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Partial Prostatectomy Using Nd:YAG Laser for Management of Canine Prostate Carcinoma

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Objective—To report a technique for partial prostatectomy by laser dissection and to evaluate outcome and complications in dogs with prostate carcinoma (PCA).
Study Design—Experimental and clinical case series.
Animals—Four normal dogs and 8 dogs with PCA.
Methods—Subcapsular partial prostatectomy, sparing the urethra and the dorsal aspect of the prostatic capsule, using Nd:YAG laser dissection to remove the prostatic parenchyma and control hemorrhage was performed in 4 normal dogs and subsequently in 8 dogs with histologically confirmed PCA. Additional treatment of PCA dogs included local application of interleukin-2 and systemic administration of meloxicam. Prostate size, complications, and survival time were recorded. Laser-associated thermal damage to surrounding tissue was evaluated by histology.
Results—In normal dogs, no damage to the dorsal prostatic capsule or urethra was detected. In PCA dogs, median survival was 103 days (range, 5–239 days). Three dogs died from complications within 16 days, whereas 5 (median survival, 183 days; range, 91–239 days) had improvement or resolution of clinical signs. Urinary incontinence did not occur.
Conclusion—Laser assisted subcapsular partial prostatectomy can be performed in dogs with PCA without development of postoperative incontinence.
Clinical Relevance—Subcapsular partial prostatectomy is a potential palliative treatment for PCA in dogs and may lead to the resolution of clinical signs for several months.

INTRODUCTION

CANINE PROSTATE carcinoma (PCA) is uncommon with an estimated prevalence of 0.2–0.6%.[1] True prevalence is unknown as population-based data is not available.[2] Canine PCA has an invasive growth pattern and commonly metastasizes to the sublumbar lymph nodes; occasionally, metastases to the lungs and lumbar vertebrae are observed.[3] Castration has no effect on disease progression, nor does it prevent occurrence of PCA; in fact, it appears that castrated males are at an increased risk of developing PCA compared with intact males.[4] Clinically, canine PCA therefore resembles late stage, hormone-independent human PCA and the dog is an appropriate model for understanding the pathogenesis of PCA in humans.

Unlike humans, total prostatectomy is not an option for treatment of PCA in dogs because of a high incidence of postoperative incontinence.[5] The cause of incontinence in dogs after total prostatectomy is uncertain. Total prostatectomy in dogs with prostatic disease is more likely to cause incontinence than prostatectomy in dogs with a normal prostate,[6,7] suggesting that primary prostatic disease rather than surgical technique may be responsible for this complication. For these reasons, therapeutic modalities for PCA in dogs need to optimize removal of neoplastic tissue without compromising urethral sphincter function, which is controlled by the

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hypogastric nerve lying dorsolateral to the prostate and bladder neck.[8] Ideally, the technique for removal of prostatic tissue should permit careful dissection of prostatic parenchyma and optimal control of hemorrhage to maintain good visibility and a high level of precision for maximal removal of neoplastic tissue, but preserving the neurovascular structures on the dorsolateral aspect of the prostate. We hypothesized that these principles could be respected by use of Neodymium:Yttrium Aluminum Garnet (Nd:YAG) laser to perform subcapsular partial prostatectomy to substantially reduce prostatic volume, alleviate clinical signs of PCA and maintain urinary continence.

Because removal of neoplastic tissue would be incomplete, adjuvant therapy is required to ensure that remaining neoplastic tissue and metastases are prevented from proliferating. Interleukin-2 (IL-2), a cytokine with a wide range of immunologic effects including the activation of cytotoxic T lymphocytes, natural killer cells and lymphokine-activated killer cells,[9,10] has been used systemically and intralesionally for treatment of various neoplasia in cows, horses, and humans, and reportedly induces regression of metastatic tumors in humans.[9–11] IL-2 has been administered intralesionally in doses ranging from 200,000 IU/tumor[12] to 6 million IU.[11] In addition, prostate cancer cells like other cancer cell types express cyclooxygenase-2 (COX-2), whereas normal prostatic cells do not. Although the exact significance of COX-2 for carcinogenesis is not entirely understood,[13] studies using cell cultures and in vivo mouse models show that inhibition of COX-2 could be beneficial in management of patients with PCA.[14,15] Meloxicam is a non-steroidal anti-inflammatory drug with high specificity for COX-2 inhibition[16] and is registered for long-term treatment of dogs.

