Overview

Transitional cell carcinoma (TCC) is the most common malignancy of the urinary tract in dogs and accounts for approximately 2% of all malignancies in dogs. In a series of 102 dogs with TCC of the bladder, in 56% of the dogs the urethra was also involved and in 29% of dogs the prostate was involved. Most TCCs are intermediate to high grade papillary infiltrative tumors that can be associated with a variety of clinical signs. The etiology of canine transitional cell carcinoma is multifactorial. Risks factors include exposure to lawn chemicals, obesity, female sex and breed. It is important to distinguish non-TCC conditions from TCC of the reproductive tract because the treatment and prognosis differ considerably.

Keywords: Transitional cell carcinoma, prostate, ductus deferens, vagina, vulva

Prostatic transitional cell carcinomas

Prostatic tumors are relatively uncommon in dogs, with a prevalence of less than 1%. Despite this low incidence, the dog is one of the few domestic species to develop spontaneous prostate cancer, thus sparking interest in the dog as a comparative model for prostate cancer in men. Human prostatic carcinomas arise almost exclusively in the peripheral zone, with fewer found in the transition and central zones. It is hypothesized that prostatic cancer in men arises from acini in the peripheral or transitional zones previously affected with inflammatory prostatitis. The surrounding prostatic epithelial cells undergo a morphological change secondary to this inflammatory insult. The morphological change is known as proliferative inflammatory atrophy (PIA). In dogs, the precise location of origin of the carcinomas is unclear but there is growing evidence that these neoplasms may stem from ductular epithelium adjacent to the periurethral zone. Much of the uncertainty regarding the site of origin of these neoplasms is due to the extensive co-involvement of the prostate gland and urethra that is present in most dogs with prostate cancer.

The early stages of human prostate cancer are characterized by the histological pattern known as prostatic intra-epithelial neoplasia (PIN). Morphologically, PIN is characterized as an intra-luminal proliferation of epithelium exhibiting varying degrees of malignant criteria. Prostatic intra-epithelial neoplasia is considered a precursor of human prostate carcinoma and occurs under the influence of androgenic stimulation in those patients at risk for prostatic carcinoma. Prostatic intra-epithelial neoplasia cells are often found in close proximity to foci of PIN and prostatic carcinomas and commonly contain somatic mutations and possess an increased rate of cell division. While histological lesions similar to PIN have occasionally been identified in canine prostate glands, the value of PIN as a cancer marker in dogs is unclear. Although PIN has been detected in dogs with existing prostatic carcinoma, it has also been detected in dogs without evidence of prostatic disease, making its role in the dog less clear. The occurrence of high grade PIN in dogs with concurrent carcinoma has been reported to range from 30-72%. Histologically, most canine prostatic carcinomas are of an intra-alveolar pattern but many also contain similar patterns to TCC.

Overall, canine prostate carcinomas are malignant epithelial neoplasms that often arise from an urothelial or ductular origin rather than acinar because most canine tumors are androgen independent. This differs from humans because most prostatic carcinomas in men are highly androgen dependent. Most tumors of the canine prostate are carcinomas and the majority are adenocarcinomas. In a report of 14 dogs with prostate cancer, ten were diagnosed by histopathology as adenocarcinoma and four were undifferentiated carcinomas. Other tumor types that have been identified in the prostate include TCC, fibrosarcoma, leiomyosarcomas and hemangiosarcoma. Transitional cell carcinoma of the prostatic urethra frequently will invade the prostate and it may be difficult to distinguish primary TCC from secondary invasion of a urethral tumor.
Elderly dogs are more commonly diagnosed with prostatic TCC, with a median age at diagnosis of 10 years. Both intact and castrated dogs develop prostatic TCC although multiple studies have suggested there is an increased risk of prostatic carcinomas in castrated dogs compared to intact dogs with an odds ratio of approximately 2.3:4.3. The Shetland sheepdog and Scottish terrier are at increased risk of developing prostatic TCC. In a case control study in Scottish terriers, exposure to lawn herbicides and pesticides was compared between Scottish terriers with TCC and a control group. Transitional cell carcinoma risk was significantly higher in Scottish terriers that had been exposed to lawn herbicides and pesticides than in the Scottish terriers that were not exposed.2 The “inert” ingredients of the lawn chemicals were speculated to be the probable carcinogens. In the same study, dogs that ate vegetables at least three times a week along with their normal diet had a reduced risk of TCC.2 Carrots given as treats were the most frequently fed vegetable in the study.2 The female: male ratio of dogs with TCC has been reported to range from 1.7:1 to 2:1.2

