VETERINARY SURGERY

Total Prostatectomy as a Treatment for Prostatic Carcinoma in 25 Dogs

Journal:	*Veterinary Surgery*
Manuscript ID	VSU-17-032
Manuscript Type:	Original Article - Clinical
Keywords:	prostate, dog, neoplasia, urogenital surgery

Total Prostatectomy for Prostatic Carcinoma In Dogs

Total Prostatectomy as a Treatment for Prostatic Carcinoma in 25 Dogs

ABSTRACT

Objective: To describe the complications and outcome following total prostatectomy in dogs with histologically-confirmed prostatic carcinoma.

Study Design: Multi-institutional retrospective case series

Animals: Twenty-five client-owned dogs

Methods: Medical records of dogs undergoing total prostatectomy were reviewed from 20014-2016. Data retrieved included signalment, presenting signs, preoperative clinical findings, including laboratory data, diagnostic imaging, surgical technique, histologic diagnosis, postoperative complications, occurrence of postoperative metastasis, and survival.

Results: Twenty-five dogs underwent total prostatectomy for prostatic carcinoma. Urinary anastomotic techniques included urethrourethral anastomosis in 14 dogs, cystourethral anastomosis in 9 dogs, ureterocolonic anastomosis in 1 dog, and anastomosis between the bladder neck and penile urethra in 1 dog. All dogs survived to discharge. Fifteen dogs were diagnosed with transitional cell carcinoma, 8 dogs with prostatic adenocarcinoma, 1 dog with prostatic cystadenocarcinoma, and 1 dog with an undifferentiated carcinoma. Permanent postoperative urinary incontinence was present in 8 dogs. The median survival time was significantly shorter in dogs with extracapsular tumor extension compared to those with intracapsular tumors. The overall median survival time was 231 days (range, 24-1255 days) and the 1- and 2-year survival rates were 32% and 12%, respectively.

Total Prostatectomy for Prostatic Carcinoma In Dogs

Conclusions: Based on information from this study, the median survival time for dogs with prostatic carcinoma undergoing total prostatectomy is longer and complication rates lower than previously reported.

Total Prostatectomy for Prostatic Carcinoma In Dogs

INTRODUCTION

Prostatic neoplasia is relatively rare in dogs[1] making evaluation of various therapeutic interventions difficult. Despite the uncommon occurrence in dogs, they are one of the few domestic species known to develop spontaneous prostatic neoplasia, with carcinomas being the most common histologic diagnosis.[2, 3] Prostatic carcinomas include transitional cell carcinoma, adenocarcinoma, and squamous cell carcinoma[4]. Attempts have been made to develop more objective methods than traditional light microscopy for differentiating prostatic adenocarcinoma and transitional cell carcinoma[4]. To the authors' knowledge there is not yet a well accepted objective method of differentiation and the distinction between adenocarcinoma and transitional cell carcinoma of the prostate remains controversial.

Prostatic neoplasia carries a poor prognosis in dogs because of aggressive local invasion and a high rate of regional and distant metastasis.[5] Hematuria, stranguria and tenesmus are common clinical signs in dogs with prostatic disease,[1,6] but a diagnosis of prostatic neoplasia is often delayed because these clinical signs are not pathognomonic for prostatic tumors. A diagnosis of prostatic neoplasia is made based on physical examination findings, diagnostic imaging, cytology, and histology. Metastatic disease is often present at the time of initial diagnosis.[1,6]

Various treatments have been described for prostatic neoplasia including non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapy, radiation therapy, photodynamic therapy, and surgery. Surgical options include curative-intent total prostatectomy and palliative-intent procedures such as partial prostatectomy, transurethral resection,

radiation therapy, photodynamic therapy, urethral stenting, and urinary diversion procedures. [7-16]

Improved survival in dogs with urogenital carcinoma has been shown with the use of non-steroidal anti-inflammatory drugs (NSAIDs) alone and in combination with chemotherapeutic agents such as mitoxantrone and carboplatin.[17-20] Reported survival times in dogs with prostatic malignancies vary widely, depending on the stage at diagnosis and treatment pursued.[6,7,9-11,13,14, 20-22] Furthermore current therapeutic strategies have been associated with poor response and high complication rates.

Total prostatectomy involves removal of the entire prostate gland and prostatic urethra with subsequent reconstruction of the lower urinary tract. Criteria for appropriate case selection for total prostatectomy in dogs have been previously suggested to include small, intracapsular primary lesions, without evidence of metastatic disease.[23] There have been few reports evaluating total prostatectomy with most concluding that complication rates are too high and survival times are too short to routinely recommend this technique for treatment of dogs with prostatic neoplasia.[21,22,24-26] The most common complication reported following total prostatectomy is urinary incontinence, which has been reported in 33-100% of cases.[24,27]

The purpose of this retrospective multi-institutional study was to report the signalment, presenting signs, intraoperative and postoperative complications, histologic diagnosis, and outcome in dogs treated with total prostatectomy for prostatic neoplasia. We hypothesized total prostatectomy would be associated with a complication rate and survival time similar to other currently available therapeutic interventions.

