Chapter

Diseases of the Canine Prostate Gland

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Abstract

In dogs, the most frequent diseases of the prostate gland are benign prostate gland hyperplasia (BPH), acute and chronic prostatitis, squamous metaplasia, and prostate tumors. New diagnostic tools comprise diagnostic markers in the blood and urine, as well as advanced imaging methods. The therapy can be initialized with the 5α-reductase-inhibitor finasteride or an anti-androgenic compound, and prolonged with a long-acting gonadotropin-releasing-hormone (GnRH)-agonist such as deslorelin. In case of prostatitis, effective antibiotics must be applied for weeks. Antibiotics must be able to penetrate into the prostate tissue; fluoroquinolones, clindamycin, and erythromycin are good choices and are in addition effective against mycoplasms. The chronical prostatitis cannot be differentiated from a neoplasia by sonography; a biopsy, histological, and bacteriological examination are required. Tumors of the prostate gland are seldom and mostly occur in castrated but in intact dogs. For the final diagnosis, a biopsy must be taken. Partial and total resection of the prostate gland by use of laser technique is possible but coincedes with many side effects and the prognosis is still futile. Immunotherapy combined with NSAIDs, targeted noninvasive thermotherapy, *BRAF* gene inhibitors, or prostate artery chemoembolization are promising methods.

Keywords: dog, prostate gland, BPH, prostatitis, tumor

1. Introduction

The prostate gland is the only accessory sexual gland in the male dog. Some authors in addition name the ampullae ductus deferentes. The canine prostate secretion is a transport medium among others for passive transportation of the spermatozoa into the uterus during ejaculation. The prostate secretions furthermore influence the motility and function of the semen cells; the exact composition and many functions are not yet known and vary dependent on the laboratory and the analysis method used [1]. The composition of mineral nutrients, as well as the amount of cholesterol, albumin [2], zinc-binding proteins [3], fertility-associated proteins like osteopontin [4], the antioxidative capacity [5], and many more have been examined. A new study investigated the composition of the seminal plasma by use of mass-spectrometry [6].

Diseases of the prostate gland frequently occur in aging dogs [7, 8]; the incidence increases with age: 6.2% in intact males with ≤ 4 years, 17.5% in 4–7 years old dogs,

32.8% in 7–10-years old dogs, and 43.5% in male dogs >10 years of age [9, 10]. Diseases of the prostate gland can be infectious or noninfectious. In aging dogs, the noninfectious benign prostate gland hyperplasia (BPH) is the most frequent disease, occurring in 80% of all intact male dogs older than 5 years and in >95% of male dogs older than 9 years [11, 12]. The BPH can be easily treated; however, the disease will become chronical with regular rezidives and only castration will finally cure the dog. Inflammatory diseases may be chronical or acute; the acute prostatitis is mostly caused by bacterial infections, either ascending via the urethra or via the bloodstream. The chronical prostatitis develops from a BPH or an acute prostatitis if treated with wrong antibiotics or for a too short period of time [7]. Highly effective antibiotics applicated for a sufficient period are essential for the successful treatment of the prostatitis.

The squamous metaplasia develops due to hyperestrogenism occurring because of endocrine testicular tumors; however, may also be caused by estrogen applications [8].

Prostate tumors are relatively rare in dogs, the incidence is on average 0.43% [13], they mainly occur in older dogs and more frequently in castrated than in intact dogs; the growth is not androgen-dependent [14–16]. In this chapter, modern diagnostics and therapeutical methods are discussed.

The aim of each treatment must be, to hinder the development of chronical diseases, for prevention of the long-term use of antibiotics that are needed for special infections [17]. Regular examinations, best starting when the dog reached 40% of life expectancy, will help to reach this goal [18].

This article provides an overview of diagnostical and therapeutical measures in different prostate gland diseases and insights into at present most actual developments.

2. Anatomy of the prostate gland

The canine prostate gland consists of two parts, surrounding the caudal part of the urethra; it is round to oval and has a sulcus dorsal and ventral that can be reached by digital rectal palpation. It is surrounded by a thick fibro-muscular capsule releasing septs of smooth muscle tissue into the gland. The urethra is situated in the middle of the prostate gland and between the two parts. The situ of the gland is dependent on age; in young dogs, it is situated in the pelvis, in aging dogs more in the abdomen, and because of an increasing size of the diseased gland, in the old dog, it can be situated in the pelvis again. In this case, it can be examined by digital-rectal palpation again. The cranio-dorsal and cranio-ventral part of the gland is covered by peritoneum. The glandular ducts open into the urethra at the site of the pars disseminata and on the colliculus seminalis. The blood supply is provided via the arteria pudenda interna, innervation by the hypogastric nerve [19].

3. Function/endocrine regulation of the prostate gland

The prostate reaches maximum secretory activity in dogs of on average four years of age [20], the secretions comprise >90% of the ejaculate; the gland continues to grow under the influence of testosterone because of stem cell differentiation, and in the aging dog will increase in size because of hypertrophy and hyperplasia. Growth and secretion are regulated by the active metabolite of testosterone (T), namely the

5α-Dihydrotestosterone (DHT). More than 95% of testosterone are converted into DHT by the enzyme 5α-reductase, after diffusion into the prostate gland cells. DHT binds stronger to the testosterone receptor than T [21, 22]. Estradiol-17ß supports the effect of DHT in a synergistic way and, in addition, causes an upregulation of testosterone receptors [11].

