

modest intravenous crystalloid boluses were used to enlarge the bladder when bladder size was significantly smaller than planned. In these cases, small bladder size was defined as the bladder walls being at least 1 cm from the PTV margin. In such cases, judicious use of fluid therapy was a successful means of managing treatment volumes and minimizing radiation exposures in normal tissues. Because of variable patient size and variable bladder size in relation to the PTV margin, there was no standard intravenous fluid bolus size. Kilovoltage CBCT was repeated for position verification approximately 10 minutes after completing fluid administration. In cases where bladder size initially exceeded that allowed for by the PTV expansion, gentle manual expression of the urinary bladder, temporary urethral catheterization, or both was performed to remove urine from the bladder; in such cases, kV-CBCT was also repeated after manipulation. Following position verification, IMRT was delivered with a linear accelerator.[d]

Offline dynamic-adaptive RT (DART) was utilized in 6 of 22 of the presently described RT plans; RT plans were adapted once in 4 of the 6 cases and twice in 2 of the 6 cases. Plans were adapted when the PTV was deemed inappropriate; in all cases in this series, an inappropriate PTV was defined by the PTV margin being larger than what was needed to encompass the CTV for each daily fraction.

Data Analysis

Toxicoses were graded according to the criteria for acute and late radiation morbidity, as defined by the Veterinary Radiation Therapy and Oncology Group.[29] Toxicosis data were analyzed using descriptive statistics. Tumor control was reported according to RECIST criteria. Survival was defined as the time from the 1st fraction of RT until the time of 1st event or death. Local tumor control was described with Kaplan-Meier survival analysis of event-free survival (EFS). Events were defined as disease progression, late radiation-associated toxicoses, death from any cause, or loss to follow-up; dogs that had not experienced an event were censored at the time of data analysis. Overall survival was studied in a similar manner. Death from any cause was considered an event, and living dogs were censored at the time of Kaplan-Meier survival analysis. Log-rank analysis was employed to compare survival times between groups. All statistical analyses were performed using a commercial software package (SigmaStat *v*3.5). A P value of $< .05$ was considered significant for all analyses.

Results

Dog Demographics and Oncologic Histories

Twenty-two treatment protocols were undertaken in 21 dogs, and 19 dogs completed 20 courses of IM/IGRT (Table 3). Seven of 21 dogs were female and 14 were male; all were neutered. Sixteen dogs had localized disease ($T_{2-3}N_0M_0$), four had locoregional lymph node metastases ($T_{2-3}N_1M_0$), and one had pulmonary metastases ($T_3N_0M_1$) at initiation of IM/IGRT. Two dogs failed to complete therapy; these dogs were included in the survival analysis. The first of these dogs died of suspected paraneoplastic polyradiculoneuropathy before completion of IM/IGRT; no gross or histopathologic CNS abnormalities were identified on necropsy. The 2nd dog had undergone ureteronephrectomy before starting IM/IGRT and developed a partial ureteral obstruction during RT; radiotherapy was discontinued before completion of the prescribed course, and the dog succumbed to acute renal failure secondary to complete ureteral obstruction 86 days after initiation of RT. Another dog completed a 2nd course of IM/IGRT (49.5 Gy, delivered to the bladder, prostate, and sublumbar lymph nodes, in 22 fractions) upon local disease progression, which occurred 776 days after completion of the 1st course; this dog died 1,043 days after initiation of the 1st course of IM/IGRT. This dog's overall survival time was included in analysis; however, tumor control and toxicity data were only analyzed for the 1st course of radiation, as the 2nd course had an altered fractionation scheme.