Total Prostatectomy for Prostatic Carcinoma In Dogs

MATERIALS AND METHODS

This investigation was a multi-institutional retrospective case series approved by the Veterinary Society of Surgical Oncology Research Committee. The study period ranged from October 2004 to August 2016. Medical records from contributing institutions were searched to identify dogs which had undergone total prostatectomy for prostatic neoplasia. Dogs were included if they had undergone total prostatectomy for confirmed prostatic carcinoma. Dogs were excluded where the diagnosis was not confirmed to be carcinoma. Data retrieved included neuter status, breed, age, body weight, presenting clinical signs, dates of presentation and surgery, results of preoperative staging and diagnostic testing, surgical technique, use and duration of postoperative indwelling urethral catheterization, histologic criteria (histologic diagnosis, surgical margin evaluation, and presence of lymphatic and/or vascular invasion), postoperative complications (incidence and severity), use of adjunctive therapy, date and method of detection of recurrent disease, and date and cause of death. Postoperative complications were classified as minor or major. Minor complications were defined as self-limiting or those managed with medical intervention. Major complications were defined as any complication that was expected to cause death without rapid intervention or those requiring a second surgical procedure. Postoperative urinary incontinence was graded from 0-4 using a scheme modified from that reported by Byron et al. (Table 1)[28] with information recorded from veterinarian assessment and owner reporting in the medical history.

Disease-free interval (DFI) was defined as the time between total prostatectomy and detection of confirmed or suspected metastasis or local recurrence of neoplasia.

Metastasis was suspected if there were consistent imaging or clinical examination findings and was confirmed with cytology or histology. Tumor recurrence was suspected if there was a recurrence of clinical signs or if imaging findings were consistent with a recurrent mass in the region of the previous surgical site; and tumor recurrence was confirmed with cytologic or histologic evidence of neoplasia.

Survival time was defined as the time between total prostatectomy and death. Cause of death was classified as either tumor-related or unrelated. Dogs for which the cause of death was unknown were presumed to have died or been euthanized as a result of tumor-related causes. Dogs that died from unrelated causes or were still alive at the time of writing were censored from the survival analysis.

Statistical Analysis

Descriptive statistics for signalment, historical, preoperative, and postoperative data were generated and reported as the arithmetic mean and range. Disease-free intervals and survival times were reported as medians with 95% confidence intervals. Median survival times (MST) were estimated from Kaplan-Meier survival analysis. A log-rank test was used to compare survival curves of dogs with transitional cell carcinoma and prostatic adenocarcinoma. $P \leq 0.05$ was considered significant. Statistical software (Medcalc version 16.8.4 for Windows, Medcalc Software, Ostend, Belgium, www.medcalc.org) was used for descriptive statistical modelling and Kaplan-Meier survival analysis.

RESULTS

Signalment

Twenty-five dogs met the inclusion criteria. The median age was 9.3 years (range 4.9-13.0 years). The median weight was 25.0 kg (range 6.1-47.4 kg). All dogs were neutered males. Breeds were Labrador retriever (n=5), mixed breed (5), German shepherd (2), and 1 each of West Highland White Terrier, Lhasa Apso, Boxer, Dachshund, Jack Russell Terrier, Australian Cattle Dog, Siberian Husky, American Staffordshire Bull Terrier, Wheaten Terrier, Rhodesian Ridgeback, Shetland Sheepdog, Boston Terrier, and Golden Retriever (Table 2).

Clinical Findings

The most common clinical signs on presentation were dysuria (n=12), dyschezia (6), gross hematuria (6), pollakiuria (6), hyporexia (4), and lethargy (4). Prostatic enlargement was detected incidentally on routine digital rectal examination in 4 dogs. Two dogs presented with pre-existing urinary incontinence (grade 2, n=1; grade 4, 1). An enlarged prostate palpated on rectal examination was the most common physical examination finding (n=16). A caudal abdominal mass was detected on abdominal palpation in 2 dogs.

Preoperative Diagnostic Tests

Preoperative serum biochemistry, hematology and urinalysis results were available for 24, 23, and 24 dogs, respectively. Serum biochemistry abnormalities included increased alkaline phosphatase (n=4; 227-634 U/L [reference range, 23-212 U/L]), increased

alanine transferase (2; 189-657 U/L [reference range, 10-125 U/L]), and hypertriglyceridemia (1; 539 mg/dL [reference range, 20-112 mg/dL]). Hematologic abnormalities included anemia (1; 4.88 $x10^{12}$ cells/L [reference range, 5.65-8.87 $x10^{12}$/L]), neutrophilia (4; 12.5-24.6 x 10^9/L [reference range, 2.95-11.64 $x10^9$/L]) and monocytosis (1; 3.01$x10^9$/L [reference range, 0.16-1.12 $x10^9$/L]). Urinalysis abnormalities included hematuria (13) and neoplastic epithelial cells on sediment examination (1). Urine was cultured preoperatively in 6 dogs and 3 of these were positive, including *Streptococcus canis* (1), Gram negative rods and Gram positive rods and cocci (1), and a positive culture without further information available (1). Preoperative imaging for clinical staging included three-projection thoracic radiographs (n=20), orthogonal abdominal radiography (3), abdominal ultrasonography (19), thoracic and abdominal computed tomography (CT) (8), and abdominal magnetic resonance imaging (MRI) (1). No dog had evidence of pulmonary metastatic disease. Prostatomegaly was detected in all but one dog. The prostate was intrapelvic and not detected on abdominal ultrasonography in this dog. Additional imaging findings included mild internal iliac lymphadenomegaly (3), pyelectasia (1), and ureteral dilation (1). Preoperative cytology (20) and histopathology (3), reports were available for 23 dogs. Cytology results included carcinoma, not further classified in (17), epithelial dysplasia (2) and squamous metaplasia (1). Histology results were in agreement with the final post-operative diagnosis in all three cases with transitional cell carcinoma in 2 dogs and prostatic adenocarcinoma in 1 dog.

