THESIS

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Canine Prostate Specific Esterase as a marker to differentiate hyperplastic prostate gland vs prostatic adenocarcinoma

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1.0 LIST OF ABBREVATIONS

ACA: Prostatic adenocarcinoma

BPH: Benign prostatic hyperplasia

BW: Body weight

COX: Cyclooxygenase

CPSE: Canine prostate-specific arginine esterase

CT: Computed tomography

DNA: Deoxyribonucleic acid

DHT: Dihydrotestosterone

ELISA: Enzyme-linked immunosorbent assay

EU: European Union

FNA: Fine Needle Aspirate

FSH: Follicle stimulating hormone

Ggl: Ganglion

GS: Google Scholar

IM: Intramuscular

IV: Intravenous

KLK-3: Kallikrein-3

LH: Luteinising hormone

NSAIDS: Non-steroidal anti-inflammatory drugs

SID: Semil in die (once daily)

PSA: Prostate-specific antigen

RBC`s: Red blood cells

SC: Subcutan

TCC: Transitional cell carcinoma

UL: Ultrasnography

VI: Norwegian Veterinary Institute

2.0 INTRODUCTION

Diseases of the prostate gland is frequently encountered in small animal practice. The canine prostate gland is continuously growing and developing under androgenic influence throughout the life of the male. Testosterone is converted to dihydrotestosterone by the enzyme 5 alpha reductase in the testicles, and this hormone is active at cellular level. Particularly benign prostatic disease is by far the most common complaint in intact canine patients. The condition is frequently associated with prostatitis and cysts development. On the contrary, prostatic carcinoma is a less common condition, however a significant risk has been detected in castrated males.

Clinical signs of the various prostatic diseases range from milder signs and discomfort to very painful or life-threatening conditions. Diagnosis can be difficult to achieve if only based on anamnesis, as the clinical signs of different prostatic diseases often overlap. Several diagnostic methods aim to differentiate between the diseases, as the treatment and prognosis vary greatly amongst the diseases. In humans, serum markers have been identified for early recognition of subclinical cases to screen for prostatic diseases. Effort has been put into investigating for such serum markers in dogs as well. Recently, an ELISA assay that are able to detect elevated serum CPSE concentrations in dogs with prostatic disease are developed.

Diseases associated with excessive hormone levels like BPH, squamous metaplasia and cystic hyperplasia has a good prognosis and are typically treated by castration. Paraprostatic cysts and abscesses require surgery to drain and remove the cysts, while bacterial infections causing prostatitis require prolonged antibiotic therapy. On the contrary, prostatic carcinoma has a poor prognosis and treatment is not feasible in most cases. Prostatic carcinoma frequently give metastasis at an early stage to surrounding structures, and in most cases, the cancer has already metastasised at time of diagnosis.

This thesis is therefore looking into whether the CPSE test can be used to differentiate BPH and prostatic carcinoma in canine patients.

3.0 ANATOMY OF THE PROSTATE GLAND

The prostate gland, the only male accessory gland in dogs, is a bilobular mobile structure located in the pelvic cavity of adult male dogs. The gland is bordered by the rectum dorsally, the pubic symphysis ventrally, the bladder cranially and the abdominal wall laterally. However, the position of the gland varies according to age and size and in response to hormone production. Thus, the gland will change its position from pelvic cavity to caudal portion of the abdominal cavity as the dog mature and the gland increase in size (Leis-Filho et.al., 2018).

The prostate gland is grey in colour, surrounded by a fibromuscular capsule. The normal prostate is smooth, firm and elastic. A median sulcus divides the oval organ into two halves, a palpable right and left lobe. Each of the two lobes are subdivided into a network of trabeculae composed of tubuloalveolar glands, in which ducts enters and secrete seminal plasma. The prostate encloses almost the entire proximal urethra and comprise openings from prostatic glandular ducts, near deferent ducts around the colliculus seminalis. The vas deferens enters the prostate craniodorsally, traversing its parenchyme and exiting in the urethra by the colliculus seminalis (Evans et. al., 2013; Khadidj, 2017; Leis-Filho et.al., 2018).

Vascular supply is provided by prostatic artery from the internal pudendal artery that branches of the internal iliac artery. Sympathetic innervation is ensured by the hypogastric nerve originating from the caudal mesenteric ggl., which is responsible for contraction of the gland and ejection of the prostatic fluid during ejaculation. Parasympathetic innervation by the pelvic nerve stimulate the secretion of prostatic fluid (Khadidj, 2017).

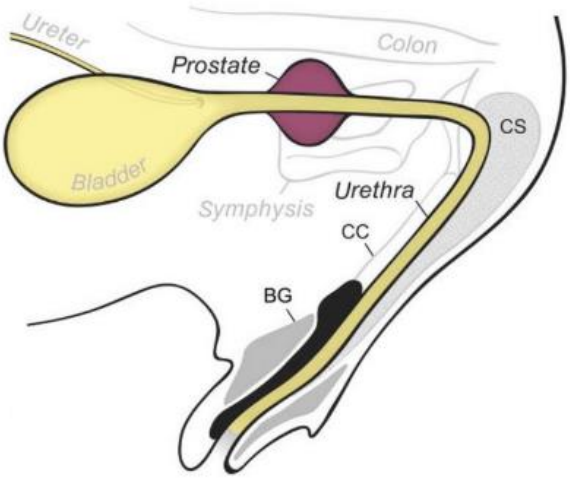

Figure 1. A illustration of the normal anatomy of the canine prostate gland (Penninck and d`Anjou, 2015).

4.0 PHYSIOLOGY OF THE PROSTATE GLAND

The main function of the prostate gland is the production of seminal plasma, accounting for 97% of the ejaculate volume. The prostatic fluid facilitates sperm survival and serve as an ideal environment for the transport. The components of the prostatic fluid of basic pH, compensates for the acidity of the vaginal secretion. The prostate also has a mechanical role preventing the passage or urine during ejaculation. During the protrusion of the penis, the prostate closes the urethra and prevents retrograde ejaculation into the urinary bladder by the aid of a sphincter (Cunto et. al., 2019; Khadidja and Adel, 2017).

The growth of the prostate commences when the male reach puberty and is continuous under the influence of sex hormones and growth factors. Theoretically, the growth of the prostate can be divided into three phases. A normal growth in the young non-sexually mature male, a continuous hyperplasia during the adult life that commences under the influence of androgen production and involution of the prostate in the senior male dog (O`Shea, 1962).

The production of prostatic secretions is ensured by hormone production, in which testosterone penetrates prostate cells by diffusion and is metabolised into other steroids by enzymes. Most of the testosterone is converted into DHT by 5α-reductase, because DHT binds and activates cytoplasmic receptors for androgens with greater affinity than testosterone. Another hormone involved in prostate development is 17β-estradiol, which is synthesized by aromatase and works in synergy with androgens. More recent studies show that 17β-estradiol increases the expression of nuclear receptors for DHT, thus increasing the sensitivity of the prostate to androgens (Cunto et. al., 2019).