The prostate gland secretion supports the transport and the function of spermatozoa after ejaculation. It contains citrate, lactate, cholesterol, and enzymes; however, few sugars and phospholipids are supposed to provide additional energy. The composition of the prostate secretions was recently investigated by means of proteomics [6, 23]. The serine-protease canine prostate specific esterase (CPSE) and the lactotransferrin-precursor are the most frequently occurring proteins in the seminal plasma [23], comprising 90% of all proteins. The CPSE has a proteolytic effect, similar to chymotrypsin [24] and after binding influences spermatozoa function by its zinc-binding properties [3]. The CPSE binds to phosphorylcholine-binding protein and choline phospholipid of the membrane and induces the efflux of cholesterol from the spermatozoa membrane during ejaculation, which is essential for capacitation. The secretion of CPSE is controlled by androgens [25] and the enzyme is believed to be a reliable marker of prostate secretion [26].

The extracellular matrix of the canine prostate (noncellular stroma and fibrous tissue) supports the development of the gland and the control of cellular functions [21], supposedly via cellular transmitters like cytokines [27].

4. Diseases

4.1 Benigne Prostate Gland Hyperplasia (BPH)

This noninfectious disease of the prostate gland only occurs in intact male dogs with endocrinally active testicles. The disease counts for 50% of all prostate diseases [9]. The incidence increases with increasing age; however, in rare cases, BPH can occur at the age of 2–3 years [28]. Sonographical and in part clinical symptoms usually can be seen in 80% of male dogs at the age of 5 years [11, 12, 20], and in >95% of males at the age of >9 years [11]. The hyperplastic increase in size is caused by:

- A change in steroid-hormone-concentrations
- An increasing estrogen: testosterone ratio in the intact, aging dog [29]
- A change in the receptor expression within the gland and especially by increasing concentrations of DHT in the epithelial, hyperplastic tissue.

Dihydrotestosterone is the active form of testosterone and produced from testosterone by the enzyme 5α-reductase. The activity of the enzyme increases in the aging dog, especially in the glandular epithelial cells; therefore, the hyperplasia mainly concerns the glandular epithel and less the stroma [30, 31]. In one experiment, BPH could be produced by long-term application of 5α-androstan-3aα, 17ß-Diol (3α-Diol), in combination with 17ß-Estradiol. 3α-Diol is produced by reduction from DHT and/or 17ß reduction from androsterone; it stimulates the intracellular cAMP production in the prostate gland [32]. In another experiment, the testosterone concentration was doubled on days 21 and 42, with the same effect [33]. The experiment points toward

the impact of these hormones and an eventual change in the enzyme and metabolic activity inside the aging gland. The role of local growth factors and relaxin is still not sufficiently investigated.

Prolactin was detected in prostate secretions of dogs with BPH and with higher concentrations than in healthy dogs; during the development of the prostate, prolactin contributes to growth and differentiation [29].

As a further predisposing factor, the breed was previously mentioned; large breeds seem to be more often concerned [34–36] and in a recent study, the Rhodesian Ridgeback was shown to be predisposed, pointing toward a genetic cause (Werhahn Beining et al. 2020). Some authors suggest a breed-specific pituitary prolactin secretion, which lacks evidence so far but deserves better investigation [35, 37].

4.1.1 Clinical symptoms

The disease starts with centrifugal increase in size; sonographically, changes in echogenicity and cystic caverns become visible. Clinical symptoms develop later on [18]. Therefore, the BPH can be termed a physiological process in aging dogs, until clinical symptoms occur (Tsutsu et al. 2000).

The first clinical sign mostly is serosanguinous preputial discharge not associated with urination; this discharge occurs because of vessel damages in the hyperplastic, well-perfused tissue [38].

The secretions reach the urinary bladder via the pars disseminata causing a bloody admixture of the urine [9, 38]. In breeding dogs, a changed composition of the prostate secretions causes an increase in pH, a decrease in motility, and bloody prostate secretions [39, 40]. Later on, morphological aberrations of spermatozoa occur [19]. BPH may cause reversible infertility. Abdominal pain because of the enlarged gland is seldom [9, 19]. The centrifugal growth of the gland causes compression of the urethra and can cause dysuria, dyschezia, stranguria, and even anuria; however, the latter is seldom [11, 41], and urination problems were seen in only 27% of dogs with BPH in one study [9]. Defecation problems more frequently occur, especially in advanced stages of BPH due to compression of the rectum, leading to acute constipation in extreme cases [19, 42].

4.1.2 Diagnosis

For an accurate diagnosis, a case history, a clinical-andrological examination of the dog including digital rectal palpation and abdominal sonography are obligatory. Furthermore, examination of urine and semen, as well as cytological examination of the prostate gland secretions can be helpful. Zambelli et al. [43] used the parameters anorexia, loss of weight, degree of tenesmus and dysuria, urinary incontinence, preputial discharge, and hematuria for clinical grading of the BPH in 4 grades, with grade 1 corresponding to asymptomatic BPH.

Digital-rectal examination reveals a symmetric increase in size, normal consistency, and no painfulness; large intraprostatic cysts may cause asymmetry [38].

Sonography is a good method for diagnosis of BPH in dogs; however, it should always be combined with further clinical methods [44]. The quality of the examination is variable and dependent on the quality of the pictures, and the reproducibility of the measurements [45], as well as the position of the probe [9]. Sonographical parameters are size, structure, echogenicity, and abnormal structures such as cysts, abszesses, mineralization, asymmetry of the lobi, etc [18, 46] (**Figure 1**).