Total Prostatectomy for Prostatic Carcinoma In Dogs

Total Prostatectomy

The prostate was approached via a caudal ventral midline celiotomy in all dogs. Pubic and ischial osteotomies (n=3) or pubic symphysiotomy (2) were required for further exposure in 5 dogs with an intrapelvic prostate. Enlarged medial iliac lymph nodes were detected intra-operatively and removed for histologic evaluation in 2 dogs. A retrograde urinary catheter was placed in all dogs prior to prostatectomy. The deferent ducts were ligated and transected. The periprostatic fat was dissected from the prostate, with dissection as close as possible to the prostatic capsule, especially dorsally, to minimize the risk of iatrogenic damage to the neurovascular supply to the urinary bladder and urethra. The prostatic vascular supply was ligated or cauterized as close to the prostate as possible. The urinary catheter was then partially withdrawn to allow for pre- and post-prostatic urethral transection before advancing the catheter back into the bladder following completion of the total prostatectomy. Urethrourethral anastomosis was performed in 14 dogs and cystourethral anastomosis in 9 dogs. One dog had gross disease extending into the bladder and post-prostatic urethra. A total cystoprostectomy was performed with bilateral ureterocolonic anastomosis in this dog. Another dog had gross disease involving a large section of the post-prostatic urethra and an anastomosis between the bladder neck and penile urethra was performed. The suture materials and patterns used for anastomosis were recorded for 19 dogs. Anastomosis was performed with a monofilament absorbable suture in all dogs using either a simple interrupted (11) or a simple interrupted and simple continuous pattern (8). Closure of the celiotomy incision was routine.

Postoperative Management

A urinary catheter was maintained postoperatively in 20 dogs for a median of 4 days (range, 1-7).

All dogs were treated with postoperative analgesia and protocols were variable including NSAIDs (n=22), opioids (20), tramadol (9), ketamine (1), and acetaminophen (1).

Surgical Complications and Outcome

All dogs survived to discharge and no intraoperative or perioperative deaths were recorded. There were 4 major complications in 4 dogs and 16 minor complications in 15 dogs.

Major complications included minor incisional dehiscence (n=2), uroabdomen (1), and prepubic herniation (1). Revision surgery was performed in all dogs with major complications. Uroabdomen was detected 1 day post-operatively in 1 dog and a 15 mm laceration was found at the bladder neck. This was presumed to be iatrogenic. Prepubic herniation occurred 20 days post-operatively in another dog and was repaired with polypropylene mesh.

Minor complications included permanent urinary incontinence (n=8), urinary tract infection (6), and superficial surgical site infection (2).

Postoperative urinary incontinence was recorded in 23 dogs overall. Eleven dogs had grade 0 urinary incontinence. Urinary incontinence resolved completely in 3 additional dogs within 1-4 weeks postoperatively. In 1 dog, continence was maintained when treated with phenylpropanolamine. Eight dogs exhibited some degree of permanent urinary incontinence: grade 1 (n=2), grade 2 (3), grade 3 (1) and grade 4 (2). One of the dogs

with grade 4 urinary incontinence had pre-existing grade 4 urinary incontinence. Fifteen dogs returned to complete urinary continence within 4 weeks; although recurrent urinary incontinence, secondary to suspected local tumor recurrence, was recorded in 1 dog 148 days after surgery (Table 2). Some degree of post-operative urinary incontinence was seen in 4 of 9 dogs with cystourethral anastomosis (one of which was pre-exisiting) and 4 of 11 dogs with urethrourethral anastomosis.

Histologic Diagnosis

Histologic examination of the excised prostate was performed in all dogs, with a report available in 20 dogs. Diagnoses included transitional cell carcinoma (n=15), adenocarcinoma (8), undifferentiated carcinoma (1), and papillary cystadenocarcinoma (1). For the two dogs with sublumbar lymph node excision, one dog had evidence of nodal metastasis and the other dog had a reactive lymph node.

Of the 20 dogs with histologic margin evaluation, 8 dogs had complete excision and 12 dogs had incomplete excision. Local recurrence was either suspected or confirmed in 3 dogs with complete histologic margins and in 4 dogs with incomplete margins. There was no significant difference in the rate of local recurrence between dogs with complete histologic margins compared to those with incomplete margins ($P = 0.84$). There was histologically diagnosed extracapsular extension in 11 dogs and no evidence of extracapsular extension in 9 dogs. There was no significant difference in the rate of local recurrence between dogs with extracapsular extension and those without extracapsular extension ($P = 0.44$). There was histologic evidence of lymphatic and/or vascular invasion in 13 dogs and no evidence of lymphatic and/or vascular invasion in 7 dogs.