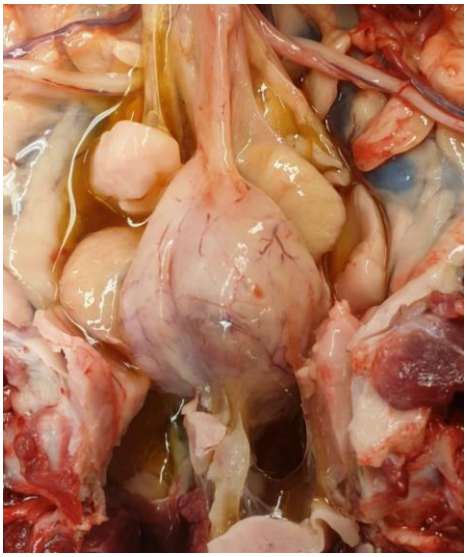

Figure 2. The picture shows a healthy-looking prostate gland of a senior English setter dog. The picture was taken during an autopsy where I participated during my lab practice at VI.

5.0 COMMON PROSTATIC DISEASES

Diseases of the prostate gland is common in the intact middle to older age male dog. BPH is the most common pathological process, frequently associated with prostatic cysts and prostatitis. Malignant neoplastic processes are fortunately less common.

Nevertheless, it is not uncommon for the canine prostate to be affected by multiple and even co-existing pathological diseases. The hyperplastic prostate may be predisposed to inflammation and infection by providing a suitable medium for bacterial growth or interfere with the normal defence mechanisms in the prostate. Thus, the presence of BPH, cysts, neoplasia or squamous metaplasia may predispose to prostatic infection (England, 2010; Johnston et al, 2000; Kutzler & Yeager, 2005; Leis-Filho, 2018; Paclikova., 2006; Pinheiro et. al., 2017).

5.1 Benign prostate hyperplasia (BPH)

The prostate is continuously developing and growing under the influence of androgens throughout the life of the intact male. The enlargement of the prostate is a spontaneous disease and part of the ageing process in the intact male dog. The enlargement, termed prostatomegaly or benign prostate hyperplasia (BPH), is a non-cancerous increase of the prostate. The enlargement includes both an increase in cell number (hyperplasia) and increase in cell size (hypertrophy) and thus an enlarged prostate gland (Christensen/Leis-Filho/Smith).

Nevertheless, the definition of BPH differ among studies. Barsanti & Finco (1986) propose that the dog has developed BPH as soon as hyperplastic histological changes can be detected. Other studies claim BPH is a natural process developing as the male ages and is regarded a pathological process only when the male develops clinical signs or predispose to other prostatic diseases (Lai et al., 2008/Smith).

Although the pathogenesis has not been fully unresolved, androgens are considered essential for the maintenance of BPH as the condition regress following castration. It is known that alteration of the oestrogen and testosterone ratio produced in the testis initiate the process. Testosterone production in the testis are converted into its active metabolite dihydrotestosterone (DHT), by the enzyme 5α-reductase in prostatic epithelial cells. DHT is the androgen active at the cellular level of the prostate gland, thus directly responsible for the growth, development and secretions by stromal and glandular components in the prostate. Although, testosterone and DHT bind to the same androgen receptors in prostate epithelial

cells and elicit the same effects, the binding of DHT is much tighter and of longer duration compared to testosterone (Christensen, 2018; Johnston, 2000; Leis-Filho, 2018; Parry et. al., 2007; Pinheiro et. al., 2017; Smith et. al., 2008).

The enlargement of the prostate gland tends to be uniform through the two lobes causing increased vascularity, resulting in vascular leakage or haemorrhages into the gland. The enlargement and swelling of the prostate causes pressure on the ducts in the gland, thus leading to cyst formation. A predisposition of cyst development and prostatitis is highly associated with BPH in intact males (Christensen, 2018).

BPH is common in intact males and although BPH may be present as early as 1-year old males, the condition is correlated with increasing age of the male (Christensen, 2018). According to (Johnston 2000) BPH is observed in 80% of intact male dogs above 5 years and affect more than 95% of the intact male dog population above 9 years old (Smith). Studies also suggest a breed predisposition to development of BPH in certain breeds of dog. Scottish terrier tends to have larger prostate compared to other breeds and may explain why this breed in larger scale develop clinical signs of BPH (Sirinarumitr, 2009). Wolf et al.(2012) observed increased prevalence of the development of BPH in Rhodesian Ridgebacks, indicating a genetic predisposition in this breed.

5.2 Prostatic cysts

Prostatic cysts are thin walled fluid filled cavities grouped into intraprostatic cysts developing in the prostatic parenchyme and paraprostatic cysts developing adjacent to the prostatic parenchyme. The cysts can range from few millimetres to several centimeters in size, especially the paraprostatic cyst can become extremely large, and can in some cases be palpated transabdominally. Prostatic cysts are most commonly seen in older intact large-breed male dogs, with average age of diagnosis at 8 years old (England. et. al., 2010).

The pathogenesis is unknown, but paraprostatic cysts are thought to result from embryonic remnants of the female reproductive tract, the Mullerian ducts. Opposed to intraprostatic cysts which are associated with androgen-dependent BPH. The increased prostatic secretions associated with hypertrophy and hyperplasia of the glandular epithelium exert a greater pressure on the excretory ducts, resulting in dilated acini which merges and subsequently causes cyst formation. If the cysts become infected, abscess formation may be a consequence (England et. al., 2010; Foster, 2012; Smith, 2008).

5.3 prostatitis

Prostatitis is a relatively common disease of all ages of intact males, and seldom seen in castrated males unless a recent history of castration is presented. Prostatitis can be acute, thus associated with systemic and local clinical signs or chronic as a secondary event by the development of BPH. Chronic prostatitis is more common compared to acute prostatitis, probably because of BPH as a possible precursor, is a common prostatic disease of intact male dogs. Prostatic cysts neoplasia or squamous metaplasia are other possible precursors to prostatitis (England, 2010; Foster, 2012).

The infection commonly arises from ascending infection from the prepuce and urethra but can also arise from the bladder secondary to cystitis or by haematogenous spread in the event of *Brucella canis* infection. Though, *Brucella canis* is more commonly associated with epididymal and testicular infection. When the bacteria are present within the prostate, a rapid growth occurs in the lumen of the ducts. The bacteria elicit an inflammatory response itself or through the production of endotoxins and exotoxins. The most common bacteria to cause prostatitis is E-coli, but other bacteria like *Klebiella, Pseudomonas, Pasteurella, Streptococcus, Staphylococcus, Proteus mirabilis, Enterobacter, Haemophilus, Mycoplasma, Ureaplasma* can also be involved. Fungal infections by *Blastomyces dermatitidis, Cryptococcus Neoformans or Coccidiosis immitis* are rare. Because prostatic fluid normally refluxes into the bladder, cystitis often accompanies prostatic infection (England, 2010; Foster, 2012; Johnston et. al., 2000).