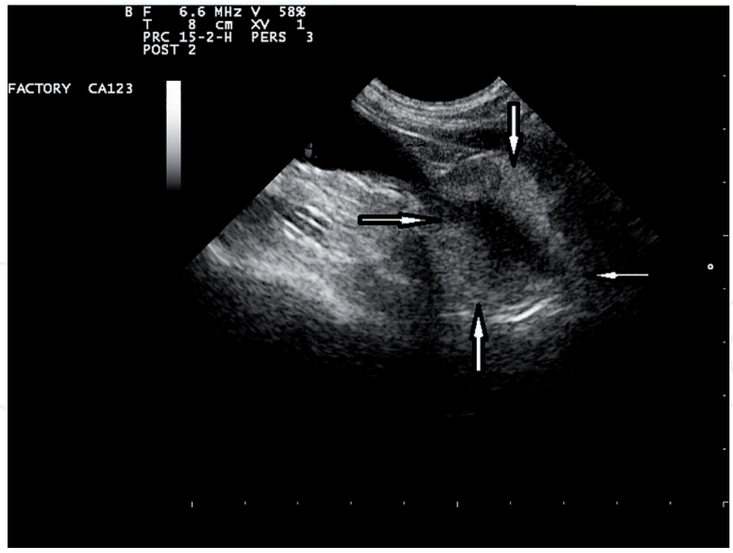

Figure 1.
Sonography (B-mode) of the physiological prostate. Prostate gland of a healthy 5-year-old beagle, the white arrows mark the contour. The size was 3 × 2 cm (L × W), the structure of the gland is homogenous, the echogenicity is physiological, and the anechoic line in the middle is the urethra.

The volume of the gland correlates with the body weight [47] and can be calculated when length (L), width (W), and height (H) were measured by using a formula; for example,

Measured L × W × H × 0.523/estimated volume (0.33 × body weight in kg × 3.28).

In dogs with BPH, this ratio will be > 2.5 [48].

4.1.2.1 Sonography

With B-mode sonography, the prostate with BPH appears enlarged, and the parenchyma is homogenous and hyperechogenic. Intraprostatic cysts of different sizes are frequent (Abb.3), and paraprostatic cysts sometimes occur [8, 12, 18, 45] (**Figure 2**). Cysts are round, thin-walled structures with anechoic contents and distal increases in echogenicity [45].

When using special doppler-sonographical methods like power or pulse-wave Doppler sonography in dogs, the examined vessels [49], as well as previous ejaculations and medications, have to be considered; a sexual rest before the examination is recommended [50]. The case history should reveal whether a gonadotropin-releasing-hormone(GnRH)-analogon was applicated previously, which will change the findings considerably [51].

An increase in perfusion of the gland was recorded in 8/16 dogs with BPH in one study, using pulse-wave Doppler sonography [46]. In another study, peak-systolic velocity (PSV) and end-diastolic velocity (EDV) were significantly higher in dogs with BPH than in healthy controls [52].

Contrast-enhanced sonography (CEUS) proved to be advantageous for evaluation of vascularization and perfusion of the canine prostate gland. For this method, ultrasoundcontrast agents (UCA) are injected intravenously. Unfortunately, the use of different UCA makes results from different studies difficult to compare [45]. In one study, healthy male dogs were injected with a micro-bubble UCA with the aim to obtain physiological reference values [53]. However, one study is not sufficient; the generation of reference values by using a large and comparable data pool, standardized methods, and settings is a big problem.

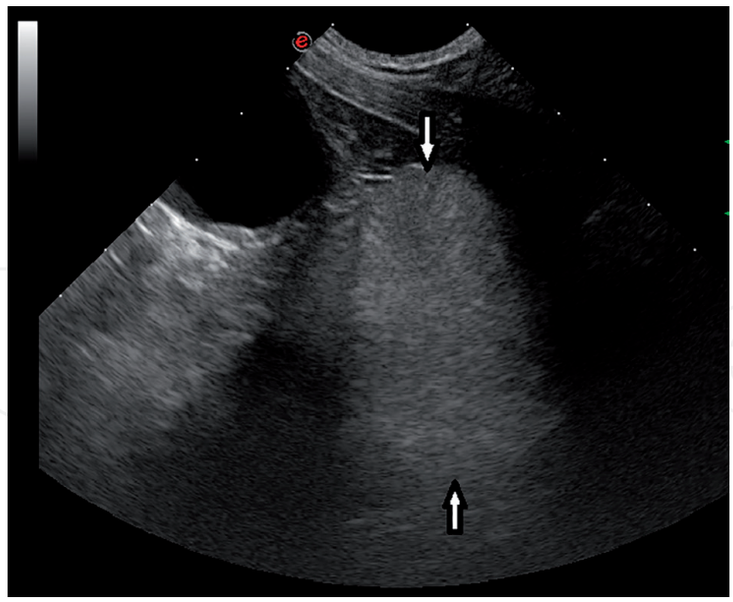

Figure 2.
Sonography (B-mode) of a prostate gland with BPH. The prostate is high-grade enlarged (arrows), the structure is homogenous, and the echogenicity is increased. The dog showed bloody preputial discharge, stranguria, and defecation problems.

In an earlier study, micro-bubble UCA and CEUS proved to be useful for detection of vessel damages and necrosis. Unfortunately, it is still not possible to differentiate between BPH and chronical and acute prostatitis, respectively [54]. However, together with further diagnostic methods, these sonographical tools provide worthful diagnostic findings.

Elastography is an interesting tool for evaluation of tissue consistency, the degree of elasticity, and rigidity. The principle is that the degree of deformation after pressure on a certain tissue is inversely proportional to the rigidity of this tissue [55]. Different methods such as acoustic radiation force impulse elastography (ARFI) [56] were evaluated in dogs. With qualitative ARFI, short acoustic impulses of high intensity are used for deformation of the tissue, then the data are converted into a statistic grey scale (Elastogram), revealing the rigidity of the examined tissue. With quantitative ARFI, an acoustic wave is sent in a certain region of the tissue, spreading at a certain velocity within this tissue, and dependent on the rigidity of the tissue. The measured velocity correlates to rigidity and viscoelasticity of the tissue [57]. For examination of the canine prostate gland with elastography, physiological values for different groups of age are available [56, 58, 59]. Unfortunately, no controlled study about the use in dogs with BPH is available. The method requires some training.