Metastatic disease was either confirmed or suspected in 7 dogs with lymphatic and/or vascular invasion and in 2 dogs without lymphatic and/or vascular invasion. There was no significant difference in the rate of metastasis between dogs with lymphatic and/or vascular invasion compared to those without lymphatic and/or vascular invasion (P = 0.29).

There was no significant difference in MSTs between dogs with and without complete histologic margins or dogs with and without lymphatic and/or vascular invasion (P = 0.23 and 0.11, respectively). The MST was significantly shorter in dogs with extracapsular extension compared to those with intracapsular tumors (P = 0.02) (Table 3).

Adjuvant Therapy

Twenty-one dogs received adjunctive therapy, including mitoxantrone and NSAIDs (n=14); NSAIDs alone (3); metronomic thalidomide, cyclophosphamide, and piroxicam (3); and carboplatin and deracoxib (1). Dosing and protocols were variable, but of the 15 dogs treated with curative-intent chemotherapy protocols, 10 dogs completed their targeted chemotherapy protocols. Of the five dogs that did not complete their protocols reasons for termination of the protocol were available for 3 dogs and were all due to the development of metastatic disease. Adverse effects were recorded for 2 dogs both of which were episodes of neutropenia during treatment with mitoxantrone and piroxicam which resolved with dose reduction of mitoxantrone.

One dog was treated with adjunctive radiation therapy to the local surgical site (27 Gy divided into 10 fractions of 2.7 Gy daily, Monday through Friday), starting 20 days following total prostatectomy and bilateral medial iliac lymphadenectomy.

Clinical Outcome

Local tumor recurrence was confirmed in 3 dogs and suspected in 5 dogs. Metastatic disease was confirmed in 4 dogs and suspected in 9 dogs. Confirmed metastatic sites included lungs (n=1), sublumbar lymph nodes (1), sublumbar lymph nodes and pelvis (1), and lungs, pelvis, vertebrae, adrenal glands and sublumbar lymph nodes (1). Sites of suspected metastasis included lungs (6), skin (1), bone (1) and sublumbar lymph nodes (1).

Data to calculate the DFI was available for 14 dogs. The median DFI was 81.5 days (95% confidence interval (CI) 48.4-263, range 11.0-630 days). Data to calculate the median DFI was available for 5 dogs with suspected or confirmed local recurrence (median DFI 85.0 days, 95% CI 27.7-208.7, range 76-247) and 9 dogs with suspected or confirmed metastatic disease (median DFI 76.0 days, 95% CI 31.4-305, range 24.0-630). Two dogs with recurrent disease were still alive at the time of writing 65 and 190 days post-operatively.

Death was attributed to tumor-related causes in 19 dogs: local recurrence in 7 dogs (confirmed in 2 dogs and suspected in 5 dogs) and metastasis in 12 dogs (confirmed in 3 dogs and suspected in 9 dogs). Three dogs were euthanized for reasons unrelated to prostatic neoplasia. Two dogs were euthanized for clinical progression of chronic kidney disease; and 1 dog was euthanized for suspected degenerative myelopathy. Three dogs were still alive at the time of writing, ranging from 65-1255 days post-operatively.

The MST for all dogs was 231 days (95% CI 138-628, range 24-1255 days). The MST for dogs with prostatic transitional cell carcinoma was 189 days (95% CI 135-628, range

299 34.0-664) and the MST for dogs with prostatic adenocarcinoma was 248 days (95% CI
300 169-789 days, range 24-1255 days). There was no significant difference in MSTs
301 between dogs with transitional cell carcinoma and adenocarcinoma (P = 0.27). The 1- and
302 2-year survival rates following total prostatectomy were 32% and 12% of dogs,
303 respectively.
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321

DISCUSSION

This report describes the surgical technique and outcome of dogs undergoing total prostatectomy for the treatment of prostatic carcinoma. The signalment and clinical presentation of dogs in the present study was similar to previous reports of dogs with prostatic tumors.[6,29]

Total prostatectomy has been associated with an unacceptably high complication rate in previous studies in dogs.[21, 23, 24-27] However, the majority of these studies included total prostatectomy for treatment of various prostatic diseases and only one specifically investigated total prostatectomy for treatment of prostatic neoplasia.[21] In this study, survival times were short (range, 5-45 days) and the incidence of urinary incontinence was not described.[21] However, urinary incontinence was the most common postoperative complication in other studies of total prostatectomy for dogs with prostatic diseases, with an incidence ranging from 33%-100%.[24,26, 27] Permanent postoperative urinary incontinence was recorded in 34.8% of dogs in the present study. The severity of urinary incontinence was subjectively graded based on owner and veterinary assessment. Of the 8 dogs with permanent urinary incontinence, 5 dogs had grade 1 or 2 urinary incontinence. A previous study classified the severity of urinary incontinence following total prostatectomy as minor if it only occurred with excitement or activity, and major if it was permanent.[27] If this classification were used in the present study then only 17.4% of dogs (4/23) would have been assessed to have major urinary incontinence. A grading system to describe the severity of urinary incontinence may assist owners in determining whether the postoperative outcome will be compatible with their expectations. Permanent urinary incontinence may lead to secondary complications such as recurrent urinary tract