5.4 Squamous prostatic metaplasia

Squamous prostatic metaplasia is caused by continuous stimulation of prostatic epithelial cells to oestrogen, causing differentiation of the prostatic epithelium, forming filaments of keratins in the lumen. The most common cause is of endogenous origin caused by a functional sertoli cell tumour in the testicles producing excess oestrogen. However, excessive oestrogen stimulation caused by exogenous oestrogen for BPH therapy is also a possibility. The squamous metaplastic epithelial cells cause a secondary excretory duct obstruction accompanied by secretory stasis and an opportunity for intraprostatic cyst development (Leis-filho et. al., 2018).

5.5 Neoplastic conditions of the prostate

Neoplasia of the prostate gland in dogs are fortunately relative uncommon. Necropsy studies demonstrate a low prevalence from 0.2% to 0.6%. Regardless of the low prevalence reported, the dog is one of the few domestic species to develop spontaneous prostate cancer, and the most common prostate disease diagnosed in castrated dogs (Bell et. al., 1995; Cornell et. al., 2000; Durham and Dietze, 1986; Teske et. al., 2002

Prostatic tumour can originate in the gland itself, primary prostate tumour, or tumours from other organs may have metastasised to the prostate. The most common cancer of the prostate is carcinomas, and the majority are adenocarcinoma (ACA). The development of prostate tumour is thought to arise from a urothelial or ductular origin rather than acinar because most tumours are androgen independent. This may explain why adenocarcinoma has been reported to occur more commonly in castrated dogs compared to intact male dogs, with an odds ratio approximately 2.3:4.3. The exact reason for the increased incidence of prostatic neoplasia in castrated dogs are not known, but hypotheses include a loss of protective effects of androgens (Bell et. al., 1995; Bryan et. al., 2007; Christensen et. al., 2018; Lai et. al., 2009; Leav et. al., 2001; Leroy et. al., 2004; LeRoy et. al., 2009; Sorenmo et. al., 2003; Teske et. al., 2002).

Other prostatic tumour types include fibrosarcoma, leiomyomasarcoma, transitional cell carcinoma (TCC) and squamous cell carcinoma. TCC originates from the transitional epithelium extending from the bladder into the prostate or from the uroepithelium of the prostatic urethra (Smith, 2008).

The aetiology behind the development of prostate tumour is not known, and it is possible that both genetic and environmental factors contribute to the tumour development. Studies has demonstrated a statistically significant increase of prostatic cancer in Bouvier des Flandres, Dobermann Pinschers, Shetland sheepdogs, Scottish terriers, beagles, miniature poodle, German shorthaired pointers, Airedale terriers and Norwegian elkhounds. Thus, suggesting a predisposition in certain breeds of dogs. Furthermore, medium and large breeds as well as middle aged to elderly dogs are particularly at risk. An environmental influence may also play a significant role in tumour development, as mixed breed dogs have also been reported as at increased risk for prostate carcinoma, regardless of neutering status (Bell et al. 1991; Bryan et. al., 2007; Teske et al. 2002).

Opposed to most prostatic cancers in men which is often benign and grows at a slow rate, prostatic neoplasia in the canine prostate is characterised by malignancy, local invasion and high tendency for regional and distant metastasis. Carcinomas tends to metastasise through the external and internal iliac lymph nodes as well as to the lungs. In a retrospective post-mortem study by Cornell et. al. 2000, 80% of the dogs with prostatic carcinoma had evidence of measurable metastatic disease. The predilection sites of metastasis were lymph nodes and lung tissue. Local invasion to the vertebral bodies and pelvis, the musculature of colon and pelvis, and urethra are also seen due to direct extension of the tumours. Several studies show a high tendency of prostatic carcinomas to metastasise to bone in up to 42% in dogs, and predominantly to the lumbar vertebrae and pelvis (Christensen et. al., 2018; Cooley et. al., 1998; Cornell et. al., 2000; Durham and Dietze, 1986; Leav et. al., 2001).
Although there are apparent similarities in prostatic carcinoma between humans and dogs, important differences also exist. Prostatic carcinoma in men is often diagnosed at a early stage due to awareness raised and effective diagnostic screening tests (PSA test), and depends on androgens as growth factors. Androgen deprivation is a foundation therapy for human with prostate cancer and they usually respond rapidly and favourably. Most prostatic neoplasia in male humans is benign and slow growing opposed to prostatic neoplasia in dogs. Prostatic neoplasia in dogs tends to be highly aggressive and metastasise at a early stage. Canine prostatic neoplasia is not androgen dependent and is more commonly diagnosed in castrated males compared to intact males. Reasons for the increased incidence of prostatic neoplasia in castrated dogs are unknown, but hypotheses include a loss of protective effects of androgens (Christensen et. al., 2018)

Studies indicate that more aggressive tumours may develop in castrated males with a higher risk of metastasis. This finding does not necessarily mean that neutering causes the cancer. The interval between castration and onset of prostatic problems was highly variable, suggesting that castration does not initiate the development of prostatic cancer in the dog, but it may facilitate tumour progression. It is possible that androgens provide a protective effect on prostatic tissue or that the relative oestrogen effect aid in neoplastic transformation. On the contrary, Bryan et al found an increased risk of adenocarcinoma in intact males. Thus, further studies are required to definitively determine the role of androgens and the impact of early or late castration (Bell et. al., 1991; Teske et. al., 2002; Leroy et. al., 2009; Shidaifat et. al., 2004).

6.0 CLINICAL SIGNS

Clinical signs of prostatic diseases are often non-specific and frequently overlap, and thus cannot be differentiated solely by the anamnesis. At least at their onset, there are no pathognomic clinical signs, and most prostatic disorders often go unnoticed in the general dog population. The situation is a bit different in breeding males, because the owner may seek a veterinarian due to fertility disorders (Alonge et. al., 2017).

The symptoms may appear suddenly as for acute prostatitis and abscesses or progressively which is often observed in case of hyperplasia or neoplasms. In many cases, the dog may not exhibit clinical signs until significant enlargement of the prostate gland, hence the size is great enough to compress surrounding structures. The canine prostate gland expands in an outward fashion compared to the inward nodular growth in human that easily compresses the urethra (Alonge et. al., 2018; Johnston, 2000; Leis-Filho et. al., 2018; Smith et. al., 2008; Pinheiro et. al., 2017).

Due to the compression of the surrounding structures, clinical signs are often of digestive or urogenital order. The compression of rectum may lead to disturbance in faecal flow resulting in altered shape of the faeces to a characteristic flat-like appearance, as well as constipation, tenesmus and difficulty with defecation. Nevertheless, if the enlarged prostate moves cranially into the abdomen, no digestive clinical signs may be seen (Alonge et. al., 2018; Johnston, 2000; Leis-Filho et. al., 2018; Smith et. al., 2008; Pinheiro et. al., 2017).