Echostructure analysis or computerized histogram analysis of sonographical pictures is a method well-known in human medicine for diagnosis of mammary tumors. Similarly in dogs, the method proved to be useful for the diagnosis of mammary carcinomas [60]. For this method, the gland is examined via B-mode sonography and the pictures are digitalized. Then so-called regions of Interest (ROI) are marked in the pictures (**Figure 3**) and objectively evaluated by using computer-assisted analysis. (software: for example ImageJ; Wayne Rasband, National Institutes of Health, Bethesda, Maryland, USA) The echostructure analysis provides information about brightness, micro- and macrotexture, homogeneity, and contrast differences within a certain tissue [60, 61]. In a previous study, the echostructure method was used to

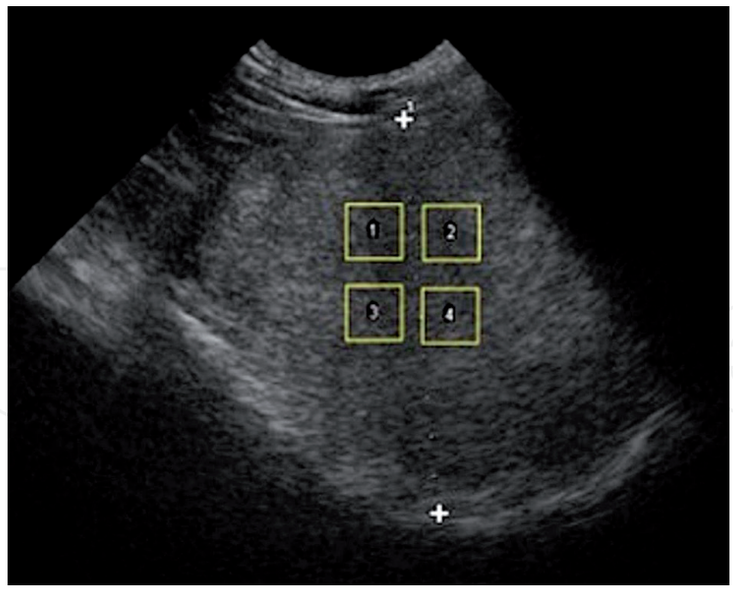

Figure 3.
Echostructure Analysis of the prostate gland, regions of interest (ROI). For the objective analysis of the digitalized, B-mode pictures, four quadrants of equal size have to be placed in the region of interest. The measures are performed automatically in these regions. Evaluation is performed by a special software.

differentiate between BPH and chronical prostatitis. In dogs with BPH, the homogeneity of the gland tissue was significantly higher than in the dogs with chronical prostatitis [62].

4.1.2.2 X-ray

X-ray of the canine prostate gland provides information about the size and situ of the gland. In healthy dogs, the diameter of the prostate is at a maximum 70% of the distance between the cranial margin of the pubic bone and the promontory of sacrum [63], an increase in size points toward BPH. By using a retrograde urethrocystogram, examination of the urethra is possible; the lumen can be confined by BPH, abscesses, or neoplasms [63]. In a previous study, power injection of a contrast medium during retrograde CT-urethrography improved the evaluation of the urethra; dilations of the urethra could be easier evaluated in relation to the degree of the filling of the urinary bladder [64].

Diseases of the prostate gland can be diagnosed by use of *computer tomography* (CT); data about the healthy canine prostate gland are available [65]. The appearance is round to ovoid, homogenous, and well definable, whereas capsule, stroma, and parenchyma cannot be well differentiated. In dogs with BPH, prostate megaly, decreased density, and heterogeneity of the tissue are characteristic; reference values for the size are available [66]. However, in the cited study, the groups were heterogeneous and the size of the dogs variable. The use of a contrast medium facilitates the diagnosis, especially evaluation of the median septum and the vascular system [65, 67]. In one study using contrast-CT, the results correlated well with the cytological findings [68]. An important advantage of CT is the possibility to recognize and localize metastases [66]. However, since the CT examinations have to be done under general anesthesia, examinations should only be done in suspected cases of prostatitis, carcinoma, or other masses.

A rather new method is the diffusion-weighted and perfusion-weighted *Magnet resonance Imaging* (MRI). In a recent study, the prostate gland of healthy beagles was

examined and physiological values for perfusion and diffusion were obtained [69]. electrical-conductivity-based MRI is a further method, helping to recognize changes in the canine prostate gland tissue by evaluating changes in the contrast [70]. Further MRI methods are available and will be discussed in the chapter about prostate carcinomas [71].

4.1.2.3 Examination of blood, urine, seminal plasma, and the sperm-rich phase

In case of canine BPH, *examination of blood* parameters usually reveals normal findings, whereas *examination of the urine* in some cases reveals hematuria [34, 38]. *Seminal plasma* and *prostate secretions* often contain erythrocytes [40], *spermatozoa* often show a decrease in motility and an increase in morphological abnormalities [19, 39, 40].

A *bacteriological examination* of prostate secretion, urine, and semen is often negative and may give a hint, however, cannot be used solely for diagnosis [38]. Prostate secretions can be obtained by digital-rectal massaging of the gland, while a urinary catheter is placed at the site of the pars disseminata. The secretions can be aspirated, provided the urinary bladder was emptied and flushed before; they can be examined cytologically and bacteriologically [19]. Collection of more prostate gland epithelial cells is possible by use of the urethra-brush method. The brush is introduced in the urethra while hidden in a plastic catheter; at the site of the prostate gland, the brush is pushed forward several times and then sterile retracted inside the catheter and outside the urethra. The brush and the collected fluid are deposited in sterile sodium chloride solution and centrifuged, the pellet can be examined cytologically and bacteriologically [40].