Thus, we report use of a Nd:YAG laser-assisted technique for partial prostatectomy in 4 normal dogs, and then outcome in 8 dogs with histologically confirmed PCA also treated with intralesional IL-2 and systemic meloxicam.

MATERIALS AND METHODS

Dogs

The technique was first tested in 4 non-survival, healthy, intact, adult male Beagles (weight, 14.5–21.5 kg; age, 5–7 years), then used in 8 patients with a suspicion of PCA, based on cytological examination of an ultrasound-guided fine needle aspirate of the prostate.

Anesthesia

Dogs were premedicated with medetomidine (20 μg/kg intravenously [IV] initially then 10 μg/kg hourly), and anesthesia was induced with propofol (1–2 mg/kg IV to effect) and maintained with isoflurane (<1% end-tidal concentration in 50% air and 50% O_2). Lactated Ringers solution (5 mL/kg/h) was administered throughout anesthesia. A combination of buprenorphine (20 μg/kg subcutaneously 4 times daily until hospital discharge) and meloxicam (0.2 mg/kg before surgery, then 0.1 mg/kg orally once daily) was administered for analgesia.

Surgical Procedure

We performed subcapsular partial prostatectomy, sparing the urethra and the dorsal aspect of the prostatic capsule including the neurovascular structures essential to the normal function of the urethral sphincter. A urethral catheter was inserted to allow localization of the urethra during surgery. The prostate was approached by caudal median celiotomy, the bladder was retracted cranially, and periprostatic fat tissue was dissected from the prostate to allow observation of the ventral portion of the prostatic capsule. An Nd:YAG surgical laser (Medilas 40N, MBB-Medizintechnik GmbH, München, Germany) with a 600 μm optical fiber (Ultraline, Heraeus LaserSonics, Milpitas, CA) was used at 10 W (continuous wave) to incise the ventral part of the prostatic capsule along the midline. Prostatic tissue was bluntly separated from the capsule, then parenchymal segments were removed using laser dissection to control hemorrhage. Prostatic tissue samples were submitted for microscopic examination to confirm a diagnosis of PCA. The urethra remained intact and prostatic tissue was removed on each side of the urethra as far dorsally as possible. Finally the edges of the capsule were trimmed and the capsule was sutured ventrally over the urethra without leaving dead space, using a continuous pattern of 3-0 polyglecaprone 25, then the celiotomy was closed in layers.

Postoperative Evaluation

Prostate size was measured pre- and post-operatively by ultrasonography and prostate volume calculated.[17] Prostate volume was divided by body weight to obtain prostatic index to compare prostate volume in dogs of differing body size. Experimental dogs were euthanatized immediately postoperatively and the prostate was submitted for histologic examination to determine laser thermal damage to the dorsal part of the prostatic capsule and urethra. Prostatic tissue was fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin–eosin.

Postoperative Treatment

After surgery in dogs with PCA, IL-2 (4.5 million IU in 1 mL 0.9% NaCl) was injected into the remaining prostatic tissue and meloxicam (0.1 mg/kg orally once daily) was administered. Dogs were examined 1 month postoperatively, then every other month. On each follow-up visit, chest radiographs were taken and abdominal ultrasonography performed.

Statistical Analysis

Survival times were reported as median and range. Prostate dimensions were as mean ± SD. Where appropriate, a t-test for paired samples was performed to compare preoperative and postoperative means. Pearson's correlation was used to test the correlation between prostate index and survival. Significance was $P < .05$ (2-tailed).