Clinical signs of urogenital origin include haematuria, stranguria, serosanguineous urethral discharge not associated with urination, haemospermia, poor semen quality and infertility. Paraprostatic cysts developing outside the prostate gland can also compress on the surrounding structures or even displace the bladder and abdominal organs depending on its size (Alonge et. al., 2018; Johnston, 2000; Leis-Filho et. al., 2018; Smith et. al., 2008; Pinheiro et. al., 2017).

In case of infectious conditions, and especially acute prostatitis, clinical signs may well exhibit systemically. Thus, signs like depression, fever, anorexia, emesis, and in severe cases septic shock may be seen. Locomotor symptoms as stiffness, lameness, paresis and oedema of the legs can sometimes be seen due to local compression related to the prostatomegaly or caused by the presence of local metastasis (Johnston et. al., 2000; Leis-Filho et. al., 2018; Smith et. al., 2008).

Although the clinical signs of neoplastic conditions often mimic symptoms of other prostatic diseases, an enlarged, firm, asymmetric and painful prostate gland in combination with lameness or neurological clinical signs of the hindlimbs can strongly suggest prostatic tumour. Especially in castrated individuals (Durham and Dietze, 1986; Przadka et. al., 2019).

Squamous metaplasia can have many of the same clinical signs as the other prostatic diseases with altered urination and defecation. However, some clinical signs are more peculiar and are caused by the excess oestrogen stimulation of the cells resulting in hyperoestrogenism. The signs include attractiveness to males, gynecomastia, symmetrical alopecia, hyperpigmentation and a pendulous prepuce (Leis-filho et. al., 2018).

7.0 DIAGNOSIS

A correct diagnosis is extremely important in order to differentiate non-neoplastic prostatic diseases from neoplastic conditions. Neoplasia of the prostate gland carry a poor prognosis with unfavourable treatment options. However, the diagnosis of prostatic tumours can be difficult, and frequently at the time of diagnosis, the tumour has already metastasised due to its aggressive nature (Cooley et. al., 1998; Cornell et. al., 2000; Leav et. al., 2001; Przadka et. a., 2019).

The majority of the prostatic diseases causes prostatomegaly, therefore a thorough anamnesis with focus on defecation and urination habits is relevant. Nevertheless, as discussed in chapter 6 about clinical signs, the clinical presentation of the various prostate conditions is very similar and cannot in most cases be differentiated solely by anamnesis. The evaluation of size, position, symmetry and pain of the prostate is a central part of the clinical examination. Clinical evaluation of the prostate with rectal palpation and US can in many cases allow a presumptive diagnosis, but the sensitivity would not be optimal. Further diagnostic methods may be necessary and include haematology and urinalysis, CPSE analysis in serum, radiography, FNA and biopsy depending on the case (Smith et. al., 2008; Paclikova et. al., 2012).

Clinical evaluation of the prostate with rectal palpation and US can in many cases allow a presumptive diagnosis, but the sensitivity would not be optimal. Other methods should then be carried out, such as the prostatic massage and/or the invasive FNA and biopsy (Pinheiro et. al., 2018).

7.1 Clinical examination

A clinical examination should always include a digital transrectal palpation of the prostate gland. Transrectal palpation is a cheap and non-invasive first step that gives a good subjective idea of the size and appearance of the prostate gland. In some dogs with advanced prostatomegaly, the prostate may fall cranially into the abdomen, and thus cannot be palpated transrectally. In this case, a supporting hand under the caudal abdomen will push the prostate caudoventrally into its place in the pelvic cavity, hence reachable for transrectal palpation. The caudate pole and most of the dorsal part of the prostate can often be reached by one finger in the rectum. Paraprostatic cysts may grow extremely large and can often be palpable transabdominal (Christensen et. al., 2018; Smith, 2008).

The size of the canine prostate gland depends on the breed and size of the dog. A normal prostate is physiologically the size of a walnut in a medium sized dog. The surface should be smooth and bilateral symmetric with a firm, but smooth consistency and indolent upon palpation (Paclikova et. al., 2012; Christensen et. al., 2018). On the contrary, a normal sized prostate in castrated males are regarded as abnormal, even if the gland is symmetric and the palpation is indolent. Squamous metaplasia of the prostate can develop as a consequence of BPH treatment due to hyperoestrogenism. Neoplastic conditions are also more frequent in the castrated males.

A study by Mukaratirwa et. al., (2007) showed that nearly all the dogs (92.6%) that presented with prostatomegaly were indolent upon palpation of the prostate. Although rectal palpation gives high specificity (75%) and is positively correlated with prostate disease (87%), the sensitivity is low (34%) and the negative correlation for disease is 34%. This indicates that rectal palpation of the prostate gland is not accurate for diagnosis alone (Mukaratirwa et. al., 2007).

7.2 Haematology & urinalysis

Haematology and serum chemistry may reveal anaemia, leucocytosis, hypercalcaemia, elevated bone alkaline phosphatase activity or signs of concurrent disease. A culture and

urinalysis may demonstrate pyuria, bacteriuria, dysplastic urinary epithelial cells or secondary bacterial urinary infections (Durham and Dietze, 1986).

7.3 Examination of prostatic fluid & semen

Most of the prostatic diseases are initially asymptomatic until the prostate gland become large enough to compress surrounding structures. Nevertheless, owners of intact breeding males may seek a veterinarian at an earlier stage in the disease process due to fertility problems. Dogs suffering with prostatic diseases may show subfertility, often accompanied by adverse colour and cell number in the ejaculate (Christensen et. al., 2018).

Prostatic fluid evaluation is a highly diagnostic method for prostatic diseases. Prostatic fluid for cytology examination and bacteria culture can be obtained by collection and fractionation of the ejaculate or by prostatic massage and aspiration. The prostatic massage is initiated after the bladder is emptied and flushed with saline. A large polyethylene catheter is inserted into the emptied bladder, and with a gloved finger placed in the rectum, the prostate is gently massaged. A few millilitres of saline water are injected through the catheter and aspirated back into the syringe to obtain prostatic fluid. However, collecting and fractionate ejaculate may give a larger volume of sample with greater concentration of potential diagnostic substance. Most intact males can be stimulated manually to ejaculate, especially with a teaser bitch present, unless the male suffer from a painful prostatic disease (Christensen et. al., 2018; England et. al., 2010; Kutzler, 2005).

For collecting the ejaculate, a sterile centrifuge tube or an artificial vagina with a sterile plastic reservoir attached, can be used. The canine ejaculate consists of three fractions. The 1st and 3rd fractions contain clear prostatic fluid, in which the 3rd fraction comprise greatest volume. The 2nd fraction is the sperm-rich fraction from the epididymis and should have a milk-white colour. The prostate is the only secretory tissue in the male`s reproductive tract, thus any fraction of the ejaculate can be used to assess prostatic fluid cytology. Nevertheless, the 1st and 3rd fraction does not contain fluid from other portions of the reproductive tract, and collection of this fraction may therefore allow better localisation of disease processes. By changing the collection device between each subsequent stage of ejaculation, the sperm-rich fraction can be separated from the prostatic fluid. A macroscopic examination can detect any colour changes from normal, for example a red tint may indicate RBC`s in the ejaculate (Christensen et. al., 2018; England et. al., 2010; Kustritz, 2006; Kutzler, 2005).