In dogs, the final diagnosis BPH can only be made by use of fine needle aspiration (FNA); this method should be performed when the dog is sedated and received analgesia. The FNA is done transcutaneously under sonographical control [8, 19]. However, even though providing the final diagnosis, this method is mostly not necessary. The cytologically obtained results correlate well with histopathology. Only for differentiation between chronical prostatitis and prostate gland carcinoma, FNA or biopsy must be performed [66, 72–74].

Measurement of the canine prostate-specificesterase (CPSE) can be helpful. The concentration of this enzyme in the blood is significantly increased in case of canine BPH and other diseases [29, 33, 48, 75–78]. Unfortunately, it is not possible to differentiate between BPH, prostatitis, and neoplasia, and the reference values for healthy dogs are variable in the literature [48, 75, 77]. The secretion of the CPSE is age-dependent in dogs, therefore, reference values must be critically considered. The diagnosis BPH should not be solely based on measurement of the CPSE. In one study, a combination of clinical symptoms, CPSE measurement, and calculation of the prostate volume (real volume/estimated volume = V ratio) were evaluated. The clinical BPH coincided with a V-ratio of >2.5 and a CPSE concentration of > 90 ng/ml; the sensitivity was 85% and the specificity 72% [48]. Meanwhile, a commercial assay is available (Odelis® CPSE, Bio Veto Test, Nice, France) and another study revealed a sensitivity of 97.1% and a specificity of 92.1% [79].

4.1.3 Differential diagnoses

When the general condition is undisturbed, BPH can be mistaken for chronical prostatitis or beginning neoplasia in dogs.

4.1.4 Therapy

Therapy is only necessary when clinical symptoms are visible. When the dog is asymptomatic, regular clinical and sonographical controls every 3–6 months are recommendable [42]. Vets can choose between different medicaments, providing the best choice for a subject [7].

The most effective method is the castration, involution starts within 6–12 weeks [7]. The clinical symptoms will disappear earlier and a decrease in size can mostly be palpated after 1–2 weeks [42]; the volume will decrease to 60% within one week [10], and by 50% after three weeks [39]. Bloody preputial discharge disappeared in 89% of cases within 4 weeks after castration [38]. Castration is the treatment of choice in case of hyperdistention, dyschezia, perineal hernia, or large retention cysts [42].

Table 1 provides an overview of useful and recommendable medicaments against BPH

Medicaments with an antiandrogenic effect likewise and rapidly reduces the size of the gland. They competitively block the binding of testosterone to its receptors and decrease libido within 3 days. One example is cyproterone acetate, furthermore delmadinone acetate. Some preparations are not licensed for use in animals. These medicaments caused a reduction in canine prostate gland size by 28% within two weeks [82], and the clinical symptoms improved earlier. The duration of effectiveness is approximately 6 months when an average dose of 3 mg/kg is chosen. Side effects in male dogs are a latent diabetes mellitus and diseases of the mammary gland (tumors, hyperplasia, cysts, and galactorrhea).

For breeding dogs, medicaments not decreasing the libido are desirable, enabling examination of the semen quality while the dogs are still under treatment. for example osaterone acetate is a gestagene with anti-androgenic effect. It decreases the uptake of DHT in the prostate gland and decreases the activity of the 5α-reductase. Osaterone acetate furthermore suppresses the nuclear DHT- and androgen-receptor expression in the gland [86]. The size of the gland was significantly reduced to 62.6% within 7 days when a daily oral dose of 0.2–0.5 mg/kg was given [10]. A daily oral dose of 0.25 mg/kg for 7 days reduced the size to 64.3% within 14 days [84]; the testosterone concentration was significantly reduced for 3 months [10], then slowly increased, which is believed to point toward a low-grade anti-gonadotrophic effect [87]. The semen quality was low grade decreased during the therapy; the volume was decreased for 4 months. An increase in the percentage of morphological changings was observed 4 weeks after beginning of the therapy and during the following 1.5 months [10]. This medicament is recommendable for breeding dogs because of its rapid effect and the maintained libido. Within three months after beginning of the therapy, the sonographical appearance of the gland and the quality of the ejaculate are back to normal. Some side effects were observed: an increase in appetite for 1–3 weeks (3/15), lethargy (2/15), and low-grade loss of hair (1/15) [7].

This medicament is applicated orally; in case of vomiting, it is therefore not recommendable. In this case, injectable preparations are available for dogs.

In case of mild BPH, the 5α-Reductase-Inhibitor Finasteride is effective (for example Proscar® 5 mg Tabl. Merck, Vienna, A) [12]. Doses for dogs and duration of application are variable in the literature (Tab. 2) [42, 83]; however, the tablets should be given for 3–4 months. Since semen quality and libido are not changed by the medication, it is recommendable for breeding dogs [12, 83]. Finasteride is a teratogenic substance; nevertheless, fertility and resulting puppies are not concerned [85]. Side effects are not described.