RESULTS

In normal and PCA dogs, use of the Nd:YAG laser provided excellent control of hemorrhage during prostatic tissue dissection. Occasional hemorrhage from larger vessels running beneath the prostatic capsule was controlled by laser or electrocautery. In normal dogs, prostatic volume was reduced by $50.5 \pm 15.0\%$ ($P = .013$) and ~ 2 mm of periurethral tissue remained. There was no visible damage to the dorsal prostatic capsule or urethra on histologic examination.

Dogs with PCA

Clinical signs associated with PCA were present for 1–4 months except for 1 dog that had urethral blood loss for >36 months (Table 1). Median survival time was 103 days (range, 5–239 days (Fig 1). There was a weak positive, but non-significant correlation ($R^2 = 0.32$, $P = .56$) between prostatic index and survival time (Fig 2). One dog was omitted from this analysis because the prostate contained large fluid filled cysts and the measured volume of the prostate did not accurately reflect the volume of neoplastic tissue. Five dogs recovered well from surgery and clinical signs improved or resolved; median survival time was 183 days (range, 91–239 days). None of the dogs developed urinary incontinence.

All dogs were eventually euthanatized because of recurrence of clinical signs like dyschezia and dysuria. In 1 dog, these signs were related to urinary tract infection that resolved with antibiotic administration. Clinical signs in all dogs recurred even though the prostate was not clinically substantially enlarged compared with its immediate postoperative size. Necropsy examination of the prostate invariably revealed an aggressive histologic pattern with invasion of tumor cells into blood vessels and the prostatic capsule.

Three dogs developed postoperative complications and died or were euthanatized within 16 days of surgery. In 1 dog, severe dysuria present before surgery did not resolve and the dog was unable to urinate postoperatively, despite administration of a sympathicolytic drug (prazosin, 0.033 mg/kg orally every 8 hours) and meloxicam. Another dog was euthanatized because of bilateral ureteral obstruction from tumor ingrowth into the trigone region of the bladder. Both dogs were admitted preoperatively with severe stranguria requiring daily catheterization. The 3rd dog, a Bouvier des Flandres mixed breed that had clinical signs of prostatic disease for 36 months before admission had 2 very large prostatic cysts that were drained and omentalized before subcapsular prostatectomy. Preoperatively, there was moderate hypoalbuminemia, slight thrombocytopenia, and slightly increased activated partial thromboplastin time (APTT). Intraoperatively, the dog had an increased bleeding tendency suggestive of a clotting disorder. Immediately postoperatively, the dog had signs of oliguria requiring aggressive fluid therapy including plasma transfusion. On the day after surgery the dog developed severe hind limb edema.

Ultrasonographic examination of the caudal abdomen revealed a dorsally enlarged prostate, possibly from a hematoma, however no evidence of abnormal circulation to the hind limbs was detected. It was not clear whether

Table 1. Signalment, Clinical Signs and Survival of 8 Castrated Male Dogs with Prostate Carcinoma Treated by Partial Prostatectomy Facilitated by Nd:YAG Laser Dissection

Breed	Age (Years)	Clinical Signs	Prostate Index*	Survival (Days)
Bearded collie†	11	Tenesmus, hemorrhagic urethral discharge	0.34	183
Labrador retriever	10	Purulent urethral discharge	0.82	201
Heidewachtel	10	Tenesmus, stranguria	0.69	114
Hovawart	10	Pollakiuria, hemorrhagic urethral discharge	0.28	91
Bouvier des Flandres Crossbreed	14	Tenesmus, hematuria, hemorrhagic urethral discharge	—‖	6
Bearded collie	11	Tenesmus, dysuria, pollakiuria	0.74	239
Golden retriever	11	Severe stranguria‡	0.49	16
Labrador retriever†	9	Tenesmus, severe stranguria‡	0.36	5

*Volume of prostate (mL) divided by body weight (kg).