Neoadjuvant therapy included NSAID administration in 14 dogs, MTD chemotherapy (that which is delivered to the "maximally tolerated dose") in 6 dogs, and surgery in 3 dogs before RT. Neoadjuvant antineoplastic drugs included carboplatin (2/6) and mitoxantrone (4/6). Four of these dogs received both an NSAID and MTD chemotherapy before RT, whereas 10 had only an NSAID and 2 had only MTD chemotherapy. Surgical procedures performed before administration of RT included cytoreductive debulking (2/3) and ureteronephrectomy (1/3). All dogs treated with neoadjuvant therapy had local progression/recurrence before presentation, and all had macroscopic carcinomas present at the time they started IM/IGRT. The NSAIDs were used in the adjuvant setting in 12 dogs. Adjuvant MTD chemotherapy was also utilized in 12 dogs, and included carboplatin (3/12), mitoxantrone (8/12), doxorubicin (2/12), and vinorelbine (2/12); some dogs received more than 1 antineoplastic drug after completing RT. No dog received a multi agent MTD chemotherapy protocol; dogs that received multiple chemotherapeutic drugs were switched from 1

Table 3. Location of index tumors.

Site of Primary Tumor	No. of Dogs with Intent to Treat	No. Dogs that Completed Treatments	Total No. of Completed Courses of Treatment
Bladder	9	7	8
Prostate*	10	10	10
Urethra**	2	2	2
Total	21	19	20

Two dogs failed to complete therapy and another dog completed a 2nd course upon local failure 2 years after completing the 1st course. In all, 19 dogs completed 20 courses of IM/IGRT. Locations of index/primary tumor are detailed in this table.

*or prostatic urethra;

**in female dogs.

agent to another upon detection of progressive disease. Of those dogs receiving adjuvant therapy, 8 had both an NSAID and chemotherapy after RT, whereas 4 had only an NSAID, and 4 had only chemotherapy. None of these dogs received concurrent MTD chemotherapy and RT.

Toxicoses

Acute radiation-associated gastrointestinal complications were most common. One dog (5%) suffered grade 2 colitis, whereas 7 (33%) others experienced grade 1 colitis. Acute urinary complications presented as hematuria (grade 1) in 1 (5%) dog and stranguria (grade 2) in another dog (5%). Integumentary changes were limited to mild erythema, pigmentary changes or both, which developed in 4 dogs (in all, 19% developed grade 1 acute integumentary toxicosis). Regardless of body system involved, all acute radiation toxicoses were mild to moderate and self-limiting.

Delayed signs of radiation intoxication were less common, though severe when documented. Late radiation-associated complications were manifested as rectal (1), ureteral (1), and urethral (2) strictures. Overall, 4/21 (19%) developed grade 3 late GI or GU toxicoses. Each presented 6–18 months after completion of IM/IGRT, and was successfully palliated with either stenting or surgery. Ureteral transposition was performed in 1 dog who was presented with ureteral obstruction which, based on unremarkable imaging studies and grossly normal appearance, was presumably because of radiation-induced fibrosis; a urethral stent was placed 1 month after the initial procedure because of partial urethral obstruction, which again was presumably because of radiation-induced fibrosis. Another dog had a rectal stent placed 10 months after IM/IGRT because of rectal stenosis; a urethral stent was later placed in the same dog to relieve obstruction caused by local tumor progression. A urethral stent was placed in one other dog to relieve clinical signs associated with malignant urethral obstruction 6 months after completion of IM/IGRT. There was no correlation between radiation prescription, delivered dose, overall radiation field size, plan adjustment via dynamic-adaptive radiation therapy or calculated CI, and incidence of late-onset toxicoses.

Outcomes

Seventy-eight percent of pet owners responded to a standardized questionnaire; the responses suggested that treatment was associated with improved quality of life in the majority of dogs. Sixty percent of respondents reported improved and 30% reported unchanged quality of life after completion of IM/IGRT. Therefore, the subjective response rate, defined as those with improved quality of life (and therefore a reasonable substitution for objective response rate which would reflect those dogs with partial and complete responses) was 60%. Because several dogs initiated RT without clinical signs attributable to their lower urinary tract disease, the combination of dogs with demonstrable clinical responses (60%) and those with unchanged quality of life (30%) after completion of RT suggests the presently described treatment protocol was associated with potential clinical benefit in 90% of dogs. The questionnaire was anonymous; therefore, the outcomes described by individual respondents cannot be correlated with known clinical data, including initial stage, neoadjuvant or adjuvant therapy, toxicoses, or tumor control (Table 4).