345 infection, pyelonephritis, and urine scalding; and owners should be aware of these
346 possible sequalae.
347 Urinary incontinence has been assessed in both normal dogs and dogs with prostatic
348 disease undergoing total prostatectomy.[24,31] For dogs without prostatic disease, total
349 prostatectomy does not result in urinary incontinence.[31] However, in another study by the
350 same authors, 93% of dogs with prostatic disease had urinary incontinence following
351 total prostatectomy with 54% of these dogs having permanent incontinence.[24] This
352 suggests that the disease process itself may play a role in the development of urinary
353 incontinence, and urinary incontinence may not solely be a consequence of the surgical
354 technique. This is further supported by a study in which the surviving 3 dogs that
355 underwent inadvertent prostatectomy during cryptorchidectomy did not have urinary
356 incontinence following surgical correction.[32] In normal dogs treated with total
357 prostatectomy, there were minimal functional changes to the urinary tract, but there was a
358 decrease in the maximal urethral closing pressure in these dogs.[31] However, this decrease
359 in maximal urethral closing pressure was not sufficient for urethral sphincter pressure to
360 be overcome by intravesicular pressure.[31] Dogs with prostatic disease have abnormally
361 low external urethral sphincter pressures.[24] This reduced external urethral sphincter
362 pressure, in combination with a decrease in maximal urethral closing pressure following
363 total prostatectomy, likely predisposes to urinary incontinence in dogs with prostatic
364 disease.
365 Surgical technique may also influence the development of urinary incontinence post-total
366 prostatectomy. The neurovascular supply to the bladder neck and prostatic urethra
367 courses along the dorsal aspect of the prostate and disruption of this neurovascular supply

during total prostatectomy may result in urinary incontinence postoperatively.[27] Total prostatectomy was performed in all dogs in the present study with close attention to the dorsal dissection technique to minimize the risk of disrupting the innervation to the bladder neck and proximal urethra.

It is possible that the comparatively low rate of urinary incontinence in the present study is related to the primary pathology. However, it has been suggested that total prostatectomy in dogs with prostatic neoplasia may be associated with a higher incidence postoperative incontinence compared to other causes of prostatic pathology.[27] The numbers in that study were small with only 3 of 9 dogs being diagnosed with prostatic neoplasia, two of which were carcinomas. Case selection may also have played in role in the lower rate of urinary incontinence in the present study as dogs may not have been deemed appropriate surgical candidates if there was gross disease extending beyond the prostatic capsule. This may have contributed to less aggressive dissection being required to excise the prostate thus limiting collateral damage to the surrounding neurovascular structures.

Adjunctive treatment was used in the majority of the dogs in this study, with 21 dogs receiving some form of adjunctive therapy following total prostatectomy. While no comment can be made on the adjunctive treatment protocol of choice, adjunctive treatment is still recommended for dogs with prostatic carcinoma because of the high risk of metastatic disease. Additionally, because very few dogs in this study were treated with total prostatectomy alone, no comparison of outcome for surgical intervention with and without adjunctive therapy can be made from this population.

There was no significant difference found between completeness of histologic margins or the presence extracapsular extension and local recurrence of prostatic carcinoma. There was no significant difference in MST between dogs with local recurrence of prostatic carcinoma compared to those without local recurrence; however the MST was significantly shorter for dogs with extracapsular extension compared to those with intracapsular tumors. The reason for this difference is unclear. Since there was no association found between extracapsular extension and local recurrence; or local recurrence and MST, it is unlikely that extracapsular extension contributed to the significant difference in MST as a consequence of an increased rate of local recurrence. Nonetheless the significantly shorter survival time of dogs with extracapsular extension indicates that this information may be of prognostic value.

There was no association found between the presence of lymphatic and/or vascular invasion at the time of surgery and the occurrence of metastatic disease. Likewise there was no association found between the presence of lymphatic and/or vascular invasion and MST. Overall metastatic disease was either suspected or confirmed in 13 of 25 dogs (52.0%). This is comparable to previous reports where metastasis to sublumbar lymph nodes, bone, and lungs was reported in 63–89% of dogs at the time of diagnosis.[8]

There was no significant difference in survival time between dogs with transitional cell carcinoma or adenocarcinoma. Some authors have referred to prostatic neoplasia with various morphologic features, such as glandular and urothelial differentiation, collectively as prostatic carcinoma[6] as we have done in the present study. This may be reasonable given the lack of a proven objective means of differentiation. Given the similar morphologic features of prostatic adenocarcinoma and transitional cell carcinoma

when assessed using light microscopy it may be difficult to distinguish the precise cell origin.[4] Immunohistochemical methods have been investigated for the purpose of differentiating prostatic adenocarcinoma from transitional cell carcinoma but as yet a valid method has not been found.[4] Accurate classification of prostatic epithelial neoplasia may be significant from a prognostic perspective though currently this remains controversial.

