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CASE REPORT

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Laparoscopic stapled partial cystectomy with intraoperative cystourethroscopy for urothelial carcinoma in two dogs

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Abstract

Objective: To describe the procedure and short-term outcomes of two dogs that underwent laparoscopic stapled partial cystectomy with intraoperative cystoscopy for excision of solitary, non-trigonal, urothelial carcinoma lesions.

Animals: A 12-year-old female spayed mixed breed and a 13-year-old female spayed Siberian Husky.

Study design: Short case series.

Methods: Two dogs were diagnosed with a solitary, ventral body to apical, urinary bladder mass (maximal dimensions 1.2 cm and 1.4 cm) on ultrasound. No gross metastatic disease was evident on staging. Both dogs underwent general anesthesia with cystourethroscopy for evaluation of the bladder tumor and lower urinary tract. Laparoscopic stapled partial cystectomy was subsequently performed for excision of the bladder mass with gross margins of 1–3 cm based on concurrent cystoscopic transillumination and assessment of mucosal changes. Two medium/thick (purple) Tri-Staple EndoGIA cartridges (60 mm and 45 mm) were utilized to complete each cystectomy, and the excised bladder tissue was removed via a specimen retrieval bag and submitted for histopathology. The bladders were leak tested with sterile saline instilled via cystoscopy.

Results: No leakage was observed from the cystectomy sites. No intraoperative or short-term complications were reported. Histopathology was consistent with completely excised urothelial carcinoma in both cases.

Conclusion: Laparoscopic stapled partial cystectomy was successfully performed with intraoperative cystourethroscopy in two dogs with apical/ventral bladder wall urothelial carcinoma. This closed cystectomy technique may reduce the risk for peritoneal seeding, though more data is needed. Further evaluation is indicated to determine the feasibility in dogs with non-apical/ventral urinary bladder masses.

1 | INTRODUCTION

Urothelial carcinoma (UC) is the most common lower urinary tract malignancy in dogs and tends to be locally invasive with a high incidence of metastasis.[1] Currently, canine UC is not considered a curable disease; however, available treatments can result in prolonged disease control with a good quality of life in the majority of dogs.[1–3] Canine UC has a predilection for the urinary bladder trigone, such that surgical excision requires radical cystectomy in the majority of cases. However, for dogs with UC in non-trigonal locations amenable to excision with preservation of the bladder neurovascular supply and urethral/ureteral vesicular junctions, partial cystectomy generally is associated with a low complication rate, adequate urinary function even with large resections (though transient pollakiuria is common), and potential for improved outcomes compared to dogs that do not undergo tumor excision.[1,4,5] However, disease progression is common, and an additional consideration involves the risk of peritoneal tumor seeding with a reported incidence of 10%–11% following partial cystectomy/cystotomy for canine UC.[5,6]

Despite the potential role of partial cystectomy in select dogs with non-trigonal UC, described surgical approaches are almost exclusively performed via laparotomy with cystotomy, with the associated morbidity of open abdominal surgery, a risk of urine and neoplastic contamination of the abdomen, and challenges with intraoperative disease visualization and the potential for locoregional recurrence. Furthermore, the impact of cystourethroscopy on surgical planning and oncologic outcomes in dogs with UC remains undefined. Given the general palliative intent of surgery and indication for adjuvant therapy, the reported benefits of minimally invasive surgery (MIS) compared to open surgery, including smaller incisions, decreased pain, earlier return to function, shorter hospitalization times, and potentially reduced postoperative surgical site complication rates, may be particularly beneficial in dogs with UC.[7,8] Minimally invasive approaches have not been evaluated for partial cystectomy in dogs with UC, and there are no clinical reports describing a closed, stapled MIS technique for neoplastic resection in dogs. Prior studies have demonstrated effective stapled partial cystectomies in canine cadaveric bladders, and there is a single case report on stapled partial cystectomy for excision of a urachal remnant in a dog.[9–11] Thus, there is a critical knowledge gap regarding the feasibility, safety, and short-term outcomes of MIS stapled partial cystectomy and the potential adjunctive role of cystourethroscopy in guiding tumor excision while limiting intraperitoneal tumor exposure. The objective of this case series was to describe the procedure and short-term outcomes of two dogs that underwent laparoscopic stapled partial cystectomy with intraoperative cystoscopy for excision of non-trigonal UC lesions. Findings of this case series may be used to guide larger studies on dogs undergoing MIS stapled partial cystectomy with intraoperative cystourethroscopy to assess for patient-centered and oncologic outcomes associated with these techniques.