Most canine prostatic TCCs are characterized by local invasion with a high propensity for regional and distant metastasis, and most dogs are diagnosed with advanced disease. The most common sites of metastasis are the regional lymph nodes, urinary bladder and lungs. Similar to high grade prostatic carcinomas in men, canine prostatic TCC has a tendency to metastasize to bone, predominately to the lumbar vertebrae and pelvis. In one study, 42% of dogs had evidence of bone metastasis. Younger dogs have been shown to be at an increased risk for metastasis to bone.2

Clinical signs in dogs with prostate TCC are variable and may be reflective of local and/or metastatic disease. Common clinical signs may include urinary tract signs (hematuria or stranguria), difficult or abnormal defecation (tenesmus or passage of flattened, ribbonlike stools), and a range of systemic signs of illness (lethargy, weight loss or inappetence) or lameness, pain and neurological deficits secondary to bone metastasis. Dogs may present with a history of clinical signs that partially improve with empiric therapy and then return once the therapy is discontinued. In a retrospective study of 76 dogs with prostatic carcinoma, clinical signs were referable to the urinary tract in 62%, tenesmus was noted in 30%, signs of skeletal involvement were seen in 36% and signs of systemic disease occurred in 42% of the dogs. If complete obstruction of urinary outflow results from prostatic compression or direct tumor extension into the urethra, hydroureter, hydronephrosis and renal failure may occur, which can present as an emergency.2

A systemic approach to the evaluation of dogs with suspected prostatic TCC is recommended to rule out other causes of prostatic disease such as benign prostatic hypertrophy, prostatitis, prostatic cysts or abscess and other neoplasias. Physical examination of the prostate gland is best achieved by a combination of rectal and abdominal palpation. The prostate on rectal palpation in dogs with prostatic TCC is typically large, firm, irregular, nodular, and/or asymmetric. A non-atrophic prostate felt on rectal examination in a neutered dog should be considered abnormal and may be compatible with prostatic neoplasia or other prostatic disease. Sublumbar lymphadenopathy may be detected on rectal palpation. Anemia, leukocytosis, hypercalcemia and elevated bone alkaline phosphatase activity may be apparent. Pyuria, bacteriuria and dysplastic urinary epithelial cells may be identified by urinalysis or urine culture. There is one report of a dog with prostatic carcinoma that had neoplastic cells in the peripheral circulation which is very rare.

Imaging should include evaluation of the prostate as well as the regional lymph nodes and lungs for evidence of regional and distant metastasis. Evidence of an enlarged prostate may be visible on abdominal radiographs and there may be evidence of mineralization within the prostate. Multifocal, irregularly shaped, parenchymal mineral densities are most commonly seen with prostatic carcinoma, but this change has also been identified in chronic prostatitis. Evidence of perosteal reactions on the lumbar vertebrae (typically the fourth through seventh lumbar vertebrae), femur or pelvic bones, or sublumbar or retroperitoneal lymphadenopathy may be noted on abdominal radiographs. Prostatic TCC that metastasizes to bone most commonly has an osteoproductive component but may also be osteolytic, osteoproducitve or mixed. Contrast studies such as retrograde urethrography may show irregularities in the prostatic urethra and contrast material that was refluxed may be found in the prostatic mass. However, presence of contrast medium reflux is not specific for prostatic neoplasia. Abdominal
ultrasonography can be useful to further evaluate the prostate, urethra, bladder, regional lymph nodes and cranial abdominal organs.

Obtaining tissue samples for histopathology analysis is considered the gold standard for diagnosis of canine prostatic TCC. Cytological evaluation of material from the prostate can be useful in the differentiation of neoplasia of the prostate from other prostatic diseases. In one report, TCC of the prostatic urethra in two dogs appeared cytologically similar to prostatic adenocarcinoma. Techniques that have been evaluated for the diagnosis of prostatic TCC include ejaculation, traumatic catheterization, prostatic massage, prostatic wash, ultrasound guided fine needle aspirate (FNA) cytology and prostatic biopsies. Cytological evaluation of samples by FNA may prove challenging as it can be difficult to differentiate dysplastic epithelial cells from neoplasia therefore obtaining tissue sample biopsies for histopathology is preferred. In one study, conflicting results between cytology and histopathology in prostatic neoplasia occurred in 20% of the cases. Risks of obtaining a histological diagnosis include hemorrhage, trauma to the urethra and tumor seeding. Histological grading of canine prostate carcinoma is not commonly performed as there is no evidence it provides useful prognostic information. A large study of 76 dogs with prostate carcinoma, including transitional cell carcinoma defined several histological sub-types of canine prostatic carcinomas, but did not find differences in survival time among the different morphological patterns.