The MST time for dogs undergoing total prostatectomy for prostatic carcinoma in this study was 231 days (Figure 1). All dogs survived to discharge and almost one-third of dogs survived longer than one year following total prostatectomy. A MST of 17 days was reported in the only other study to report a MST following total prostatectomy in dogs with prostatic neoplasia[21] Published survival times for prostatic carcinoma including various other treatments range from 17 to 654 days (Table 4).[7-9,11,14,21,22,30, 33] However a number of these studies included cases with urogenitial carcinomas arising from locations other than the prostate and did not provide separate analysis of survival for patients with prostatic carcinoma alone.[11, 18, 33]

The MST in this study population is markedly longer than that previously published for dogs with prostatic carcinoma following total prostatectomy. The study by Vlasin, et al.[21] reporting a MST of 17 days in dogs was prospective and randomised. This study design may have contributed, in part, to the poor overall survival of those dogs as randomization may have prevented selection of cases most appropriate for total prostatectomy. In contrast the retrospective nature of our report may have resulted in reporting of cases deemed more suitable for total prostatectomy by the surgeon. While no reported effort was made to select cases with primary lesions under a certain size and without

extracapular extension or pre-existing metastatic disease, it is reasonable to assume that these factors played a role in case selection. Only one case in this study had documented metastatic disease prior to total prostatectomy.

The limitations of this study are shared with other multi-institutional retrospective studies. Medical records can be inaccurate or incomplete. There was no standardization of perioperative or adjunctive treatments, and the surgeons performing the procedure differed. The cause of death was only confirmed by post-mortem evaluation in 4 dogs. Retrospective inference of the degree of post-operative urinary incontinence from owner and veterinarian descriptions may be inaccurate. Also, the power of statistical analyses performed was likely limited by the small sample size.

Based on our findings, total prostatectomy may be considered as a viable treatment option in dogs with prostatic neoplasia, particularly if presenting with urethral obstruction. However, we propose that case selection is likely to play an important role in postoperative complications and survival. Our study suggests that the incidence and severity of urinary incontinence in dogs with prostatic carcinoma treated with total prostatectomy may be lower and survival times longer than previously reported. Further prospective evaluation of risk factors for post-operative complications and outcome following total prostatectomy in dogs is necessary to determine appropriate case selection criteria.

459

460 **DISCLOSURE**

461 The authors have no conflicts of interest related to this report.

462

463

464

465

466

467

468

469

470

471

472

473

474

475

476

477

478

479

480

481

Total Prostatectomy for Prostatic Carcinoma In Dogs

REFERENCES

1. Bell FW, Klausner JS, Hayden DW, et al: Clinical and pathologic features of prostatic adenocarcinoma in sexually intact and castrated dogs: 31 dogs (1970-1987). *J Am Anim Hosp Assoc* 1991;199:1623-1630
2. Krawiec DR, Heflin D: Study of prostatic disease in dogs: 177 cases (1981-1986). *J Am Vet Med Assoc* 1992;200:1119-1122
3. Teske E, Naan EC, van Dijk EM, et al: Canine prostate carcinoma: epidemiological evidence of an increased risk in castrated dogs. *Mol Cell Endocrinol* 2002;197:251-255
4. Leroy BE, Nadella MVP, Toribio RE: Canine prostate carcinomas express markers of urothelial and prostatic differentiation. *Vet Pathol* 2004;41:131-140
5. Leroy BE, Northrup N: Prostate cancer in dogs: comparative and clinical aspects. *Vet J* 2008;180:149-162
6. Cornell KK, Bostwick DG, Cooley DM, et al. Clinical and pathologic aspects of spontaneous canine prostate carcinoma: a retrospective analysis of 76 cases. *Prostate* 2000;45:173-183
7. Sorenmo KU, Goldschmidt M, 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
8. 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

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

10. Withrow SJ, Gillette El, Hoopes PJ, et al: Intraoperative irradiation of 16 spontaneously occurring canine neoplasms. *Vet Surg* 1989;18:7-11

11. 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

12. Blackburn AL, Berent AC, Weisse CW, et al: Evaluation of outcome following urethral stent placement for the treatment of obstructive carcinoma of the urethra in dogs: 42 cases (2004-2008). *J Am Vet Med Assoc* 2013;242:59-68

13. Lucroy MD, Bowels MH, Higbee RG: Photodynamic therapy for prostatic carcinoma in a dog. *J Vet Intern Med* 2003;17:235-237

14. L'Epplattenier HF, Klem B, Teske E, et al: Preliminary results of intraoperative photodynamic therapy with 5-aminolevulinic acid in dogs with prostate carcinoma. *Vet J* 2008;178:202-207

15. Beck AL, Grierson JM, Ogden DM et al: Outcome of and complications associated with tube cystostomy in dogs and cats: 76 cases (1995-2006). *J Am Vet Med Assoc* 2007;203:1184-1189

16. Smith JD, Stone EA, Gilson SD: Placement of a permanent cystostomy catheter to relieve urine outflow obstruction in dog with transitional cell carcinoma. *J Am Vet Med Assoc* 1995;206:496-499

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

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

19. 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;2:73-80

20. Allstadt SD, Rodrigeuz CO Jr, Boostrum B, et al: Randomized phase III trial of piroxicam in combination with mitoxantrone or carboplatin for first-line treatment of urogenital tract transitional cell carcinoma in dogs. *J Vet Intern Med* 2015;29:261-267