2 | MATERIALS AND METHODS

2.1 | Dog 1

A 12-year-old female spayed mixed breed dog was presented to an emergency service for hematuria, and a bladder mass was identified during point-of-care abdominal ultrasound. A CADET BRAF test (Antech Diagnostics, Fountain Valley, California) was positive for the V595E mutation, consistent with a diagnosis of UC. The dog was then presented to the Cornell University Hospital for Animals soft tissue surgery service. Past pertinent history included multiple mast cell tumor excisions (low grade and completely excised for the only mass with histologic data available). Ongoing medical management included diphenhydramine (2.5 mg/kg orally every 12 h), loratadine (0.5 mg/kg orally every 24 h), omeprazole (1 mg/kg orally every 12 h), and piroxicam (0.3 mg/kg orally every 24 h). On physical examination, three dermal/subcutaneous masses were identified with no other abnormalities noted (including on rectal examination). The dog weighed 20.4 kg and had a body condition score of 5/9. Fine needle aspiration and cytology of two of the masses (one dermal and one subcutaneous, located on each flank, maximal dimensions of 1.5 cm, mobile on palpation) were consistent with mast cell tumors, and the other was consistent with a lipoma. Abdominal ultrasound performed by a board-certified radiologist revealed a 1.4 cm diameter urinary bladder mass in the ventral wall near the apex, small splenic nodules consistent with myelolipomas, a mild hepatopathy, and renal degenerative changes. Three-view thoracic radiographs were unremarkable. Preanesthetic labwork (complete blood count, biochemistry panel) results were within normal limits aside from a mildly elevated alanine aminotransferase (99 U/L; RR: 17–95) and mildly elevated blood urea nitrogen (30 mg/dL; RR: 9–26) with a normal creatinine (1.0 mg/dL; RR: 0.6–1.4).

2.2 | Dog 2

A 13-year-old female spayed Siberian Husky was presented to the Cornell University Hospital for Animals soft

tissue surgery service for evaluation of primary hyperparathyroidism. Nine months prior to presentation, senior bloodwork revealed total hypercalcemia, and malignancy panel results were consistent with hyperparathyroidism (ionized calcium 1.7 mmol/L [RR: 1.25–1.45], parathyroid hormone 21.5 pmol/L [RR: 1.1–10.6], parathyroid hormone-related protein 0 pmol/L [RR: 0–1]). The dog had a history of controlled hypothyroidism, a grade 3 mast cell tumor excision 5 years prior, dermatitis, generalized alopecia, and multiple subcutaneous masses that were being monitored by the referral veterinarian. Ongoing medical management included prednisolone (0.1 mg/kg orally every 24 h), levothyroxine (0.02 mg/kg orally every 12 h), diphenhydramine (2.8 mg/kg orally every 12 h), and famotidine (0.6 mg/kg orally every 12 h); the dog was also receiving amoxicillin/clavulanic acid (21.1 mg/kg orally every 12 h) for a dermatitis episode. On physical examination, the dog weighed 17.8 kg and had a body condition score of 3/9. Multiple dermal/subcutaneous masses were identified as well as diffuse alopecia of the cervical and dorsal regions. No other abnormalities were noted (including on rectal examination). Labwork (complete blood count and biochemistry panel) revealed a mild lymphopenia (700/uL; RR: 900–4700), total hypercalcemia (13.8 mg/dL; RR: 9.4–11.1), hypophosphatemia (2.2 mg/dL; RR: 2.7–5.4), mildly elevated alanine aminotransferase (115 U/L), mildly elevated gamma-glutamyl transferase (12 U/L; RR: 0–8), and markedly elevated alkaline phosphatase (1302 U/L; RR: 7–115). Cervical and abdominal ultrasound were performed by a boarded radiologist and revealed multifocal, small (0.2–0.4 mm), nodule-like structures associated with the thyroid/parathyroid glands, a 1.2 cm diameter mass arising from the ventral wall of the urinary bladder near the apex, urinary bladder sediment, hepatic changes prioritized as vacuolar hepatopathy secondary to chronic steroid administration as well as a hepatic cyst, bilateral adrenal nodules (≤1.2 cm), cholecystopathy with mineralized debris, mild bilateral renal degenerative changes, and few small splenic nodules (presumed myelolipomas). Thoracic radiographs were unremarkable. The owner declined additional diagnostic assessment.