Without treatment, the prognosis for dogs with prostatic TCC is poor. These tumors are highly metastatic and as noted previously, most dogs are diagnosed at advanced stages. Median survival times for dogs without therapy are often less than 30 days. In one study of 76 dogs, a median survival time of approximately 21 days was reported, with most dogs euthanized at the time of diagnosis due to quality of life concerns. If treatment is attempted, it is directed towards local disease control as well as control of regional and distant metastasis. Currently there is no standard of therapy for canine prostatic carcinoma, although treatment is largely considered palliative. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is often recommended as palliative therapy.

Therapeutic options for managing local disease include prostatectomy, radiation therapy and medical management. Surgery is generally considered to be a palliative procedure and the goals of surgery are to minimize clinical signs secondary to the primary tumor while maintaining normal urethral function. Prostatectomy should be considered for dogs with diffuse intra-capsular tumors or an intra-capsular tumor surrounded by normal prostatic tissue with no evidence of metastasis. Total prostatectomy has not been widely adopted for treating canine prostate carcinomas because it is associated with a high rate of postoperative morbidity, in particular urinary incontinence and because it is not clear that this surgical procedure will improve survival. In a prospective randomized study of 21 dogs, 10 dogs had a total prostatectomy (TP) and 11 dogs had subtotal intracapsular prostatectomy (SIP). Post-operative survival was longer for dogs in the SIP group than the TP group (mean 112 days vs. 20 days) and dogs in the SIP group had a decreased rate of postoperative complications. Two of the 11 dogs in the SIP group and seven dogs in the TP group were euthanized within two weeks of surgery due to severe urinary complications.

If the prostate tumor is causing urethral obstruction, palliative measures may be attempted to alleviate the obstruction. Placement of a cystostomy tube allows urinary diversion and bladder emptying, however due to the presence of the mass, stranguria and incontinence may persist. While cystostomy tubes are well tolerated, careful patient and owner selection are necessary. Owners should be informed of possible complications of cystostomy tube placement including ascending urinary tract infections and tumor dissemination. Palliative stenting of the urethra in the obstructed area is a reasonable alternative to cystostomy tubes. In one study, with eight dogs that had a urethral stent, the complication rate was low (only in two dogs), and the procedure immediately alleviated the obstruction in all dogs. Median survival time in this study was short, at 20 days. Treatment with effective adjunctive therapy such as cyclooxygenase (COX-2) inhibitors and earlier placement could make placement of cystostomy tubes or palliative urethral stents more beneficial to canine patients with prostatic TCC.

Photodynamic therapy (PDT) is a localized treatment reported in one dog for treating prostatic carcinoma. Following treatment, clinical signs of hematuria and a bloody preputial discharge resolved.
and the prostate remained stable in size for at least six months. A more recent study showed rapid local recurrence in a dog with prostatic carcinoma, despite intra-operative PDT after a partial prostatectomy, most likely due to insufficient light penetration. Challenges in delivering a homogenous dose may limit the utility of PDT in advanced canine prostatic carcinomas. Currently, PDT remains investigational and not widely available.

Although optimal dose and fractionation are unknown, radiation therapy may be useful in the palliation of clinical signs related to local prostatic neoplasia as well as to palliate painful skeletal metastases. In an early study of ten dogs treated with 20-30 Gy intraoperative orthovoltage radiation therapy, the prostate was radiated in nine dogs and affected regional lymph nodes were treated in three dogs. The median survival time of the nine treated dogs with prostatic carcinoma was 114 days. The results of radiation therapy have been disappointing and severe adverse effects have developed. It is clear that when radiating the urinary tract, prostate gland, and pelvic region, the total dose and dose per fraction must be carefully considered to avoid serious complications. Complications of radiation therapy to the pelvic region have been described in a total of 66 dogs in two studies. A high rate (30-50%) of complications were reported and included chronic colitis, gastrointestinal stricture or perforation, necrotic drainage/ulceration in the skin and subcutaneous tissues within the radiation field, urinary bladder thickening, chronic cystitis, urethral stricture, ileosacral osteosarcoma and perianal pain. While many of these side effects did not affect survival, they did affect patient quality of life and owner expense.