The median time to 1st event in all dogs was 317 days. Although there was a trend toward improved survival in dogs with primary prostatic disease (median EFS of 317 days) as compared to those with primary bladder disease (median EFS of 226 days), this difference was not statistically significant.

The median overall survival time (OST) was 654 days; as with EFS, there was no significant difference based upon site of primary disease.

Six dogs were censored from the EFS analysis, and 8 were censored from OST analysis. Median follow-up time for censored dogs was 310 days (range 142–632 for EFS and 142–688 for OST). Thirty-three percent (7/21) of dogs experienced confirmed local disease progression (confirmed via imaging, or pathologic evaluation of tumor tissue). Two of 7 dogs had a geographic miss, with local disease progression proximal and distal to the site of the primary urethral disease. The remaining 5 dogs suffered in-field progression of CGUC. Two of these 7 dogs also developed regional lymph node metastases after completing IM/IGRT. The first of these dogs had tomographically normal lymph nodes which were prophylactically irradiated; 29.1 Gy was delivered to 95% of the planning target volume for the sublumbar/pelvic nodal bed. The 2nd dog with local lymph node metastases also had tomographically normal lymph nodes at initial staging; this dog did not have nodal irradiation. The dog presented with local recurrence (in-field progression) as well as local lymph node metastases 776 days after completing the 1st course of IM/IGRT. A 2nd course of RT was completed and 49 Gy was delivered to 95% of the PTV for the recurrent primary disease as well as the sublumbar/pelvic nodal bed. There were no clinically detectable adverse events

Table 4. Summary of results from a standardized client questionnaire.

Difficulties/challenges of radiation treatment:

	Extremely Difficult or Challenging	Very Difficult or Challenging	Moderately Difficult or Challenging	Minimally Difficult or Challenging	Not Difficult or Challenging
Cost*	1 (7.1%)	3 (21.4%)	8 (57.1%)	–	2 (14.3%)
Duration of treatment	1 (7.1%)	3 (21.4%)	4 (28.6%)	4 (28.6%)	2 (14.3%)
Distance traveled	1 (7.1%)	6 (42.9%)	2 (14.3%)	2 (14.3%)	3 (21.4%)

How informed did you feel you were about the:

	Very Inadequately Informed	Inadequately Informed	Adequately Informed	Very Adequately Informed
Potential side effects?	1 (7.1%)	1 (7.1%)	4 (28.6%)	8 (57.1%)
Expected outcome (tumor control and prognosis)?	2 (14.3%)	1 (7.1%)	7 (50.0%)	4 (28.6%)

Overall, how would you rate your pet's quality of life during or immediately following RT?

Much Worse than Before RT	Worse than Before RT	Unchanged	Better than Before RT	Much Better than Before RT
–	2 (15.4%)	5 (38.5%)	2 (15.4%)	4 (30.8%)

How often did your pet experience the following potential side effects since completing RT?

	Always	Most of the Time	Some of the Time	Infrequently	Never
Pain while defecating	1 (7.7%)	1 (7.7%)	4 (30.8%)	3 (23.1%)	4 (30.8%)
Difficulty defecating when he/she seems to desire to go	1 (7.7%)	3 (23.1%)	3 (23.1%)	2 (15.4%)	4 (30.8%)
Pain while urinating	1 (7.7%)	1 (7.7%)	2 (15.4%)	4 (30.8%)	5 (38.5%)
Difficulty urinating when he/she seems to desire to go	1 (8.3%)	2 (16.7%)	2 (16.7%)	3 (25%)	4 (33.3%)

Overall rating of pet's quality of life since radiation therapy:

Much Worse than it was Before RT	Worse than it was Before RT	Unchanged	Better than it was Before RT	Much Better than it was Before RT
–	1 (10.0%)	3 (30.0%)	1 (10.0%)	5 (50.0%)

Given what you know today, how likely would you be to:

	Very Likely	Likely	Neutral	Not Likely	Very Unlikely
Still have opted to treat your pet's tumor with radiation:	13 (92.9%)	–	–	–	1 (7.1%)
Recommend radiation to a family member or friend who has a pet with similar problems:	11 (78.6%)	2 (14.3%)	–	–	1 (7.1%)

*The average cost of consultation, CT simulation, RT planning, and IM/IGRT delivery for management of CGUC ranges from $5,500 to $6,000 at CSU-ACC.

attributable to either course of radiation. The dog was euthanized 267 days after completion of the second course of RT and 1043 days after completion of the 1st course of RT because of progressive azotemia associated with bilateral ureteral obstruction. The ureter had been stented 1 month before euthanasia because of suspected ureteral stricture. Though there was mild left-sided periureteral fibrosis detected on necropsy, gross and histologic findings were consistent with malignant obstruction because of in-field disease progression, rather than functional obstruction because of ureteral fibrosis and stricture. An additional 14% (3/21) of dogs in this series experienced distant (pulmonary) metastases before death; one of these dogs was euthanized because of clinical signs associated with these distant lesions, whereas the other 2 dogs were euthanized because of progressive locoregional disease.

Discussion

Inclusion of IM/IGRT in multimodal treatment protocols for CGUC was well-tolerated. Acute toxicoses were generally limited to grade 1 or 2 GI toxicoses which were self-limiting. Late grade 3 GI or GU toxicoses occurred in 19% of dogs, but were typically well-managed and occurred late in the course of disease.

Although direct and statistically valid comparisons cannot be made between these data and those reported in historical literature, outcomes in this study appear superior to previously reported data. The median event-free survival time in this study was 317 days (10.4 months), and the median overall survival time was 654 days (21.6 months). This compares favorably with the aforementioned outcomes for dogs receiving

no treatment (where survival has been reported to range from 0.7 to 3 months), surgery alone (3.5–8.2 months), NSAIDs (approximately 6 months), chemotherapy (4.3–11 months), and multimodal protocols including palliative intraoperative RT or both (3.8–15 months).[1,13–22]

Limitations of this study include the small and retrospective nature of the case series. Inherent to such study design was considerable variability in neoadjuvant and adjuvant therapy, as well as post treatment monitoring. Complete restaging data were not available for all subjects. This, in combination with the inherent difficulties in determining responses by traditional restaging methods such as abdominal ultrasonography, makes it impossible to report an accurate, reliable objective response rate or both.[30] In lieu of this deficiency, a subjective response rate (60%) was determined using owner-reported changes in quality of life. Overall, 93% of respondents were satisfied with outcomes of treatment, and would opt for such treatment if another pet was affected by CGUC. Most would also recommend such therapy to friends or family if their pet was thusly afflicted, lending further support to the reported potential clinical benefit in 90% of dogs. And although follow-up was incomplete, data nears maturity, with 8 of 21 dogs alive at the time of submission and a median follow-up time of 310 days for the censored dogs.

Despite these limitations, improved survival with limited morbidity makes it clear that there may be an important role for inclusion of IM/IGRT in treatment of CGUC. However, with 7 of 21 (33%) dogs suffering locoregional failure, it is important to evaluate the patterns of failure to improve the efficacy of RT. In all, 5 of 7 dogs experienced in-field local recurrence and 2 failed because of presumed geographic misses; 2 of these dogs also had lymph node metastases at the time of necropsy.

Because in-field recurrence appears to be the most important reason for locoregional failure after completion of IM/IGRT, dose-escalation should be considered as a potential means for improving the efficacy of this therapy. It has been suggested that dynamic-adaptive RT (DART) is one potential means for safely escalating dose.[31,32] Plan adaptation can be performed as a daily on-line or off-line procedure. Whichever technique is used, the goal of DART is to minimize normal tissue exposures by adapting PTV margins to reflect a particular dog's anatomy. In this case series, all plan adaptations were performed via offline DART. In each case, the plan was adapted because bladder size was smaller than planned, enabling use of a smaller than originally planned PTV.