2.3 | Cystourethroscopy and partial cystectomy

Both dogs underwent general anesthesia for cystourethroscopy and concurrent partial cystectomy pending endoscopic findings. The dogs were premedicated with methadone 0.2 mg/kg IM and acepromazine 0.02 mg/kg IV (Dog 1) or dexmedetomidine 3 mcg/kg IM (Dog 2); diphenhydramine 2.0 mg/kg IM was also administered to Dog 1. After preoxygenation, anesthetic induction was achieved with IV propofol titrated to effect. After placement of an endotracheal tube, anesthesia was maintained with isoflurane delivered in 100% oxygen. Cefazolin 22 mg/kg IV was administered preoperatively and every 90 min intraoperatively.

Figure 1 depicts the operating room setup for laparoscopy and cystourethroscopy. Dogs were positioned in dorsal recumbency and the ventral abdomen and perineal regions were clipped, prepared, and draped using standard aseptic technique. In each dog, a 30°, 1.9 mm, rigid cysto-urethroscope (Karl Storz, Tuttlingen, Germany) was used for cystourethroscopy due to the inability to pass a long, 2.7 mm, rigid cysto-urethroscope (Karl Storz) through the urethral papilla. Ingress with sterile saline and egress tubing were utilized to maintain flow for visualization while ensuring the bladder did not become turgid. In Dog 1, slightly proliferative lesions were identified within the mid-urethra; a conglomeration of these mucosal irregularities was present within a short distance cranial/caudal and encompassed the majority of the urethral circumference. In both dogs, an approximately 1.5 cm diameter, pedunculated, irregular, erythematous mass was identified within the ventral bladder wall near the apex (more left-sided in Dog 1 and right-sided in Dog 2). No additional gross mucosal lesions were identified. Both owners elected to proceed with partial cystectomy under the current general anesthesia event, and in Dog 1 endoscopic biopsies were also obtained of the urethral lesions as well as bladder mass via flexible biopsy forceps (Karl Storz) passed through the endoscopic working channel.

Laparoscopic partial cystectomy was subsequently performed (Figure 2, Video S1). A subumbilical modified Hasson approach was made and a three-dimensional (3D)-printed, silicone, single incision multiple access port (SIL) was placed. The abdomen was insufflated to a maximal pressure of 8–10 mmHg, and a 5 mm, 30° telescope (Karl Storz) was introduced. In Dog 1, no significant findings were appreciated on laparoscopic abdominal explore. In Dog 2, mild splenic mottling and a hepatic cyst were identified. A 5 mm blunt probe and laparoscopic Babcocks were used to manipulate the bladder and surrounding tissues, and a 5 mm vessel sealing device was used to transect the ventral median ligament of the bladder as well as adhesions to the bladder in Dog 2. No serosal lesions or abnormalities were evident laparoscopically. The bladder mass in each dog was identified laparoscopically via a combination of transillumination from the cystoscope (with modification of the brightness settings as needed) and concurrent cystoscopic assessment of mucosal changes relative to manipulation of the bladder wall with a laparoscopic blunt instrument (Figure 3). In Dog 2, the cysto-urethroscope length and