The benefit of systemic therapy to manage canine prostatic carcinomas, especially TCC, is unclear. Recently, there has been interest in the anti-cancer effect of NSAIDs for a variety of prostatic carcinomas. The precise mechanisms involved in tumor response to NSAIDs, especially carcinomas are not clearly defined, but are likely multi-factorial and may involve COX-2 inhibition and consequent inhibition of angiogenesis, stimulation of apoptosis, alterations in immune function and other mechanisms. It was demonstrated in one study that there was a clear survival benefit in dogs with prostate carcinomas treated with a NSAID such as piroxicam or carprofen compared to those left untreated (6.9 months vs. 0.7 months). Other palliative treatment options that may benefit canine patients with skeletal metastasis include bisphosphonates. Bisphosphates are osteoclast inhibitors that are an integral part of the management of skeletal metastasis in men with prostate carcinomas and appear to have similar benefits in dogs with skeletal metastasis.

**Transitional cell carcinoma of the ductus deferens**

Diseases of the ductus deferens (DD) in dogs have rarely been reported in the veterinary literature. Transitional cell carcinoma of the DD has been reported in one dog. This dog was a neutered male with a one year history of recurring urinary tract infections. Although no gross hematuria was reported, the dog had stranguria, which resolved upon treatment with NSAIDs and appropriate antimicrobials based on the multiple urine cultures and antibiotic sensitivity tests. The stranguria would reoccur within days after discontinuation of treatment. On rectal examination, a firm, slightly prominent symmetric prostate was palpated with no signs of pain. Abdominal ultrasonography revealed a normal sized prostate with irregular margins. The prostate also had numerous mineralized foci. A tubular structure that was 4 cm long and 1 cm in diameter was also identified between the bladder and the colon. Although the origin of this structure was not clearly identified with abdominal ultrasonography, the distal part of the structure appeared to be connected to the prostate. It was found on exploratory laparotomy that the right DD was dilated and fluid-filled and extended caudally into the prostate parenchyma. Dilation of the DD of the canine patient is not commonly reported in the veterinary literature. In the one reported canine patient, the dilated DD appeared as a fluid-filled structure dorsal to the bladder. If distention or dilation of the DD is observed, an underlying prostatic disease should be suspected.

Histologically, the right DD from this dog had an irregular lumen, with irregular, disorganized transitional epithelium with extension into adjacent smooth muscle. The DD is normally lined by pseudostratified columnar epithelium, whereas transitional epithelium lines the bladder and the prostatic urethra. Therefore, TCC could not be a primary tumor of the DD. It is possible in this case, that local proliferation of prostatic TCC led to tumor invasion of the DD, considering that there is continuity.
between the prostatic urethra and the epithelium of the ductus deferens. It could also be speculated that TCC was seeded in the DD via urine. At the time of straining, because of the increased pressure in the prostatic urethra, urine could have been pushed into the DD.

Eight months after diagnosis of TCC in the right DD, the dog had urinary incontinence and developed severe hindlimb lameness. Euthanasia was elected because the dog was no longer responding to palliative therapy with NSAIDs and antimicrobials, and because metastasis to bone was suspected. Because normal DD is rarely seen during abdominal ultrasound in dogs, identification of a tubular, fluid-filled structure dorsal to the bladder may indicate an abnormal DD. Transitional cell carcinoma of the DD should be included in the differential diagnosis of affected patients with clinical signs of the reproductive and urinary tracts.

Vaginal and vulvar transitional cell carcinoma

Vaginal and vulvar tumors account for 2 to 3% of all canine tumors. In a study of 2,917 tumor bearing dogs, 56 (2%) had tumors of the vagina and/or vulva. These usually occur in middle aged to older intact female dogs. The majority of the tumors at this site are benign. In a survey of a total of 3,073 tumor bearing female dogs there were 85 (2.8%) dogs with tumors of the vagina or vulva with the majority (78%) of the tumors diagnosed as leiomyoma. Leiomyomas are benign tumors of smooth muscle origin. In a review of 99 dogs with vulvar or vaginal tumors there were 72 benign and 27 malignant tumors. The malignant tumors included TCC, leiomyosarcomas, mast cell tumors and squamous cell carcinoma. Transitional cell carcinomas arising from the bladder or urethra may manifest as a vaginal mass. They can manifest near the urethral papilla and/or may develop on the labia of the vulva. Presence of a mass protruding from the vulva is the most common clinical sign of vaginal and vulvar TCC, although vaginal bleeding or discharge is often noted. Other clinical signs may include perineal swelling, stranguria, hematuria, excessive vulvar licking and dystocia.