Figure 3. Semen collection in a dog using disposable semen collection cone and sterile centrifuge tube for collecting the ejaculate (Kutzler, 2005).

The collected fluid is centrifuged at 1000xg for 10 minutes, and the pellet in the bottom of the tube can be used for both cytology and bacterial culture. The cytology sampled is gently rolled onto a microscope slide, dried and stained with Diff-Quick. In a normal healthy dog, the cytology comprise parabasal epithelial cells with low numbers of RBC`s and neutrophils, classically <5 RBC`s or polymorphonuclear neutrophils per high-power field. In case of BPH, a dramatic increase of RBC`s with >20 per high-power field and increased number of prostatic epithelial cells can be seen (Christens et. al., 2018).

Cytology often reveals a marked inflammatory response with bacteria, in dogs suffering from prostatitis. Especially the third fraction may contain a high number of RBC`s and be tinged red in case of BPH and prostatitis. In chronic prostatitis, macrophages, plasma cells and lymphocytes are also commonly seen. The prostatic fluid shows large numbers of neutrophils, often with degenerative changes and intracellular bacteria. However, lack of neutrophils in the third fraction does not necessarily rule out prostatitis, because the neutrophils may be in another part of the prostate not communicating with the secretory ducts. Interpretation of cytology may be complicated if a concurrent urinary bladder infection is present. In these cases, pre-treating with ampicillin IV for 24 hours prior collection, will concentrate in the urinary bladder but not penetrate the prostate (Christensen et. al., 2018; England et. al., 2010; Kustritz, 2006).

The prostatic fluid should be cultured for both aerobe and anaerobe bacteria to exclude prostatitis. The most common bacteria associated with prostatitis is *Escheria coli*, although

bacteria ascending from the urethra may also cause prostatitis. Fungal infection is rare and associated with a systemic infection If the culture is negative, the prostate is more likely to be diseased with BPH. Semen collection may reveal increased DNA fragmentation of spermatozoa as well as increased number of primary morphologically defects (Christensen et. al., 2018; England et. al., 2010).

7.4 CPSE

The main function of the prostate gland is the production of seminal plasma contributing to the ejaculate. The secretions contain high concentrations of proteins synthesised by the prostate epithelial cells. The identification of specific and novel secretory proteins has led to the generation of biomarkers for diagnosis and prognosis of prostate function and disease (Christensen et. al., 2017).

In humans, a protein called prostate-specific antigen (PSA) produced by prostatic epithelial cells, is widely studied and used as a serum marker to diagnose prostatic carcinoma in human medicine. PSA is accurate, reliable and effective test in human medicine. Effort has been put into developing a similar test to detect prostatic carcinoma in canine patients. The kallikrein-3 (KLK 3) gene encodes for the PSA protein in humans. However, dogs are deficient of this gene in their genome and a PSA homologue, kallikrein-2 also called Canine prostate-specific arginine esterase (CPSE), is produced in its place (Christensen et. al., 2017; Leis-Filho et.al., 2018; Pinheiro et. al., 2017).

Mutually, CPSE in dogs and PSA in humans are under hormonal regulation, thus an increase or decrease of serum testosterone activity result in increase or reduction in serum and seminal plasma concentration. Under physiologically conditions, CPSE in dogs is synthesised and secreted by prostatic epithelial cells into the lumen of the prostate ducts and does not come into the contact with the bloodstream. Nevertheless, when the prostatic architecture is disrupted due to prostatic lesions and disease, the proteins is released into the bloodstream and can therefore be used as an indicator of prostatic disease in dogs (Leis-Filho et.al., 2018; Pinheiro et. al., 2017).

Virbac has established an ELISA assay to detect elevated serum CPSE concentrations. Odelis CPSE ™ is a simple test for the practitioner to perform and an objective complementary examination to detect dogs with subclinical pathological prostatic condition. It is also a useful

aid to follow up the medical treatment of BPH in intact breeding males in which castration is unfeasible (Pinheiro et. al., 2017).

Serum CPSE concentrations are previously reported to be increased in dogs affected by BPH, bacterial prostatitis and prostatic carcinoma compared to normal dogs. However, the CPSE serum concentration did not differ significantly among the pathologies. A possible reason could be coexistence of prostatitis or neoplasia together with BPH (Bell et. al., 1995).

Although previous studies have found no significant difference between serum concentrations of CPSE in dogs with BPH, prostatitis and carcinoma. A recent study by Pinheiro et. al., 2017, could accurately differentiate dogs diseased with BPH to normal dogs and dogs suffering with other prostatic pathologies. The median values for dogs diseased with BPH was 160.7 ng/ml compared to the control group with the value 29.1 ng/ml.

Alonge et. al., 2018 developed a threshold value of 52.3 ng/ml to identify asymptomatic dogs that show ultrasonographic abnormalities of the prostate and a cut off value of 90 ng/ml, indicative of a prostate that is 2.5 times enlarged. Based on the study by Levy et. al., 2009, a cut-off concentration of CPSE of 61 ng/mL for diagnosis BPH is recommended, according to the results in this study showing 97.1% sensitivity and 92.7% specificity. These studies indicate that CPSE can be used as a preventative screening method in breeding males to detect prostatic diseases at an earlier stage with the cut-off values stated.

7.5 Radiography

Radiography of the prostate gland can give a valuable overview of the anatomical position, size, form, contour, and density of the prostate. For a complete evaluation, both ventrodorsal and lateral projections is necessary. However, radiography is non-specific and of limited diagnostic value, as there is no indication of whether the changes in the prostate are due to hyperplasia, infection or neoplasia (Johnston et. al., 2000; Smith, 2008).

Radiography may reveal an enlarged soft tissue opacity in the pelvic inlet or caudal abdomen, just caudal to the bladder. The urinary bladder can in some cases be enlarged due to inadequate emptying caused by the increased pressure on the prostatic part of the urethra. The contrast in the pelvic cavity is unfortunately poor, making it difficult to visualise the prostate gland. To overcome this problem, retrograde cystourethrography can be performed, demonstrating prostatomegaly and the urethral architecture. Opposed to a contrast cystogram

which enables the urinary bladder to be visualised, a retrograde cystourethrography enable the visualisation of the prostatic part of the urethra. With prostatomegaly there is often a diffuse uptake of contrast medium from the urethra into the glandular tissue. The distance in millimetre of this uptake into the gland can be used subjectively to assess the severity of the disease. For example, a more severe case will be seen with prostatitis or neoplastic conditions compared to BPH. If prostatic carcinoma involves the urethra by the invasion of tumour cells, urethral irregularity may be seen (England. et. al., 2010; Smith, 2008).

Mineralisation in the prostate gland is often associated with prostatic cysts and neoplastic conditions and can be visualised on radiography. If neoplasia is suspected, evidence of metastatic lesions in the skeletal systems, lymphadenopathy and metastatic nodular lesions in pulmonary tissue should be excluded (England et. al., 2010).