†Patients diagnosed with metastases to the local lymph nodes.

‡Severe stranguria was defined as stranguria requiring daily catheterization.

‖Prostate contained large cysts, therefore prostate size was not considered a relevant indicator of the volume of neoplastic tissue.

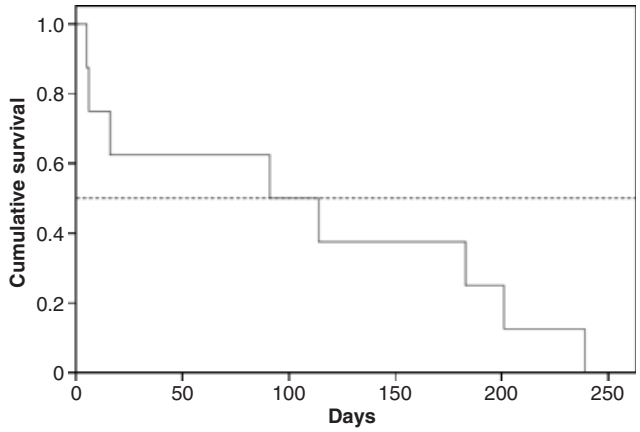

Fig 1. Kaplan–Meier cumulative survival curve for 8 dogs with prostate carcinoma (PCA) treated by partial prostatectomy facilitated by use of Nd:YAG laser dissection.

the edema was caused by hypoalbuminemia, if changes in the prostate region caused disturbance of lymphatic drainage from the hind limbs, or whether it was a reaction to the plasma transfusion. Despite continued fluid therapy, blood transfusion, and medical management the dog did not recover appropriately. The owners insisted on taking the dog home and it died 6 days after surgery.

Two of the 8 dogs had metastases to the sublumbar lymph nodes at the time of surgery. A 3rd dog developed visible pulmonary metastases during follow-up (2 metastases were visible on thoracic radiographs 1 month postoperatively and remained visible during subsequent rechecks).

DISCUSSION

In normal dogs, the technique we report was effective in removing prostate parenchyma and controlling hemorrhage and resulted in a significant reduction in prostate volume. Ideally, these dogs should have been followed postoperatively to check for incontinence and other complications; however, that experimental design was considered ethically unacceptable in the Netherlands. The absence of histologic evidence of thermal damage to important regional anatomic structures suggests that Nd:YAG laser may safely be used to dissect prostatic tissue within millimeters of either the urethra or the dorsal prostatic capsule with its associated neurovascular structures. This assumption was confirmed by the outcome of the procedure in dogs with PCA where none developed urinary incontinence.

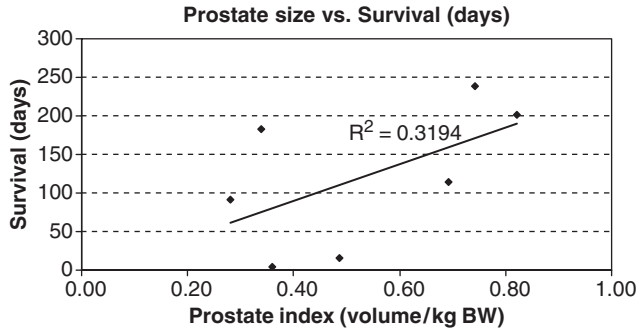

Fig 2. Linear regression curve showing survival as a function of prostatic index (prostate volume [mL] divided by body weight [kg]).