While DART can limit dose to nearby tissues, its limitation lies in the inability to physically spare normal tissues that lie within the PTV. Because it has been suggested that CGUC behaves like a late-responding tissue (ie., it has a low α/β ratio), finer fractionation cannot be exploited to spare normal tissues without decreasing the probability of local tumor control.[33] With this in mind, preemptive stenting of the urethra, ureters, or both might allow for escalation of prescribed dose without increasing the risk of clinically manifested late radiation-associated complications.[7,8,34]. Morbidity associated with stent placement is an important consideration, and preemptive stenting should likely be reserved for those experiencing partial or complete ureteral or urethral obstruction at the time of initial presentation.

Another potential mechanism for improving local tumor control is the combination of RT with either neoadjuvant or concurrent chemotherapy. The goal of neoadjuvant chemotherapy would be cytoreductive downstaging of local disease before initiation of RT, with the aim of reducing the number of tumor clonogens to increase tumor control probability, rather than physical reduction in the size of macroscopic tumor. Concurrent chemoradiotherapy may also provide a cytoreductive advantage. However, the true benefit of concurrent therapy would likely lie in radiosensitization of tumor cells. Neoadjuvant chemotherapy, concurrent chemoradiation protocols or both have proven beneficial in bladder-sparing treatment of human muscle-invasive bladder cancer (MIBC); inclusion of platinum-based, gemcitabine therapies or both can improve local tumor control by 5–9% without potentiating either acute or late radiation-associated toxicosis.[35–37]

It is important to consider the role of chemotherapy not only in the neoadjuvant/concurrent setting (as previously discussed), but also in the adjuvant setting. MTD chemotherapy protocols are often used for treatment of grossly evident CGUC, and such therapy is typically not discontinued until there is demonstrable disease progression in the face of chemotherapy. However, this practice should be reconsidered in dogs having received definitive local therapy for CGUC; in this setting, it may be adequate to prescribe a finite course of MTD chemotherapy to address potentially occult micrometastatic disease. Frequent restaging of local disease is recommended for dogs receiving such therapy and local disease recurrence/progression should be aggressively managed with additional local, systemic therapy or both. When considering the need for additional local therapy it is imperative to consider the clinical response to initial therapy. Because neoplastic cell kill can be slow in the post-RT setting and remodeling/resorption of tumor stroma is often incomplete, a partial response or stable disease may signify adequate local tumor control in the post-RT setting. Because of risk for significant treatment-associated morbidity, aggressive re-treatment should be reserved for dogs with clear evidence of progressive disease.

Appropriate case selection is an important factor in determining how likely a dog is to (1) complete therapy and (2) realize clinical benefit from therapy. Adequate bladder capacity is perhaps the most important selection criterion. Dogs with pollakiuria because of diminished bladder filling capacity secondary to neoplastic infiltration of the entire urinary bladder or associated chronic inflammation and fibrosis are unlikely to experience normalization of frequency of urination even if 100% local tumor control is attained.

Finally, because 64.3% of clients at CSU-ACC found the duration of treatment and the distance they had to travel for IM/IGRT to be at least moderately challenging, and because most veterinary RT centers do not have direct access to either image-guided or intensity-modulated RT, it is important to consider how definitive RT may be safely applied in the setting of less sophisticated radiation planning and delivery systems. First, dogs should be positioned in lateral recumbency, and a PTV margin of at least 1 cm should be utilized to ensure adequate target coverage if position verification is being performed with two-dimensional kilovoltage or megavoltage portal imaging rather than a three-dimensional soft tissue-target localization system (such as CBCT, surgically implanted fiducial markers or electromagnetic tracking).[26] Second, in the absence of IMRT, it is essential to limit the risk for late radiation-associated complications by limiting the dose per fraction to less than 3 Gy.[23] Finally, size of the radiation field should be considered as another risk factor for late complications.[24] Therefore, inclusion of lymph node beds in the portal may increase the risk for adverse effects such as chronic colitis and rectal, ureteral, or urethral stricture. Bladder size will also affect the size of the portal, and so, efforts should be made to treat a small bladder. The authors have also considered use of rectal balloon catheters to limit the volume of rectum receiving high radiation doses, and facilitate repeatable positioning of the rectum and prostate. However, this is not employed in our practice because bowel preparation and insertion of the balloon is associated with physical mucosal trauma that can exacerbate radiation-associated acute colitis/proctitis.