Radiographic evaluation of prostatic dimensions has been described in previous literature. In a study by Atalan et. al., 1999, radiographic assessment of prostatic dimension in healthy male dogs were performed. The distance between the cranial aspect of the pecten os pubis of the pubic bone and the sacral promontory, the pubic brim-sacral distance, were measured and the prostatic depth and length were expressed as a mean percentage of 56% in healthy male dogs. Furthermore, the study found evidence to support prostatomegaly if the diameter of the prostate is larger than 70% of the pubic brim-sacral distance, as visualised on lateral radiographs. Prostatic enlargement of >90% of the pubic brim-sacral distance, indicates prostatic neoplasia, abscessation or prostatic cyst development. On ventrodorsal projections, the prostate is considered enlarged if it is more than 50% of the space between the wings of ileum (Atalan et. al., 1999; Johnston et. al., 2000; Smith, 2008).

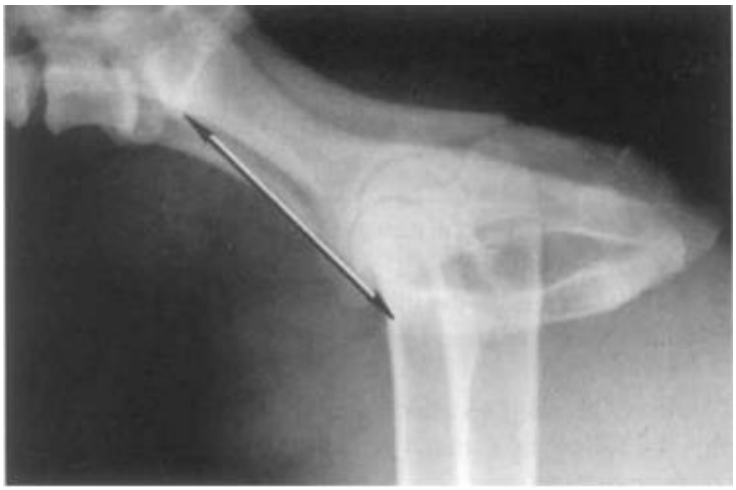

Figure 4. Lateral pelvic radiograph of an adult male dog, illustrating the position of the pubic brim-sacral distance measurement (arrow) (Atalan et. al., 1999).

7.6 Ultrasound

Ultrasonographic (US) examination of the canine prostate is an excellent and non-invasive objective method in the evaluation of the position, size, contours, and parenchymal echogenicity, as well as in the evaluation of the prostatic urethra. However, the quality and accuracy of the ultrasound examination is highly dependent on the operator`s ability and experience. Computed tomography (CT) examination would be a more precise and repeatable method, but due to its expense, time consumption, accessibility and the requirement of general anaesthesia, US is a preferred diagnostic method for this organ (Alonge et. al., 2017; Christensen et. al., 2017; Leroy et. al., 2013; Pinheiro et. al., 2018; Smith, 2008).

A study by Alonge et. al., 2017 showed that 60% of the asymptomatic dogs presented with an altered prostate gland on UL examination. This result confirm that prostatic diseases are often asymptomatic, at least initially, and under-diagnosed in many canine patients.

By means of a formula, the volume of the prostate can be calculated using the equations in the table below. Previous literature has published normal prostatic measurements for dogs of different ages and weights. The following formulas is based on 97.5% of the normal population and is calculated (Christensen et. al., 2018; Penninck and d`Anjou, 2015).

Table 1. Prostatic measurements in healthy intact males and correlation to age and BW.

	Ruel et. al., 1998	**Atalan et. al., 1999**
Length	1.7 – 6.9	1.8 – 5.0
Height	1.3 – 4.7	1.4 – 3.6
Width	1.8 – 6.9	1.4 – 4.3
Volume (cm3)	2.3 – 80.0	8.1 – 28.2
Correlation between prostatic length (L) in cm, age (A) in years, and BW kg	L= (0.055xBW) + (0.143xA) + 3.31	
Correlation between prostatic height (H) in cm, age (A) in years, and BW kg	H= (0.044xBW) +(0.083xA) + 2.25	
Correlation between prostatic width (W) in cm, age (A) in years, and BW kg	W= (0.047xBW) + (0.089xA) + 3.45	
Correlation between prostatic volume (V) in cm3, age (A) in years, and BW kg	V= (0.867xBW) + (1.885xA) +15.88	V= 8.48 + (0.238xBW) V= 9.79 + (0.871xA)

The dog can be standing or put in dorsal or lateral recumbency, often without the need of sedatives. The inguinale area often scarce with hair, thus clipping is often not necessary. To obtain diagnostic images, acoustic gel and alcohol are used directly on the skin. The hypoechoic urinary bladder is often used as a landmark. The probe, either linear or curvilinear probe (5.0-8.0 mHz), is put lateral to the prepuce. Three-dimensional measurements can be taken of length, width and height. Sagittal orientation of the probe gives the length, while transverse orientation gives the width, and the two combined gives the height of the prostate gland. A minimum of three views of each orientation should be attained, and the average for each orientation is calculated (Christensen et. al., 2018; England et. al., 2010).

Normal prostate parenchyme has a homogenous and echodense pattern throughout the gland. The shape is rounded to oivoid on sagittal images, with smooth margins. On traverse images, the two prostatic lobes should be symmetrical. The urethra is visible as a hypoechoic structure between the two lobes of the prostate and can be associated with edge shadowing on transverse images, which should not be mistaken of a lesion. Prostatic size in intact males are often correlated with age and BW of the patient. The uniform enlargement of the organ with a uniform echogenic parenchyme is consistent with BPH, which is common spontaneous condition in the middle to older aged dog (Christensen et. al., 2018; England et. al., 2010; Johnston et. al., 2000; Penninck and d`Anjou, 2015; Smith, 2008).

In the event of acute or chronic prostatitis, usually secondary to ascending urethral bacteria into a gland with BPH, the prostate may be enlarged or of normal size. Although, the changes in echogenicity and echotexture tend to be more severe in case of prostatitis compared to BPH, differentiation based on a US examination is often not possible. Prostatic abscesses can develop subsequent to prostatitis and may resemble prostatic cysts. The wall may be thicker around the abscess cavity compared to cysts, with septa traversing the abscess. The fluid is echogenic, and sometimes gas inclusions in case of gas-producing bacteria may be seen. In chronic prostatitis, dystrophic mineralisation can be encountered (Johnston et. al., 2000; Penninck and d`Anjou, 2015).

Intraprostatic cysts manifest as circular to irregular shaped anechoic areas of variable size in the prostate gland. It is important to differentiate large paraprostatic cyst from the urinary bladder by catheterisation and if necessary, injection of saline into the urinary bladder (Penninck and d`Anjou, 2015).

