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# Development of a Canine Prostatectomy Model for Use in the Toxicity Evaluation of Oncology Drugs

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## ABSTRACT

Tumor surgical resection is a common approach for cancer treatment; however, it comes with several downsides including metastasis and tumor recurrence. Local administration of antitumor therapy, along with tumor resection, has become preferred over systemic administration for many types of cancer, but this has major side and nonspecific target effects. In this study, a unique canine model was developed to allow antitumor therapy to be locally administered at the tumor resection site and gradually released. This approach allows for the concentration of the therapeutic agent at the site of the disease to produce effective treatment and reduce systemic toxicity. Several surgical models were developed for proper safety profiling of therapies. As there are many shared anatomical similarities between dogs and humans, the dog was considered an ideal animal model for human prostate disorders, including prostate cancer. In men, a total prostatectomy is commonly performed to remove cancerous tissue, however, this procedure is difficult to model in dogs due to a high rate of serious complications.

The purpose of this study was to develop a canine prostatectomy model that would allow the investigation of locally applied test material. The goal of the model was to mimic human prostatectomy procedures while minimizing post-operative complications associated with canine prostatectomy. In this study, male beagle dogs (n=3) underwent a partial prostatectomy. A pocket was then created within the periprostatic fat through an abdominal incision with approximately 25% of each prostatic lobe removed via wedge resection. The resection sites allowed for direct application of up to 2 mL of a test material, after which the pocket and abdominal incision (3 layers) was closed with absorbable suture. Euthanasia was performed 5 days post-operation to assess gross abnormalities. A partial prostatectomy was successfully performed in all animals with no major surgical-related complications, such as urinary incontinence or retention noted following surgery. Clinical observations findings were limited to decreased activity and food consumption that were resolved 2 days post-surgery. Urinalysis performed prior to termination revealed hematuria and proteinuria. At necropsy, gross observations included focal discoloration in renal tissue at the resection site that correlated with minimal to mild vacuolation and intracellular brown pigment in the renal tubular epithelium that was not considered adverse.

In conclusion, these results suggest that canine partial prostatectomy can be accomplished with minimal complications and could serve as a reliable model for human prostatectomy procedures. This model offers an opportunity for the evaluation of new therapeutics using carefully refined procedures while mimicking the manipulation and removal of prostate tumors.

## INTRODUCTION

After the surgical removal of a prostate tumor, the importance of local cancer treatment cannot be overstated. Thus, local prostate cancer treatment becomes critical in addressing any residual cancer cells and in the prevention of recurrence. Animal models play a pivotal role in assessing the effectiveness and safety of these new treatments. Due to many shared anatomical similarities, the canine is an ideal animal model for human prostate disorders, such as prostate cancer. In men, a total prostatectomy is commonly performed to remove cancerous tissue. However, this procedure is difficult to model in dogs due to a high rate of serious complications. The purpose of this study was to develop a canine prostatectomy model that would allow future investigation of locally applied test material. The goal of the model was to induce manipulation and removal of prostate tissue to represent human prostatectomy procedures while minimizing post-operative complications associated with canine prostatectomy.

## METHOD

- Male, beagles (n=3) underwent a partial prostatectomy
- Sedated with dexmedetomidine (0.005 mg/kg, IM), acepromazine (0.025 mg/kg, IM), and buprenorphine (0.01 mg/kg, IM), induced with alfaxalone (2 mg/kg, IV), intubated, and maintained on isoflurane.
- Carprofen (4.4 mg/kg, SC), buprenorphine ER (0.2 mg/kg SC), and cefazolin (20 mg/kg IV) were given pre-operatively.
- See Figures 1-6 for procedures.
- Carprofen (4.4 mg/kg, PO) was given for 2 days post-op. Euthanasia was performed 5 days post-op to assess gross abnormalities.

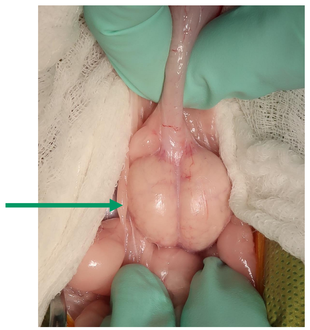

**Figure 1.** Through a caudal ventral abdominal incision, a pocket was created within the periprostatic fat, and the prostate gland (arrow) was exposed.