Agent	Effect	Preparations	Dosage	Application	Decrease in size after (days)	Duration of efficacy (months)	Side effects	Authors
Cyproterone-acetate	AntiAndrogen	Injectable (Depot)	2–5 mg/kg SID (can be repeated after 1 week)	s. c.	7–14	6	Apathy, thirst, mammary tumors, increase in appetite, loss of libido	[31, 80, 81]
		Tablets	2–3 mg/kg daily	p.o.				
Delmadinone-acetate	AntiAndrogen	Injectable	1–3 mg/kg SID (can be repeated after 1 week)	i. m.	14	6	Diabetes mellitus, mammary tumors, increase in appetite, loss of libido	[82, 83]
Osaterone-acetate	AntiAndrogen	Tablets	0.2–0.5 mg/kg/day (7 days)	p. o.	7–14	6	Decrease in semen quality, increase in appetite, loss of hair, lethargy	[7, 10, 84]
Finasteride	5α-Reductase-Inhibilor	Tablets	0.1–0.5 mg/kg/day (16 weeks)	p. o.	30–120	Dependant on duration of application	-	[12]
			1 mg/dog/day (3–21 weeks)	p. o.				[85]
			1 mg/kg/day (3 weeks)	p. o.				[42, 83]
			1.25 mg /dog /day (195 days)	p.o.				[42]
Deslorelin	GnRH-Agonist	Subcutaneous implant	4.7 or 9.4 mg /implant (repeated application possible)	s. c.	37	6–12	Flare-up within 1 week	[51]

Table 1.

For prolongation of an anti-androgenic therapy, long-lasting agonists of the gonadotropin-releasing hormone (GnRH) are suitable for dogs with BPH. Subcutaneous implants containing, for example, deslorelin (Suprelorin® 4.7 or 9.4 mg, Virbac, F) are licensed for male dogs and male ferrets. Many studies using different GnRH agonists and dosages are available, but difficult to compare [7]; however, deslorelin is the only licensed preparation. After resorption of a certain amount of GnRH, down-regulation of the GnRH receptors in the pituitary gland leads to a decrease in the secretion of the gonadotropins "follicle stimulating hormone" (FSH) and "luteinizing hormone" (LH), and consecutively to a decrease in the secretion of testicular testosterone by 90% and the spermatogenesis. The volume of the prostate gland decreases within 6 weeks by 50%, when a 4.7 mg implant is used [7, 51, 88], beginning after 37 days [51].

In dogs, the initial therapy leads to an increase in testosterone secretion; this flare-up can be suppressed by oral application of an antiandrogen. This is important in case of an acute enlargement of the gland with acute symptoms [7].

GnRH antagonists can be used for therapy of canine BPH, unfortunately, the second generation of these drugs caused anaphylaxis in some cases. Meanwhile better agonists, which are potent,long-acting, and without side-effect, are available; however, they are only licensed for use in humans. Acyline is a preparation of the third generation and was used in one study at a dose of 330 mg/kg s.c. in dogs, leading to a reversible decrease in FSH, LH, and testosterone over 9 days. When a long-acting GnRH-agonist was used in dogs, Acyline successfully prevented a flare-up. In addition, the prostate volume was decreased by 38% after 30 days, echogenicity and heterogeneity were decreased, and the resistency-index (Doppler sonography) was normal again.

[89]. Monthly injections are required, rendering this medicament for short-term and exceptional use only. Further investigations with long-acting preparations would be of interest. Other medicaments like estrogens, antiestrogens, aldosterone-receptor antagonists, alpha1A-adrenerge-receptor antagonists, phosphodiesterase (PDE)-5 inhibitor, vitamin D receptor agonists, and intraprostatic injection of botulinus toxin type A (BT-A) were investigated; however, they are now obsolete or proved to be ineffective [7].

4.1.5 Prognosis

In dogs, the clinical symptoms can be effectively treated; however, the course of the disease is recurrent. Castration will finally resolve the problem. In stud dogs, special medicaments not decreasing the libido are available and fertility prognosis is good.

4.1.6 Prophylaxis

Regular clinical and sonographical controls of the dogs are a good prophylaxis since only treatment or castration in time will prevent the disease. These controls are recommendable when the dog reached 40% of its estimated lifetime [18].

4.2 Prostate gland cysts

4.2.1 Causes

Cystic changes of the canine prostate gland (intraprostatic cysts) mostly develop in the aged gland, changed by BPH, because of accumulation of prostatic secretions in the dilated prostatic acini; furthermore because of obstruction, compression of intraprostatic channels, or accumulation of urine, when a connection between the cyst and the

urethra exists [90, 91]. Paraprostatic cysts are dilated residua of the Wolff channels; they can be situated in the cranio-lateral, ventral or caudal region of the prostate, and reach a remarkable size. In some cases, they become mineralized [90, 92]. Secondary infections and abscesses can be complications. In one study the prevalence of prostatic cysts was 14% (12/85) and 42% out of these were secondary infected [90].

4.2.2 Clinical findings

The symptoms are dependent on the disease. Many small intraprostatic cysts are asymptomatic in dogs until the enlarged gland causes problems. Intraprostatic cysts frequently occur in the course of BPH and prostatitis; later on, they can cause enlarged abdomen, abdominal pain, decreased well-being, and in case of rupture or secondary infection, an acute abdomen, and sepsis.

4.2.3 Diagnosis

In dogs, diagnosis should be done by sonography or X-ray. Sonographically, cysts appear as hypo- or anechoic, round structures with a thin wall, sometimes sediment or internal cysts can be visualized [45]. (**Figures 4** and **5**). The cysts can be punctured and the contents examined cytologically and bacteriologically.

4.2.4 Differential diagnoses

As described in the chapter BPH.