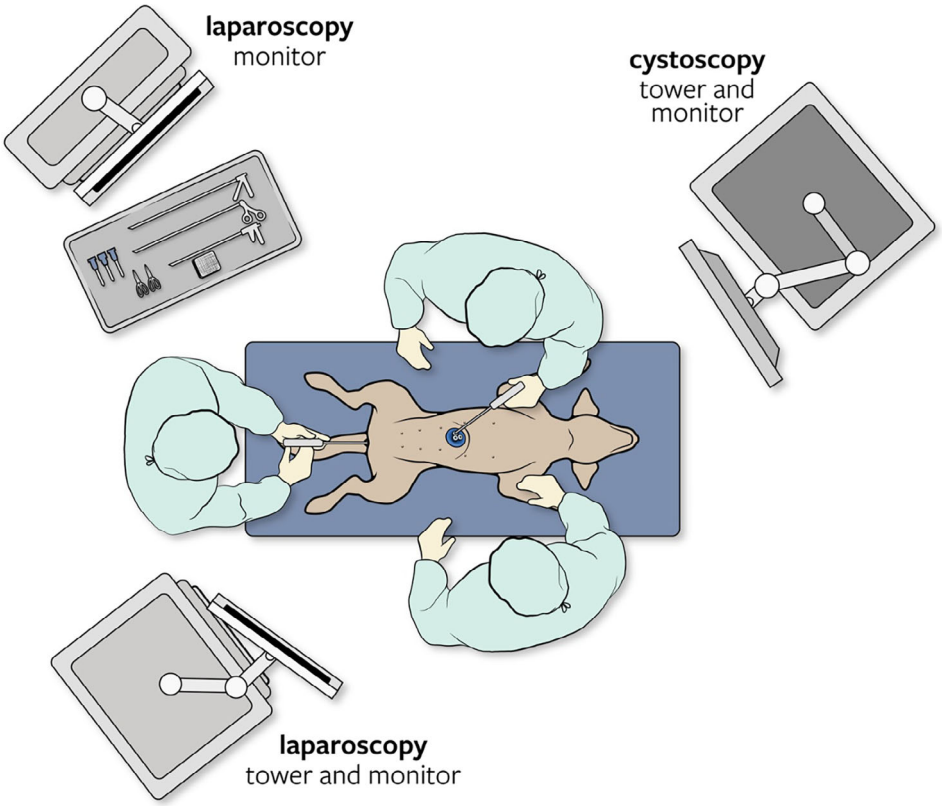

FIGURE 1 Operating room setup demonstrating the cystoscopy tower and monitor positioned at the dog's cranial end and the laparoscopy tower and monitors positioned at the dog's caudal end.