In conclusion, this study has demonstrated that IM/IGRT is generally well-tolerated and provides an effective treatment option for locoregional control of CGUC. These findings support the need for prospective evaluation of definitive RT in the setting of locoregionally extensive CGUC; they also suggest that although IM/IGRT can be utilized to maximize survival in affected dogs, there is still room for improvement in local therapy for CGUC.

Footnotes

[a] Vac-Lock™ Cushions; CIVCO Medical Solutions, Kalona, IA
[b] AccuForm™ Cushions; CIVCO Medical Solutions
[c] Eclipse™ (v8.6); Varian Medical Systems, Inc, Palo Alto, CA
[d] Varian Trilogy™; Varian Medical Systems, Inc

Acknowledgments

The authors thank Frank Conway, Chana Fuller, Karen Waldchen, and Dr Hiroto Yoshikawa for their contributions to this study.

The authors have nothing to disclose.

References

1. Sorennmo KU, Goldschmidt MH, Shofer FS, et al. Evaluation of cyclooxygenase-1 and cyclooxygenase-2 expression and the effect of cyclooxygenase inhibitors in canine prostatic carcinoma. Vet Comp Oncol 2004;2:13–23.

2. Montgomery RD, Hankes GH. Ureterocolonic anastomosis in a dog with transitional cell carcinoma of the urinary bladder. J Am Vet Med Assoc 1987;190:1427–1429.

3. Stone EA, Withrow SJ, Page RL, et al. Ureterocolonic anastomosis in ten dogs with transitional cell carcinoma. Vet Surg 1988;17:147–153.

4. Smith JD, Vaden SL, Stone EA, et al. Management and complications following trigonal-colonic anastomosis in a dog: Five-year evaluation. J Am An Hosp Assoc 1996;32:29–35.

5. Mann FA, Barrett RJ, Henderson RA. Use of a retained urethral catheter in three dogs with prostatic neoplasia. Vet Surg 1992;21:342–347.

6. Smith JD, Stone EA, Gilson SD. Placement of a permanent cystotomy catheter to relieve urine outflow obstruction in dogs with transitional cell carcinoma. J Am Vet Med Assoc 1995;206:496–499.

7. Weisse C, Berent A, Todd K, et al. Evaluation of palliative stenting for management of malignant urethral obstructions in dogs. J Am Vet Med Assoc 2006;229:226–234.

8. Berent AC, Weisse C, Beal MW, et al. Use of indwelling, double-pigtail stents for treatment of malignant ureteral obstruction in dogs: 12 cases (2006–2009). J Am Vet Med Assoc 2011;238:1017–1025.

9. Liptak JM, Brutscher SP, Monnet E, et al. Transurethral resection in the management of urethral and prostatic neoplasia in 6 dogs. Vet Surg 2004;33:505–516.

10. Stone EA, George TF, Gilson SD, et al. Partial cystectomy for bladder neoplasia: Surgical technique and outcome of 11 dogs. J Small Anim Pract 1996;37:480–485.

11. Norris AM, Laing EJ, Valli VE, et al. Canine bladder and urethral tumors: A retrospective study of 115 cases (1980–1985). J Vet Intern Med 1992;6:145–153.

12. Helfand SC, Hamilton TA, Hungerford LL, et al. Comparison of three treatments for transitional cell carcinoma of the bladder in dogs. J Am Anim Hosp Assoc 1994;30:270–275.

13. Knapp DW, Richardson RC, Chan TCK, et al. Piroxicam therapy in 34 dogs with transitional cell carcinoma of the urinary bladder. J Vet Intern Med 1994;8:273–278.

14. McMillan SK, Boria P, Moore GE, et al. Antitumor effects of deracoxib treatment in 26 dogs with transitional cell carcinoma of the bladder. J Am Vet Med Assoc 2011;239:1084–1089.