4.2.5 Therapy

Canine intraprostatic cysts up to 3 cm in diameter can be treated with a 5α-reductase-inhibitor (Finasteride) or with anti-androgens; mostly they regress

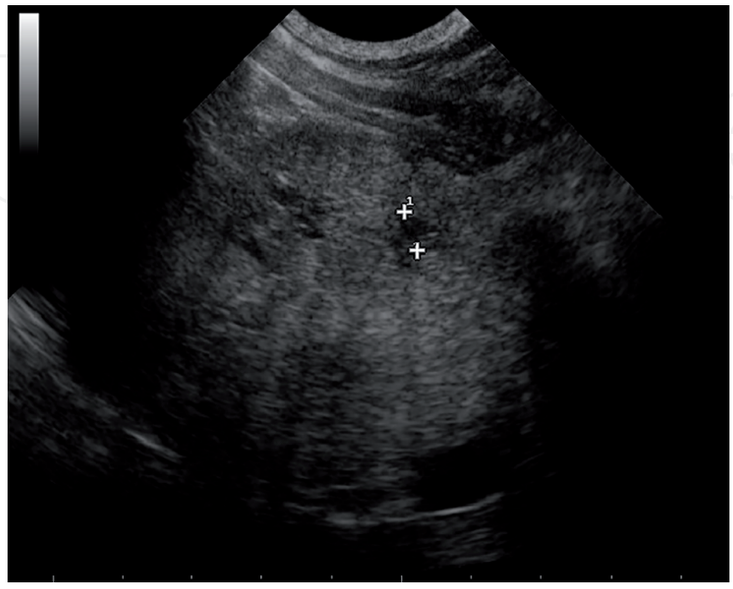

Figure 4.
Sonography (B-mode) of a prostate gland with BPH and intraprostatic cysts. A small cyst is visible (white crosses). Cysts up to 3 cm in diameter can regress with anti-androgen therapy. Cysts filled with urine have a higher recidive rate, also after puncture.

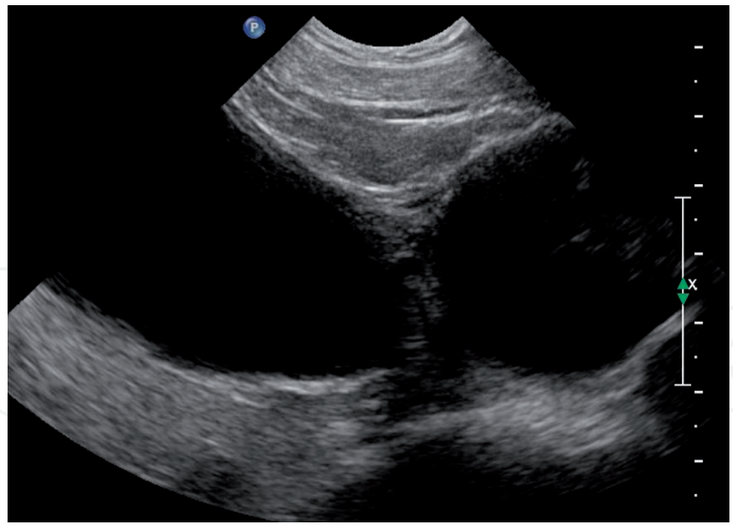

Figure 5.
Sonography (B-mode) of a paraprostatic cyst. On the left side, the urinary bladder is visible; the mucus membrane is irregular and thickened. To the right, a paraprostatic cyst is situated, filled with hypoechoic fluids. The dog showed mild symptoms of a BPH with bloody preputial discharge and stranguria.

within 2–3 weeks. When the treatment is ineffective or in case of larger cysts, they have to be punctured and the secretions aspirated or the cysts must be surgically removed. The puncture should be done with the aid of sonography and transcutaneously (**Figure 6**). The treatment mostly has to be repeated one to four times and only if these measures stay without success, the operation should be considered [93]. The ultrasound-guided percutaneous drainage with alcohol sclerotherapy is controversial,

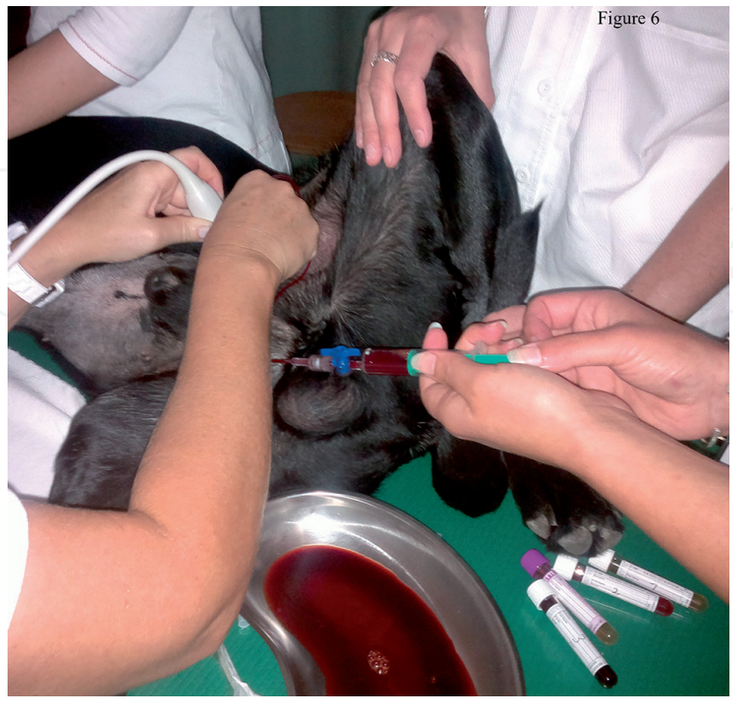

Figure 6.
Transabdominal puncture of a prostate abscess. The gland was visualized with a 7.5 MHz convex probe, the cyst was punctured with a 0.9×40 mm needle, connected to an extension and a three-way cock. The contents were sucked off with a sterile syringe and examined cytologically and bacteriologically.

even though some reports are promising [94]. Recently, canine autologous platelet-rich plasma (PRP) obtained through separation of liquid and solid components from whole blood, it was instilled after removal of cystic fluid in dogs with BPH and prostatic cysts [95]. The PRP dose was half the fluid removed from the cyst. Sixty days later, the cysts were no longer detectable sonographically. The PRP is known to affect antibacterial, analgesic, and anti-inflammatory [96]. The surgical treatment and the treatment of abscesses will be discussed in the following chapter.