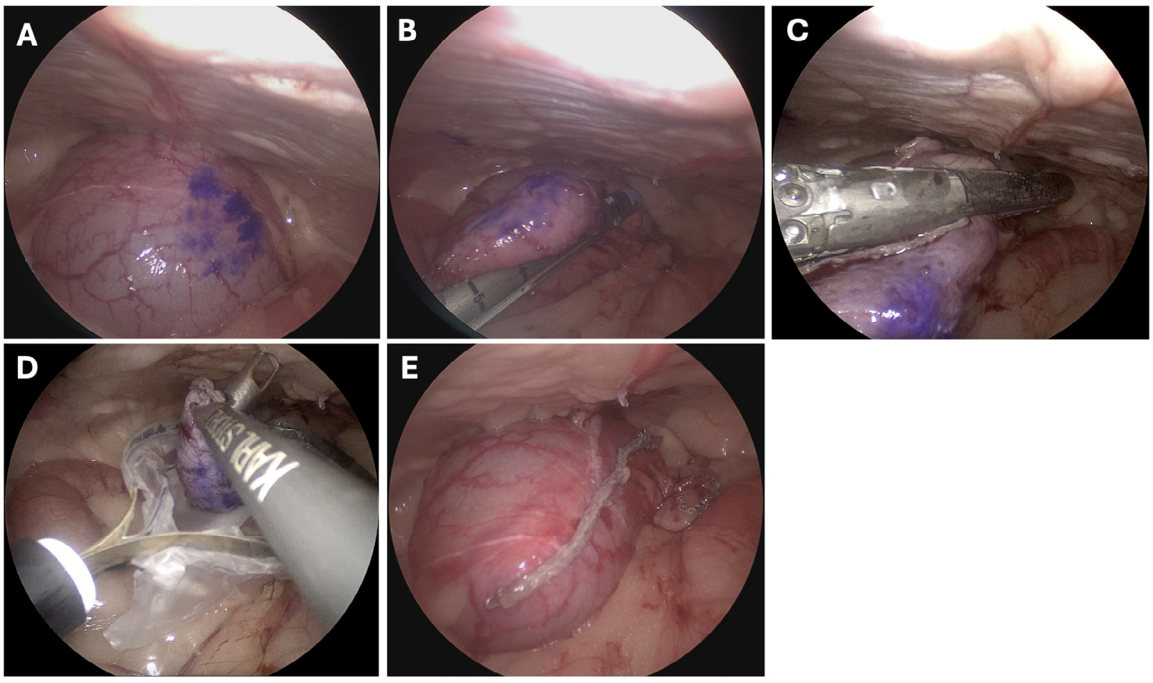

FIGURE 2 Laparoscopic images from Dog 2. (A) A marking pen has been used to delineate the gross disease margins via cystoscopic guidance. (B) A 60 mm medium/thick Tri-Staple EndoGIA has been applied across the bladder for the planned partial cystectomy, incorporating grossly normal bladder margins of 1–3 cm relative to the markings. (C) The bladder to be excised is retracted, and a 45 mm medium/thick Tri-Staple EndoGIA has been applied to complete the partial cystectomy. (D) The excised bladder is placed in a specimen retrieval bag prior to removal from the abdomen. (E) The partial cystectomy site is assessed for leakage laparoscopically following cystoscopic instillation of saline.