15. Henry CJ, McCaw DL, Turnquist SE, et al. Clinical evaluation of mitoxantrone and piroxicam in a canine model of human invasive bladder cancer. Clin Cancer Res 2003;9:906–911.

16. Marconato L, Zini E, Lidner D, et al. Toxic effects and antitumor response of gemcitabine in combination with piroxicam treatment in dogs with transitional cell carcinoma of the urinary bladder. J Am Vet Med Assoc 2011;238:1004–1010.

17. 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;25:1385–1390.

18. Moore AS, Cardona A, Shapiro W, Madewell BR. Cisplatin (cisdiamminedichloroplatinum) for treatment of transitional cell carcinoma of the urinary bladder or urethra: A retrospective study of 15 dogs. J Vet Intern Med 1990;4:148–152.

19. Turrel JM. Intraoperative radiotherapy of carcinoma of the prostate gland in ten dogs. J Am Vet Med Assoc 1987;190:48–52.

20. Walker M, Breider M. Intraoperative radiotherapy of canine bladder cancer. Vet Radiol 1987;28:200–204.

21. Withrow SJ, Gillette EL, Hoopes PJ, et al. Intraoperative irradiation of 16 spontaneously occurring canine neoplasms. Vet Surg 1989;18:7–11.

22. Poirier VJ, Forrest LJ, Adams WM, et al. 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;40:131–136.

23. Anderson CR, McNiel EA, Gillette EL, et al. Late complications of pelvic irradiation in 16 dogs. Vet Radiol Ultrasound 2002;43:187–192.

24. Arthur JJ, Kleiter MM, Thrall DE, et al. Characterization of normal tissue complications in 51 dogs undergoing definitive pelvic region irradiation. Vet Radiol Ultrasound 2008;49:85–89.

25. Murphy S, Gutierrez A, Lawrence J, et al. Laparoscopically implanted tissue expander radiotherapy in canine transitional cell carcinoma. Vet Radiol Ultrasound 2008;49:400–405.

26. Nieset JR, Harmon JF, LaRue SM. Use of cone-beam computed tomography to characterize daily urinary bladder variations during fractionated radiotherapy for canine bladder cancer. Vet Radiol Ultrasound 2011;52:580–588.

27. Feuvret L, Noel G, Mazeron J-J, et al. Conformity index: A review. Int J Radiat Oncol Biol Phys 2006;64:333–342.

28. Paddick I, Lippitz B. A simple dose gradient measurement tool to complement the conformity index. J Neurosurg (Suppl) 2006;105:194–201.

29. LaDue T, Klein MK. Toxicity criteria of the veterinary radiation therapy oncology group. Vet Radiol Ultrasound 2001;42:475–476.

30. Hume C, Seiler G, Porat-Mosenco Y, et al. Cystosonographic measurements of canine bladder tumors. Vet Compar Oncol 2010;8:122–126.

31. Vestergaard A, Sondergaard J, Petersen JB, et al. A comparison of three different adaptive strategies in image-guided radiotherapy of bladder cancer. Acta Oncol 2010;49:1069–1076.

32. Murthy V, Master Z, Adurkar P, et al. 'Plan of the day' adaptive radiotherapy for bladder cancer using helical tomotherapy. Radiother Oncol 2011;99:55–60.

33. Parfitt SL, Milner RJ, Salute ME, et al. Radiosensitivity and capacity for radiation-induced sublethal damage repair of canine transitional cell carcinoma (TCC) cell lines. Vet Comp Oncol 2011;9:232–240.

34. Liatsikos E, Kyriazis I, Kallidonis P, et al. Ureteric response to abdominal radiotherapy and metallic double-pigtail ureteric stents: A pig model. BJUI 2009;104:862–866.

35. Choudhury A, Swindell R, Logue JP, et al. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. J Clin Oncol 2011;29:733–738.

36. Meta-analysis group. Adjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:189–201.

37. Meta-analysis group. Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:202–206.