21. Vlasin M, Rauser P, Fichtel T, et al: Subtotal intracapsular prostatectomy as a useful treatment for advanced-stage prostatic malignancies. *J Vet Intern Med* 2006;47:512-516

22. L'Epplattenier HF, van Nimwegen SA, van Sluijs FJ, et al: Partial prostatectomy using Nd:YAG laser for management of canine prostate carcinoma . *Vet Surg* 2006;35:406-411

23. Lawrence JA, Corey FS: Tumors of the male reproductive system, in Withrow SJ, Vail DM, Page RL (eds) *Withrow and MacEwen's small animal clinical oncology* (ed 5). St Louis, MO, Saunders Elsevier, 2014, pp 557-571

548 24. Basinger RR, Rawlings CA, Barsanti JA, et al: Urodynamic alterations associated
549 with clinical prostatic diseases and prostatic surgery in 23 dogs. *J Am Anim Hosp*
550 *Assoc* 1989;25:385-392
551 25. White RAS: Prostatic surgery in the dog. *Clin Tech Small Anim Pract*
552 2000;15:46-51
553 26. Hardie EM, Barsanti JA, Rawlings CA: Complications of prostatic surgery. *J Am*
554 *Anim Hosp Assoc* 1984;20:50-56
555 27. Goldsmid SE, Bellenger CR: Urinary incontinence after prostatectomy in dogs.
556 *Vet Surg* 1991;20: 253-256
557 28. Byron JK, March PA, Dennis J, et al: Effect of phenylpropanolamine and
558 pseudoephedrine on the urethral pressure profile and continence scores of
559 incontinent female dogs. *J Vet Intern Med* 2007;21:47-53
560 29. Johnston SD, Kamolpatana K, Root-Kustritz MV, et al: Prostatic disorders in the
561 dog. *Anim Reprod Sci* 2000;60-61:405-415
562 30. L'Epplattenier HF, van Nimwegen SA, van Sluijs FJ, et al: Partial prostatectomy
563 using Nd:YAG laser for management of canine prostate carcinoma . *Vet Surg*
564 2006;35:406-411
565 31. Basinger RR, Rawlings CA, Barsanti JA, et al: Urodynamic alterations after
566 prostatectomy in dogs without clinical prostatic disease. *Vet Surg* 1987;16:405-
567 410
568 32. Schulz KS, Waldron DR, Smith MM, et al: Inadvertent prostatectomy as a
569 complication of cryptorchidectomy in four dogs. *J Am Anim Hosp Assoc*
570 1996;32:211-214

33. Nolan MW, Kogan L, Griffin JT, et al: Intensity-modulated and image-guided radiation therapy for treatment of genitourinary carcinomas in dogs. *J Vet Intern Med* 2012;26:987-99

Table 1 Urinary Incontinence Scoring System*

0	Dog always continent
1	Dog urine soils where is has been sleeping more than 50% of the time. Does not dribble urine or have a wet prepuce/ventrum when awake.
2	Dog urine soils where it has been sleeping more than 50% of the time. Dribbles urine or has a wet prepuce when awake up to 25% of the time.
3	Poorly continent. Dog urine soils where it has been sleeping more than 50% of the time and has a wet prepuce/ventrum 25-75% of the time.
4	Dog is never continent. Dribbles urine when awake and when sleeping. Constantly has a wet prepuce/ventrum and leaves urine when rising from a sitting to standing position.

*Modified from Byron, et al.[28]

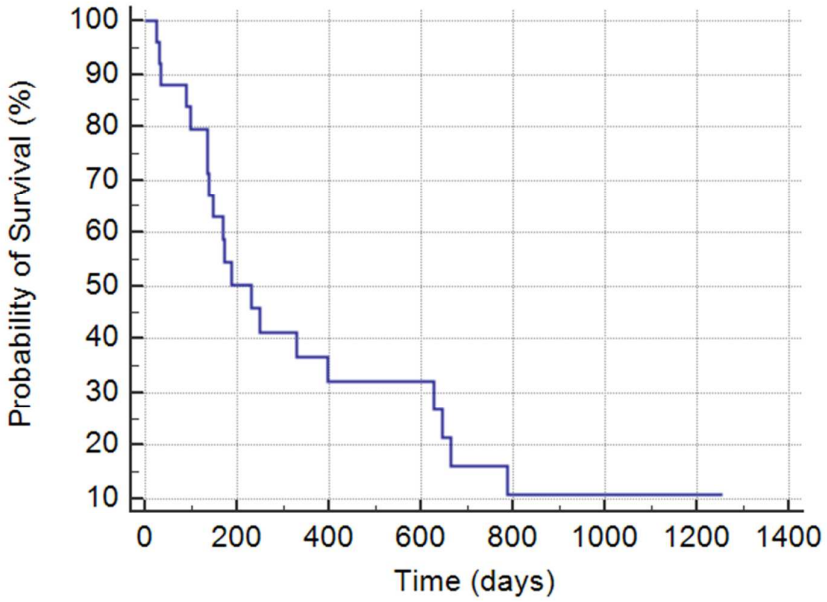

Figure 1 Kaplan-Meier survival curve for 25 dogs with prostatic carcinoma that underwent total prostatectomy. Dogs were censored from analysis if they were still alive at the time of writing or if they had died from causes unrelated to prostatic neoplasia.