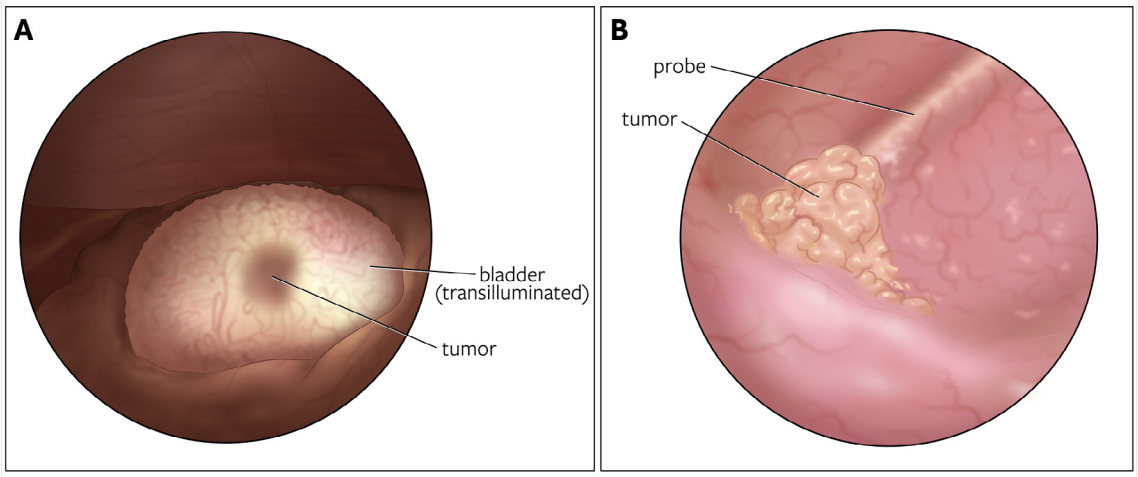

FIGURE 3 Artist's rendition of illustrations depicting findings from Dog 1. (A) Laparoscopic view of cystoscopic transillumination of the bladder mass. (B) Cystoscopic view of the bladder mass with laparoscopic blunt probe usage to evaluate gross disease margins.

brightness were not able to sufficiently transilluminate the bladder tumor with laparoscopic brightness set at 100%. However, when the laparoscope brightness was reduced, the gross tumor outline could be identified laparoscopically. A marking pen tip (removed from a marking pen with hemostats) was grasped with laparoscopic 5 mm right-angle forceps and used to mark the gross margins of the bladder tumor mucosal changes along the serosal surface (while cystoscopically visualizing manipulation with the pen tip). The bladder was emptied via cystoscopic egress. A paramedian incision was made lateral (right in Dog 1, left in Dog 2) and cranial to the SIL port site with an 11-blade under telescope guidance, and a 5 to 12 mm Versaport Plus V2 cannula (Medtronic, Minneapolis, Minnesota) was inserted. A 60 mm EndoGIA with medium/thick (purple) Tri-Staple cartridge (Medtronic) was inserted through the paramedian port. Laparoscopic Babcocks were used to grasp and manipulate the bladder within the articulated stapler such that the bladder mass and grossly normal bladder margins of approximately 1–3 cm were incorporated in the partial cystectomy site. The EndoGIA was closed, and the bladder mucosal surface was inspected cystoscopically to ensure no gross disease was identified within the bladder to be retained. Tissues were evaluated laparoscopically to ensure no incorporation of the urethra, ureters, or bladder neurovascular supply within the region to be stapled. The EndoGIA was fired, and in both cases a second 45 mm cartridge (purple Tri-Staple) was utilized to complete the resection at the caudal aspect of the cystectomy. The stapler was removed and a 10 mm Endo Catch specimen retrieval bag (Medtronic) was placed in the paramedian port and utilized to retrieve the excised bladder tissue from the abdomen within the closed bag. Saline was then instilled in the bladder cystoscopically, and laparoscopy was used to evaluate for any leakage along the staple line. Gloves and instruments were changed, and routine abdominal closure was performed.

The margins of the excised bladder mass in both dogs and excised dermal/subcutaneous masses in Dog 1 were marked with ink and submitted for histopathology. In Dog 1, the endoscopic urethral incisional biopsy samples were also submitted for histopathology, and an endoscopic biopsy of the bladder mass was submitted for aerobic/anaerobic culture. Postoperatively, both dogs were maintained on IV isotonic crystalloids (60–90 mL/kg/day), methadone 0.1 mg/kg IV as needed up to every 6 h, maropitant 1 mg/kg IV every 24 h, cefazolin 22 mg/kg IV every 8 h for 24 h perioperatively, gabapentin approximately 10 mg/kg orally as needed up to every 8 h, and trazodone approximately 3–5 mg/kg orally as needed up to every 8 h.

3 | RESULTS

In both dogs, no intraoperative complications occurred, and no leakage was noted from the partial cystectomy site upon saline instillation and laparoscopic assessment. Each dog recovered uneventfully from surgery and anesthesia. Dog 1 had one episode of regurgitation following anesthetic recovery; pantoprazole 1 mg/kg IV every 12 h and ondansetron 0.5 mg/kg IV every 8 h were administered during hospitalization. Both dogs were noted to be continent and voiding urine appropriately postoperatively with no hematuria, though mild stranguria was noted in Dog 1. One day postoperatively, point-of-care abdominal ultrasound revealed no peritoneal effusion in