Evaluation of a suspected vaginal mass should include vaginal and rectal palpation and evaluation of the stage of the estrous cycle (vaginal cytology and serum progesterone level). A presumptive diagnosis of vaginal and vulvar neoplasia may be made based on patient signalment and tumor location, although definitive diagnosis requires histopathology. Vaginoscopic examination and vaginal cytology are often the first steps performed in evaluation of vaginal and vulvar tumors. Retrograde vaginography or urethrocytography may also be used to help delineate the extent of the mass. For some tumor types including vaginal or vulvar TCC, cytology of the tumor may be diagnostic; alternatively, incisional biopsy may be performed. Additional diagnostics such as abdominal ultrasound and thoracic radiographs to assess for regional and pulmonary metastasis should be performed.

Surgical excision is the treatment of choice for vaginal and vulvar TCC. The majority of vaginal tumors, including TCC can be easily resected by episiotomy and local resection, but some more invasive tumors may require a more aggressive resection. A combination of vulvovaginectomy and perineal urethrostomy allows resection of more extensive vaginal and/or vulvar tumors. These surgical techniques allow resection of the distal urethra if necessary and dogs maintain urinary continence. Chemotherapy is warranted in the management of metastatic vaginal and/or vulvar TCC, incompletely excised or inoperable tumors of the vagina or vulva. The goal of chemotherapy would be to delay or prevent the onset of metastatic disease and try to temporarily decrease the size of the tumor. Radiation therapy can be used as a palliative treatment option and may help decrease discomfort associated with the mass. The prognosis for vaginal and/or vulvar TCC must be considered poor due to high rates of local recurrence and metastasis.

Conclusion

The actual incidence of TCC of the reproductive tract in dogs is rare. Most TCCs of the canine reproductive tract involve the prostate. Canine prostatic carcinomas including TCC, have served as an important model for studying human prostatic disease. The canine prostate gland and the human prostate have many morphological and functional similarities. The dog is also one of the few domestic species to develop spontaneous prostate neoplasia, resulting in the substantial interest of the dog as a model for
prostatic carcinoma in men.\textsuperscript{3} Human prostatic neoplasia is the second most frequently diagnosed cancer and the sixth most common fatal cancer among men worldwide and its incidence is climbing.\textsuperscript{2} This increase appears to be due to a combination of lifestyle and environmental factors as well as heightened public awareness. However, the incidence of prostate carcinoma is much lower in dogs.\textsuperscript{3} Using the dog as a model for human prostate cancer presents the important challenge that most early stage prostate carcinomas in men are highly androgen dependent.\textsuperscript{3} Unlike humans, dogs with prostate carcinoma usually present with advanced disease that does not respond to androgen deprivation therapy.\textsuperscript{2} High grade prostate cancer in men behaves similarly to the disease in dogs, with significant local invasion and the tendency to metastasize.\textsuperscript{3} Comparable to humans, affected dogs often develop osteoblastic bone metastasis in the pelvis and/or lumbar spine and present with associated pain or neurological deficits.\textsuperscript{3} Other clinical signs such as weight loss, lethargy, abnormal urination and/or defecation are also similar among humans and canines.

It is apparent that better methods of early detection and more effective therapies including palliative options are needed for prostatic cancer, including TCC in dogs and advanced prostate carcinoma in men.\textsuperscript{3} Dogs with prostate neoplasia are relevant models for the disease in humans and pre-clinical studies of new diagnostics and therapies in dogs may benefit both humans and dogs with prostate neoplasia.\textsuperscript{3} It has been shown that it would appear appropriate to limit exposure to lawn chemicals especially in breeds with high risk for TCC.\textsuperscript{2} The owners of high risk breeds, such as the Shetland sheepdog and Scottish terrier should be informed of the TCC risk and be encouraged to take note of urinary tract signs if they should occur.\textsuperscript{2}

References