Various partial prostatectomy techniques have been described using either electrocoagulation,[18] ultrasonic aspiration,[19,20] or Nd:YAG laser excision[21] in normal dogs or dogs with benign prostatic disease. Subcapsular dissection as we describe was similar to previously reported techniques using electrocoagulation[18] and ultrasonic aspiration.[19,20] The absence of postoperative incontinence in our dogs corresponds to similar results reported for other dissection techniques. Another study reported partial prostatectomy using a Nd:YAG laser[21] not for subcapsular dissection of prostate tissue but resection of prostatic capsule and parenchyma on each side of the urethra, including the dorsolateral aspect of the capsule. With that technique no incontinence occurred in normal dogs but the postoperative incidence in dogs with prostatic disease was similar to the incidence after total prostatectomy. Our results corroborate our hypothesis that partial prostatectomy maintaining the dorsolateral aspect of the prostatic capsule intact is seemingly necessary to avoid postoperative incontinence.

Canine PCA is an invasive tumor and complete removal of the prostate to obtain sufficient tumor margins leads to intractable and thus, unacceptable urinary incontinence. Marginal, partial prostatectomy without additional radiotherapy is, by definition, a palliative procedure. In most of our dogs clinical signs improved substantially or resolved completely. Dogs survived up to 240 days after surgery before clinical signs recurred and the dogs were euthanatized. Interestingly, clinical signs recurred in the absence of substantial prostatic enlargement. The invasive nature of PCA seen at necropsy indicated that recurrence of signs was probably because of tumor progression into the lumen of the urethra or the wall of the rectum.

Published information on outcome after diagnosis of PCA in dogs is very sparse. In 1 report describing clinical aspects of PCA in dogs without surgical treatment, 58 of 72 dogs were euthanatized at diagnosis and mean survival time for those surviving >1 week was 30 days. Reports of surgical treatment of PCA in dogs is limited to a few cases. Surgical placement of a retained urethral catheter in 3 dogs with PCA and stranguria enabled the dogs to survive 3–5 months after surgery.[22] In another report, 3 male dogs with prostatic neoplasia were treated by

transurethral resection using an electrocautery loop (combined with intraoperative radiation therapy in 2 dogs).[23] Survival times were 32, 74, and 264 days; however, 2 dogs were diagnosed with prostatic transitional cell carcinoma and 1 with undifferentiated carcinoma, therefore it is uncertain whether these results are comparable with our patients. Treatment of PCA by transurethral photodynamic therapy allowed 1 dog to survive nearly 9 months after treatment.[24] Survival times of the dogs in our study therefore compare favorably with previously published results of surgical treatment of PCA in dogs. It is possible that other forms of adjuvant treatment directed toward local control of remaining neoplastic tissue could allow prolonged survival times after laser surgery in dogs with PCA.

Severe complications developed in 3 dogs. Because of the high level of emotional distress of owners it was not possible to collect necropsy information. In 2 dogs, complications were associated with persistence of dysuria and stranguria. Because these 2 dogs had severe stranguria before surgery, we believe these complications likely resulted from tumor ingrowth into the urethra, rather than from a direct effect of the surgical procedure on the proximal urethra. In the 3rd dog, the complications were systemic (hypoalbuminemia, shock, hind limb edema) and not specifically related to the prostate. These complications probably resulted from the clotting disorder diagnosed preoperatively, however a treatment-related effect cannot entirely be excluded. Severe stranguria preoperatively (i.e., stranguria requiring catheterization) may be a negative prognostic factor for survival after treatment, as evident in these dogs. Duration of clinical signs before diagnosis, tumor size at admission, and metastases to the sublumbar lymph nodes did not significantly correlate with survival time.

We lack a control group. Inclusion of a control group (dogs that did not have surgery) however, was considered a bias because these dogs often have the worst clinical signs. Additionally, owner motivation of a dog that has had surgery cannot be compared with that of an owner of an unoperated dog. Owner motivation to pursue treatment is an aspect of prime importance influencing the choice of time for euthanasia and therefore survival time after beginning treatment. Based on our experiences with these PCA dogs, we believe that partial prostatectomy facilitated by Nd:YAG laser dissection and accompanied by adjuvant treatment can be considered as a palliative treatment that can provide resolution of clinical signs for at least several months postoperatively.

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