either dog, and venous blood gas, packed cell volume, and total solids values were appropriate; Dog 2 had an ionized calcium of 1.52 mmol/L. Both dogs were assessed to be comfortable, and the incisions were clean, dry, and intact. Both dogs were discharged 1 day postoperatively with gabapentin approximately 10 mg/kg orally up to every 8 h for 10–14 days. Dog 1 was also discharged with omeprazole 1 mg/kg orally every 12 h for 5 days and owners were instructed to continue piroxicam administration when eating well. Dog 2 was also discharged with amoxicillin/clavulanic acid 21.1 mg/kg orally every 12 h for 10 days for continued treatment of dermatitis/pyoderma as well as trazodone 4.2 mg/kg orally up to every 8 h for 10–14 days.

Histopathology results for Dog 1 were as follows: bladder mass consistent with high grade UC, complete but narrow excision with tumor cells within 1 mm of the transected margin; urethral lesions consistent with mild, diffuse, chronic lymphoplasmacytic urethritis. In addition, for two mast cell tumors that were excised with wide margins following partial cystectomy and glove and instrument changes, histology was consistent with a completely excised, Kiupel low grade, Patnaik grade 2 dermal mast cell tumor and a completely excised, subcutaneous mast cell tumor with low grade features. The bladder culture from Dog 1 grew Streptococcus canis, and a 7 day course of amoxicillin/clavulanic acid 18.4 mg/kg orally every 12 h was initiated. Histopathology results for the excised bladder mass in Dog 2 were consistent with low grade UC, completely excised with histologic margins of 15 mm.

Three days postoperatively, Dog 1 was noted to have mild stranguria and minimal hematuria. At 25 days postoperatively, Dog 1 was doing well with no urination changes noted. Dog 2 was noted to be hyporexic initially following discharge, but this improved by 3 days postoperatively; no urinary changes were noted. At 14 days postoperatively, Dog 2 was clinically normal. At the time of last follow-up, 206 and 185 days postoperatively for Dogs 1 and 2, respectively, Dog 1 had intermittent urinary tract infections responsive to antimicrobials and Dog 2 had no lower urinary tract signs. Neither owner elected postoperative staging or abdominal imaging. Adjuvant therapy was declined, though meloxicam was administered intermittently to Dog 1.

4 | DISCUSSION

This manuscript represents the first described cases of laparoscopic partial cystectomy for the treatment of canine UC. No intra- or postoperative complications were observed in these dogs, and short-term outcomes were good. The combination of intraoperative laparoscopy and cystourethroscopy resulted in appropriate identification of the gross disease extent for partial cystectomy performed in a closed fashion (i.e., without cystotomy) via MIS. The effect of cystourethroscopy on outcomes of dogs with UC undergoing cystectomy has not yet been evaluated, and further study is warranted. However, in these cases, the use of intraoperative cystoscopy was deemed to be valuable in guiding MIS excision of the bladder mass by transilluminating the mass for subsequent identification laparoscopically and guiding laparoscopic marking of the serosal surface to represent gross tumor mucosal extent as evident on cystoscopy. Moreover, cystourethroscopy was beneficial in not only assessing the bladder tumor to guide MIS excision, but also in assessing the entire lower urinary tract and enabling biopsy of additional mucosal lesions.

In these dogs, the surgical margins relative to gross disease were not measured precisely. Instead, margins of approximately 1–3 cm of grossly normal bladder were incorporated in the partial cystectomy, and cystoscopy confirmed removal of all gross disease within the stapled cystectomy tissues. More accurate surgical margins could be measured laparoscopically (i.e., by utilizing the 1 cm markings at the tip of a laparoscopic blunt probe). However, in both dogs R0 resections (according to the residual tumor classification scheme) were achieved, and to date for dogs with UC, no known association has been determined relative to surgical or histologic margins and risk of locoregional recurrence or oncologic outcomes, likely in association with the field cancerization effect.[4,5,12]