Table Signalment, diagnosis, surgery details, incontinence and outcome for dogs undergoing total prostatectomy

Dog	Age (years)	Breed	Surgical Technique	Postoperative urinary catheter duration (days)	Diagnosis[†]	Urinary Incontinence Score[‡]	Survival Times (days)	Cause of death
1	10.6	Labrador retriever	CU	2	PA	3	789	Euthanasia (renal insufficiency)
2	11.3	West-Highland terrier	CU	2	TCC	0[§]	190	Alive
3	4.9	Lhasa apsoa	UU	1	TCC	0	628	Euthanasia (suspected metastasis)
4	12.75	mixed breed	CU	4	TCC	2	34	Euthanasia (confirmed pulmonary metastasis)
5	9.3	boxer	UU	4	TCC	1	489	Euthanasia (renal insufficiency)
6	10.58	dachshund	UU	1	TCC	0	231	Euthanasia (confirmed local recurrence)
7	9.25	mixed breed	CU	1	TCC	2	135	Euthanasia (suspected local recurrence)
8	8.5	Jack Russell terrier	CU	2	PA	0	172	Euthanasia (suspected local recurrence)
9	7.9	Australian cattle dog	UU	2	TCC	4	134	Euthanasia (suspected local recurrence)
10	8.25	Siberian husky	UU	3	PA	0	65	Alive
11	11	German shepherd	UU	5	PA	0	798	Euthanasia (suspected degenerative myelopathy)
12	8	mixed breed	UU	7	PA	0	1255	Alive
13	7.66	American Staffordshire bull terrier	CU	3	PA	0[§]	169	Euthanasia (suspected metastasis)
14	6.5	wheaten terrier	UU	n/a	TCC	2	99	Euthanasia (suspected local recurrence and metastasis)
15	10	golden retriever	UU	n/a	TCC	0[¶]	189	Unknown
16	10	Labrador retriever	CU	n/a	TCC	0[§]	396	Euthanasia (suspected metastasis)
17	10	Labrador retriever	CU	n/a	TCC	4 (pre-existing)	647	Euthanasia (suspected metastasis)
18	9	Rhodesian ridge back	UU	5	TCC	0	664	Euthanasia (confirmed local lymph node metastasis)
19	10	mixed breed	UU	7	PA	0	248	Euthanasia (suspected local recurrence)
20	9	Shetland sheepdog	UU	5	PA	1	31	Euthanasia (confirmed multifocal metastatic disease)
21	12	Labrador retriever	UU	5	TCC	0	88	Euthanasia (suspected metastasis)
22	9	Boston terrier	Anastomosis between bladder neck and penile urethra	7	PA	Unknown	24	Euthanasia (suspected metastasis)
23	13	German shepherd	Ureterocolonic anastomosis	n/a	TCC	n/a	138	Euthanasia (melena and lethargy)
24	9	mixed breed	UU	7	TCC	0	149	Euthanasia (confirmed local recurrence)
25	9	Labrador retriever	CU	5	PCA	0	330	Euthanasia (suspected metastasis)

*Urethrourethral anastomosis (UU), cystourethral anastomosis (CC)
[†] Prostatic carcinoma (PA), transitional cell carcinoma (TCC), prostatic cystadenocarcinoma (PCA)
[‡] Modified from Byron et al[28]
[§] Had initial post-operative incontinence which resolve
[¶] No incontinence when on phenylpropanolamine. Incontinence recurred 148 days post-operatively, suspected secondary to local recurrence

Table 3 Comparison of MST with and without lymphatic/vascular invasion, extracapsular extension and complete histologic margins

MST	With Lymphatic/vascular Invasion	Without Lymphatic/vascular Invasion	With Extracapsular Extension	Without Extracapsular Extension	With Complete Histologic Margins	Without Complete Histologic Margins
MST	149	248	138	248	248.	172
95% CI	99.0-189	135-664	88.0-169	172-628	99.0-628	134-396
P value	0.12		0.02		0.23	

Table 4 Published Survival Times in Dogs with Prostatic Carcinoma

Reference	Treatment	MST (range)
Vlasin et al[21]	Total prostatectomy	17 days (5-45)
Vlasin et al[21]	Subtotal intracapsular prostatectomy	130 days (2-220)
Liptak et al[8]	Transurethral resection	32, 74, and 264 days
L'Epplattenier et al[30]	Partial prostatectomy with Nd:YAG laser	103 days (5-239)*
Weisse et al[11]	Urethral stenting	20 days (6-105) †
L'Epplattenier et al[14]	Photodynamic therapy with 5-aminolevulinic acid	41 days (10-68)
Turrel et al[9]	Intraoperative radiation therapy	114 days (41-750)
Nolan et al[33]	Intensity modulated and image guided radiation therapy	654 days‡
Sorenmo et al[18]	NSAIDS	6.9months
Sorenmo et al[18]	Untreated	21 days

*Excluding the three dogs that died within 16 days MST =183 (91-239)
†Survival time for all 12 dogs in this study (survival for cases with prostatic carcinoma not reported separately).
‡ Survival time for all 21 dogs in this study (survival for cases with prostatic carcinoma were not reported separately).