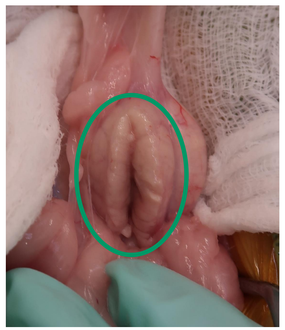

**Figure 2.** Approximately 25% of the prostatic lobe was removed via wedge resection with a #11 scalpel blade. Care was taken to avoid the urethra. (Circle = resection site)

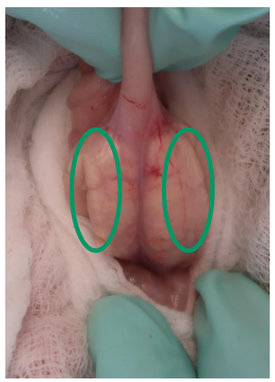

**Figure 3.** Hemostasis was achieved with manual pressure and hemostatic gelatin sponges. Following bilateral resection, the prostate capsule was not closed to allow for direct application of test material. (Circle = resection site)

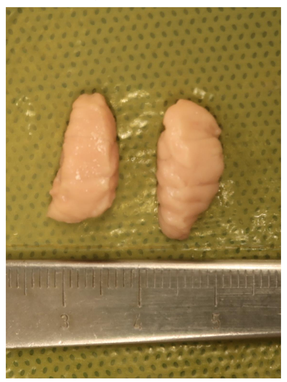

**Figure 4.** Approximately 25% of each prostatic lobe was removed via wedge resection. Ruler on scalpel blade handle used for size reference.

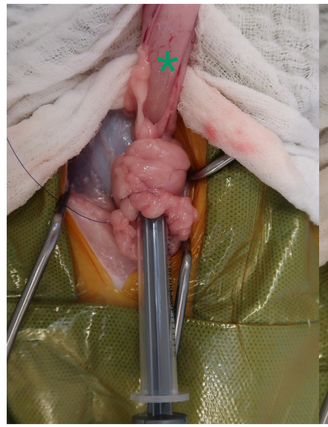

**Figure 5.** The periprostatic pocket was partially closed, the test material was applied directly onto resection sites within the pocket via a syringe, and then the remaining pocket was closed. (* = urinary bladder)

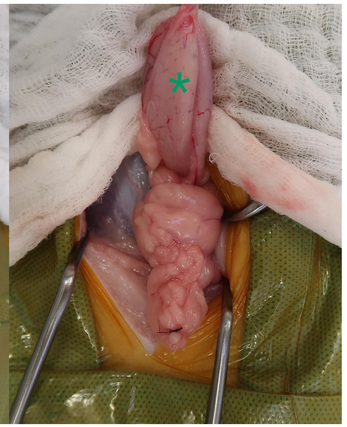

**Figure 6.** The periprostatic fat pocket was closed with an absorbable suture in a simple continuous pattern. The abdominal incision (3 layers) was then closed with an absorbable suture in a simple continuous pattern. (* = urinary bladder)

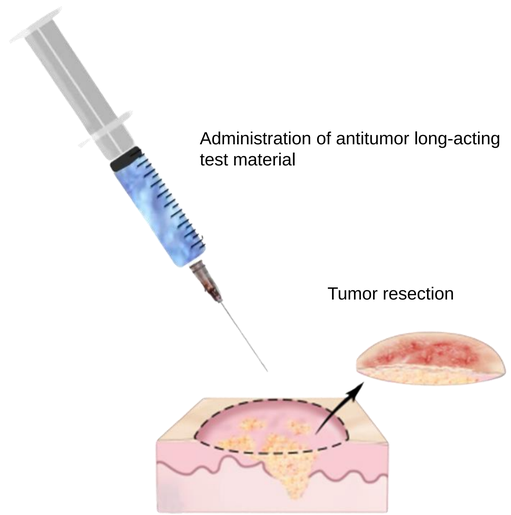


**Figure 7.** Therapeutic approach model for the administration of antitumor long-acting formulation that can be administered at the resected tumor cavity. This approach concentrates an effective dose at the tumor site.

## RESULTS

- A partial prostatectomy was successfully performed in all animals.
- Created cavity and sutured pocket allowed for injection of long-lasting antitumor therapy to stay longer in the target area. (See Figure. 7)
- No major surgical-related complications, such as urinary incontinence or retention were noted following surgery.
- Free-catch urinalysis prior to termination revealed hematuria and proteinuria
- Gross observations:
  - Focal discoloration in renal tissue and resection site
  - Focal adhesion (n=1) between the urinary bladder and omentum
- Histological findings: minimal to mild vacuolation and intracellular brown pigment in the renal tubular epithelium that was considered non-adverse

## CONCLUSION

Canine partial prostatectomy can be accomplished with minimal complications and may serve as a reliable model for human prostatectomy procedures. Total canine prostatectomy often results in urinary incontinence or retention. Thus, this model offers a refinement to the more invasive procedure, while mimicking the manipulation and removal of prostate tissue.

Follow-up studies will utilize this model to investigate locally applied test material in efficacy and safety studies. In conclusion, this model may open up the door for new therapeutics for those suffering from prostate cancer or other prostate disorders.

*Note: All pictures are from a cadaver*