By implementing a stapled cystectomy technique that did not involve opening the urinary bladder, it is possible that the risk of peritoneal tumor seeding may be reduced. However, although the abdomen was protected from neoplastic contamination via urine leakage or contact with gloves/instruments that had previously contacted the tumor, seeding of tumor cells may still theoretically occur across the B formation staples that traverse the bladder wall or potentially through direct neoplastic invasion of the bladder wall itself. Ultimately, a larger sample size and long-term follow-up are needed to determine the effect of closed, stapled, partial cystectomy on oncologic outcomes as well as any potential for delayed complications associated with stapled partial cystectomy. In a historical canine research study in which bladder closures were performed with stainless steel staples (TA-55 3.5 mm), all stapled sites healed appropriately but 4/52 cases developed exposure of staples; one of these had a small amount of crystal formation associated, but no dogs developed stone formation within 4 months postoperatively.[13] In humans that have undergone stapled bladder closure, several studies have reported no long-term

adverse effects, though reports on use of stapler devices for urinary diversion with neobladders have documented potential for stone formation at a mean time of 34 months postoperatively.[14–16] Given these findings and the relatively poor prognosis of dogs with UC, it is unknown if any adverse events associated with stapled bladder closure may develop or be of clinical consequence in these dogs' remaining lifespans, and additional data is needed.

An alternative, non-stapled, closed cystectomy technique described in both cadaveric and live dogs involves the use of bipolar sealing devices (BSD).[17,18] However, in clinical dogs, oversewing the seal outside the peripheral thermal effect zone is needed to prevent urine leakage.[18] Similar to staples, the oversew suture pattern also carries the theoretical potential to seed tumor cells from the mucosal to serosal bladder surface. Additionally, in considering the application of this technique to an MIS approach, the need for oversewing the BSD seal would enhance the complexity of partial cystectomy performed with traditional straight laparoscopic instruments, and this may be particularly challenging for small-sized patients with limited working space in the caudal abdomen. The use of articulated laparoscopic instruments or robotic equipment warrants evaluation in this setting. In both cases of the current report, no leakage from the staple line occurred intraoperatively or short-term postoperatively, and an oversew suture was not required; however, a larger sample size is needed to determine the risk for leakage in clinical cases.

The main limitations of this report include the small sample size and the lack of long-term data. Future large-scale studies are needed to determine the feasibility, optimal laparoscopic approach, and any indicated modifications in stapler sizes or equipment for partial cystectomies in dogs (as well as cats) of varying sizes and conformations, as well as for bladder tumors in locations other than the apex or ventral wall. It is anticipated that different bladder tumor locations will require alternate patient positioning and port placement to allow identification of, access to, and removal of tumors of varying locations. In addition, larger cohorts with long-term follow-up including abdominal imaging will be needed to identify any delayed staple-related complications in dogs, such as migration, exposure, and urolith formation. Furthermore, large-scale studies are required to determine the role of cystourethroscopy on diagnostic assessment and oncologic outcomes, as well as the impact of an MIS approach and closed partial cystectomy technique on oncologic and patient outcomes in dogs with UC.

In conclusion, the described technique for laparoscopic partial cystectomy in dogs with apical/ventral bladder wall UC with concurrent cystourethroscopy was feasible and resulted in good short-term outcomes. Future large-scale, adequately powered studies with long-term follow-up are needed to guide case selection, optimize the approach relative to patient and tumor properties, and determine the effects of MIS stapled partial cystectomy and cystourethroscopy on outcomes in dogs with UC.

AUTHOR CONTRIBUTIONS

Griffin M, DVM, DACVS (Small Animal); Folk C, DVM, DACVS (Small Animal); Buote N, DVM, DACVS (Small Animal): Contributed to case management, data acquisition and analysis, and composition and review of the manuscript for publication.

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SUPPORTING INFORMATION

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

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