The ultrasonographic images of neoplastic conditions are variable. Prostatic adenocarcinoma is regarded the most common cancer of the prostate. Prostatomegaly with irregular areas with hypoechoic to heterogenous echotexture are typical. The prostatic lobes are usually asymmetrical on transverse images. Mineralisation is frequently seen, and the surrounding fat may become hyperechoic. Metastases to medial iliac or hypogastric lymphnodes and irregular bony proliferation of the ventral margin of the caudal lumbar vertebrae can often be seen in neoplastic conditions of the prostate gland (Christensen et. al., 2018; England et. al., 2010; Penninck and d`Anjou, 2015; Smith, 2008).

7.7 FNA & biopsy

If cytology samples cannot be obtained by ejaculation or prostatic massage, US-guided transabdominal FNA is a good method to obtain prostatic fluid for cytology and tissue for histologic analysis. Cytology obtained by FNA samples show high agreement with histopathology from biopsied tissue. Evidence suggest that prostatic tissue sample culture is more specific than culture of prostatic fluid. This is not true for prostatic neoplasia, where cytology by prostatic wash is more likely to yield a diagnosis compared to an ejaculated sample (Christensen et. al., 2018; Pinheiro et. al., 2017; Smith, 2008).

Some authors discourage FNA if infection or neoplastic conditions are suspected, because the needle track may cause seeding of the infectious agent or neoplastic cells into the abdomen. However, according to Christensen et. al., 2018, there is no evidence of such neither in the human field nor in the veterinary field (Christensen et. al., 2018; Pinheiro et. al., 2017; Smith, 2008).

For a definitive diagnosis, biopsy for histopathological analysis is often necessary. However, the procedure is regarded as invasive and is only considered in those cases where less invasive diagnostic tests do not give a conclusive diagnosis (Christensen et. al., 2017, Johnston et. al., 2000).

8.0 TREATMENT

The treatment options and prognosis depend greatly on the condition. Prostatic tumours in canine patients are often characterised by high malignancy with advanced local progression and high rate of metastasis at time of diagnosis. In human medicine, prostatic cancer in men are androgen dependent, and thus responds rapid and favourably to androgen deprivation

therapy. This is opposed to the situation in canine patients, where prostatic carcinoma seems to not be androgen dependent, thus render the patient with a poor prognosis and treatment is in many cases unfeasible. The median survival times without therapy are often <30 days and most owners therefore decide to euthanise their dog. If therapy is attempted, it is largely considered palliative (Christensen et. al., 2017; Cornell et. al., 2000; Durham and Dietze, 1986; Johnston et. al., 2000; Sorenmo et. al., 2003).

On the contrary, several treatment options are available for BPH and the respond is often rapid and favourably. Prostatic cysts predispose to abscess formation and therefore drainage or removal of the cyst depending of the localisation is often recommended. Castration is recommended in most prostatic diseases except in case of neoplasia of the prostate gland (Cornell et. al., 2000; Durham and Dietze, 1986; Johnston et. al., 2000; Sorenmo et. al., 2003).

8.1 Castration

The canine prostate is an androgen dependent organ, hence castration is the treatment of choice in prostatic diseases associated with excessive hormone. This includes BPH, squamous metaplasia and cystic hyperplasia. Castration results in involution of prostatic tissue, causing 50-70% decrease in prostate volume after 3 weeks, alleviating clinical signs. Though the complete involution may take up to 3 months. Predominantly due to a decrease in the number of luminal epithelium cells whereas the number of basal cells remains unchanged (Leis-Filho and Fonseca-Alves, 2018; Nizanski et. al., 2014; Parry, 2007; Teske et. al., 2002).

Unfortunately, unlike in the human, canine prostatic carcinoma does not seem to have androgen receptors and does therefore not respond to castration. Castration is therefore not recommended in cases with prostatic neoplasia, as castration will not affect the outcome (Bell et. al., 1995; Bryan et. al., 2007; Gobello et. al., 2002; Sorenmo et. al., 2003; Teske et. al., 2002).

8.2 Medical therapy

Medical therapy is mainly indicated in intact breeding males with BPH where castration is unfeasible. Regular evaluation at a 4-6 monthly interval is recommended to monitor the

disease progression. Many drugs on the market may also have adverse side-effects, therefore, castration is recommended once the intended breeding period of the male ends (Parry, 2007).

Treatment of the past associated with severe adverse effects comprise oestrogenic compounds which effectively treat BPH, but due to severe toxic effects on the bone marrow (anaemia, thrombocytopaenia, and pancytopaenia) as well as causing prostatic squamous metaplasia and decreased spermatogenesis, these drugs are not used frequently anymore (Christensen et. al., 2017; Parry, 2007).

8.2.1 antiandrogens

The most commonly used medical treatment for BPH in dogs is Finasteride. Originally, the drug is licenced for humans, but its use in the veterinary field have shown to reduce the prostate size in affected dogs. Finasteride is an azasteroid that selectively inhibits the enzyme 5α-reductase, thus preventing the conversion of testosterone into its active metabolite DHT. The production of testosterone is preserved, while the production of DHT is eliminated. The removal of DHT decrease androgenic stimulation, which consequently reduces the size of the prostate gland by apoptosis of hyperplastic cells. Administered dose at 0.1 mg/kg SID (maximum 5mg in total per dog) results in a 50-70% decrease of prostatic volume after 4 months treatment. Treatment can be tapered to every alternate day, however to continuously relieve the clinical signs, treatment must be continued during the breeding career of the male, until castration can be performed. In humans, side-effects comprise erectile or ejaculatory dysfunction, and teratogenic effect in pregnant women. Nevertheless, these adverse effects are not seen in dogs, in fact research report normal libido and fertility in dogs treated with Finasteride (Christensen et. al., 2017; Leis-Filho; Nizanski et. al., 2014; Parry, 2007; Sirinarumitr et. al., 2002).

Osaterone acetate (Ypozane®) is marketed in France and in some EU countries. The drug is a testosterone analogue which effectively bind to androgen receptors and exert an effective anti-androgenic activity. Reduction of androgen receptors, the enzyme 5α-reductase and testosterone transport into prostatic cells are inhibited. Studies report a quick resolution of clinical signs and nearly 40% decrease of prostatic volume in half of the dogs after only 2 weeks treatment. Libido and semen quality do not seem to be affected (Christensen et. al., 2017).

8.2.2 Progestins

Medroxyprogesterone Acetate is a progestin with antiandrogen effect. Studies show decrease in clinical signs of most dogs treated, but only half of the dogs show a decreased prostatic volume after 6 weeks treatment. Libido and semen quality are not affected. However, concerns are raised regarding the development of diabetes mellitus and mammary nodules (Christensen et. al., 2017).

The progestogen delmadinone acetate (Tardak®) has been proved effective at a dose of 3mg/kg as a SC or IM injection. Although, the drug reduces the size of the prostate, it has been linked with adverse side-effects. Dogs treated were at increased risk of developing glucocorticoid insufficiency if exposed to stressful situations. Other side-effects were of minimal importance (Christensen et. al., 2017; Parry, 2007).

8.2.3 Antioestrogen therapy

Oestrogens are thought to have a causative or permissive role in the pathogenesis of BPH. Tamoxifen citrate is originally marketed for breast cancer in women but has proved to have a rapid prostatic effect and a transient contraceptive effect at a dose of 2.5mg/dog SID for 28 days. The drug effectively reduces prostatic volume, testicular size, spermatozoal motility, libido and serum testosterone during the treatment (Christensen et. al., 2017).

8.2.3 GNRH agonist

Deslorelin acetate (Suprelorin) is a slowly releasing implant licenced as a reversible chemical castration in dogs. The implant is delivered as a SC chip under the loose skin between the lower neck and the lumbar region in dogs. No anaesthesia is required, although the insertion of the implant under the skin may be painful for the dog. The implant function as a potent GnRH agonist that suppresses FSH and LH, resulting in less testosterone in the circulation, reduced libido and stop in the spermatogenesis. Consequently, no DHT is produced, reducing the volume of the prostate gland and the testes. The implant has a duration of 6 or 12 months, but the effect may last longer. However, the male dog will reach full fertility when the effect ceases (Christensen et. al., 2017).

8.3 Surgical removal of prostatic neoplasia

In the event of early detection and absence of metastases in neoplastic conditions, therapeutic options include surgery, radiotherapy and chemotherapy. Complete prostatectomy is associated with a high rate of postoperative morbidity and complications, especially urinary incontinence (Durham and Dietze, 1986; Przadka et. al., 2019).

A study by Vlasin et. al., 2006, compared dogs that underwent total prostatectomy to dogs that underwent subtotal intracapsular prostatectomy, concluding with longer mean survival time (112 days versus 20 days) and less postoperative complications for the latter procedure. Moreover, 70% of the dogs in the total prostatectomy group where euthanised within 2 weeks post-surgery compared to around 20% in the subtotal intracapsular group (Vlasin et. al., 2006).

Radiotherapy has been initiated in dogs without extending quality of life and may be associated with multiple adverse side-effects. Thus, more studies are needed to determine the best protocol for treating these patients (Christensen et. al., 2017).

There are few studies on chemotherapy treatment of prostatic neoplasia. Therefore, benefits of chemotherapy have not been well-documented. However, several studies exist on the chemotherapeutic properties of NSAIDS, piroxicam and carprofen. It is thought that COX-2 inhibition plays a key role by stimulating apoptosis, inhibit angiogenesis and altering the immune function. Studies shows that normal prostatic cells and neoplastic cells express COX-1 receptors while only neoplastic cells express COX-2. The survival time are also increased for canine patients treated with COX-2 inhibitors, almost 7 months compared to less than 1 months respectively (Christensen et. al., 2018).

9.0 MATERIALS & METHODS

This thesis is written based on a systematic literature review of peer-reviewed articles. The information is obtained by searching bibliographic databases accessed by a computer. The articles used in this thesis is selected based on a wide search and by reading the abstract touching my topic. Several combinations of key words have been used. Key words include but are not limited to “prostatic disorders canine”, “benign prostatic hyperplasia” “CPSE canine”, “canine prostate carcinoma”, “canine prostatic neoplasia”, “canine prostatic disease diagnosis”, “canine prostatic disease treatment”, “radiology”,

"ultrasound", "semen collection dog". The main bibliographic search engine used is Google Scholar (GS) which includes articles and journals. Books has also been used for more detailed information.

10. DISCUSSION

Diseases of the prostate gland are a frequent complaint in the intact male dog. Studies even indicate that most intact male dogs will develop BPH during their lifetime. BPH is a benign growth with good treatment possibilities opposed to prostatic carcinoma. Canine prostatic carcinoma is a fast-growing tumour with high chances of metastatic seeding to surrounding structures. During disease development of most prostatic diseases, there a few or no clinical signs. Only when the prostate is of a certain size, the organ will compress surrounding structures and frequently causes altered defecation and urination habits. However, the clinical signs for the different prostatic pathologies overlap and can therefore be difficult to differentiate from another.

Several diagnostic tools are available for diagnosing prostate diseases from physical examination to ultrasonography, radiography, assessment of ejaculate's third fraction, prostatic massage, prostatic FNA and biopsy. With the exception of biopsy which is a more specific but invasive method of diagnosing prostate diseases, most of the diagnostic methods are non-invasive and can give valuable information about the prostate gland. However, imaging diagnostic methods are often subjective, thus the experience of the practitioner is important for correct diagnosis. Efforts have been put into developing an objective test that could diagnose and differentiate prostatic diseases in a fast and convenient matter.

Identification of novel proteins in the seminal plasma, has led to the development of biomarkers for diagnosis and of prostate function and disease. In humans, PSA produced by prostatic epithelial cells, is widely studied and used as a serum marker to diagnose prostatic carcinoma in men. Virbac has established an ELISA assay to detect elevated serum CPSE concentrations in dogs with subclinical pathological prostatic diseases. CPSE in dogs and PSA in humans are both under hormonal regulation, thus an increase or decrease of serum testosterone activity result in increase or reduction in serum and seminal plasma concentration

Serum CPSE concentrations were found to be significantly elevated in dogs with BPH compared to normal dogs. This thesis investigated whether this test could differentiate between prostatic diseases, and especially between benign and malignant growth of the prostate gland.

Canine prostatic carcinoma is a fast-growing tumour with high chances of metastatic seeding to surround structures. Thus, early diagnose is essential if treatment should be in the question. Although, there are similarities in prostatic carcinoma in humans versus in dogs, significant differences also exist. Many screening tests and treatment options successfully used in human medicine fails to be relevant in canine veterinary medicine. Prostatic carcinoma in humans are often benign and slow-growing and the cancer usually respond favourably to androgen deprivation treatment, opposed to the situation in dogs. Canine prostatic carcinoma is found to not be androgen dependent, and studies have even found a significant elevated risk in castrated individuals. The cancer is therefore more commonly diagnosed in castrated individuals, and the malignancy also seem to be particularly aggressive and often metastasise at an earlier stage in castrated canine patients. However, this could be due to the lack of initial clinical signs before the prostate gland reach a certain size or before the cancer has metastasised, and the fact that clinical signs of prostatic diseases often are non-specific. Reasons for the increased incidence of prostatic neoplasia in castrated dogs are unknown, but hypotheses include a loss of protective effects of androgens.

Unfortunately, there is little evidence that CPSE can be used as a diagnostic test to detect prostatic carcinoma in canine patients. The test is widely used to detect BPH in patients with prostatomegaly, and the test is also a useful aid to follow up the medical treatment of BPH when castration is unfeasible in intact breeding males. Several studies have established reference and cut-off values for the diagnosis of BPH.

The aggressive nature of canine prostatic carcinoma and the lack of screening tests makes the diagnosis and treatment extremely challenging. More research is needed to identify early markers and develop diagnostic methods that can detect prostatic neoplasia at an earlier stage in affected patients.

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