4.2.6 Prophylaxis

As described in the chapter BPH

4.3 Inflammatory diseases of the prostate gland

4.3.1 Causes

In dogs, inflammatory diseases can be acute or chronical; they are mostly complicated by infections that ascend via the urethra or spread via the blood circulation [39, 97]. Prostatitis therefore may occur in both castrated and intact dogs. In some cases, a BPH, squamous metaplasia or neoplasia is complicated by an infection. In one study, in 66.6% of male dogs with clinical BPH, bacteria were isolated in the sperm-rich phase of the ejaculate; out of these, 61.1% were positive for mycoplasms, and out of these, 54.5% were positive for *Mycoplasma (M.) canis* [36]. In 2/3 of all cases of prostatitis, a mixed bacterial culture can be found, and only in 1/3 of patients a monoculture [98]. Infectious agents mostly are *E. Coli*, Staphylococcus spp., Streptococcus spp., Proteus spp., Pseudomonas spp., Klebsiella spp., *Brucella canis,* etc., as well as anaerobe germs; Seldom are viruses like the canine distemper virus, or blastomyces and cryptococci in urine, semen, or prostate secretions [9, 39, 97, 99]. It is important to know that abscesses in the prostate gland can be infectious or sterile [7, 41, 99].

4.3.2 Clinical findings

The acute prostatitis can cause severe symptoms like acute anuria or obstipation. A frequent symptom in dogs is purulent-bloody preputial discharge. Fever, inappetence, vomiting, and diarrhea are possible. In case of an abscess, palpation of the gland is highly painful and fluctuation is typical; rupture will cause septic shock.

The chronical prostatitis usually starts with symptoms of the BPH, and then the course is recurrent, causing loss of weight and shaggy hair. Superinfections frequently occur.

4.3.3 Diagnosis

The diagnosis should be done by clinical examination of the dog, sonography, and examination of urine and semen inclusive bacteriological examination. In addition, prostate secretions and the contents of cysts can be examined cytologically [19]. Rectal palpation will be painful. The gland can be asymmetric; the consistency will be elastic in case of acute inflammation, in case of chronical inflammation increased and sometimes hard, the surface can be uneven.

In dogs, hematuria and bloody preputial discharge frequently occur, and pyuria or purulent discharge may occur in case of prostate gland abscess. Bacteriological examination is mostly positive [41].

Blood picture: in case of acute prostatitis and abscesses, leucocytosis and neutrophilia are frequent, in chronical prostatitis, these findings may be lacking. An increased concentration of the enzyme canine-prostate-specific esterase (CPSE) may indicate a prostatic disease; however, differentiation between BPH, prostatitis, and neoplasia is not possible in dogs. Furthermore, the literature provides variable cut-off values [48, 75, 77] and the secretion of the CPSE is age-dependent in dogs. The measured values, therefore, have to be carefully interpreted; the diagnosis must include other findings.

Semen collection in case of acute prostatitis will not be possible but may be helpful in case of the chronical prostatitis. The semen quality initially shows the same abnormalities as in BPH and will decrease in case of infection. Admixture of erythrocytes is a frequent finding, furthermore decreased motility and an increase in morphological abnormalities [19, 39, 40]. The bacteriological examination of the semen or prostatic secretions is mostly positive [7, 9, 39]; additional cytological examination of the prostatic secretions is useful, in case of acute prostatitis and abscesses, granulocytes, blood cells, and bacteria are frequently found, whereas prostate cells appear normal [42, 99].

In dogs, the cytological findings correlate well with the patho-histological findings [39]; however, not with the bacteriological findings [100]. Collection of prostatic secretions is not sterile because of the physiological mixed flora in the urethra [101]; therefore, the quantitative bacteriological findings have to be considered as well.

The transcutaneous, sonographically guided fine-needle-aspiration (FNA) of the prostate tissue and puncture of fluid-filled cysts are important for differentiation between canine BPH and chronical prostatitis or neoplasia [39, 41, 44, 102] (**Figure 6**). The collected material should be examined cytologically and bacteriologically. Up to 70% of prostatitis cases were correctly diagnosed by use of FNA [102]. Complications rarely occur; in some cases, low-grade bleeding and inflammation were observed, especially in case of inflammatory changings [93]. Even though at the time of puncture or FNA it is not known, whether the obtained material is infectious or not, the procedure is safe for the patient, when performed in a sterile manner. The dog should receive nonsteroidal anti-inflammatory drugs (NSAID) for 3 days after the puncture and should be treated as soon as possible with suitable antibiotics according to the resistance test. In rare cases, spreading of tumor cells is possible [103].

B-mode-Sonography: in dogs, enlargement, asymmetry, and heterogeneity are prevailing symptoms. In case of acute prostatitis and abscesses, hypoechogenic sites can be found (**Figure 7**); in chronical prostatitis, hyperechoic sites are frequent, and in case of neoplasia also mineralization (**Figure 8**) [45, 63, 104].

Unfortunately, it is not possible to differentiate between chronically inflammatory and tumorous changings, not with B-mode and Doppler sonography; in these cases, an FNA or biopsy is obligatory in dogs [8, 44, 73]. With grey-scale or pulse-wave Doppler-sonography, it was not even possible to differentiate between inflammatory and normal canine tissue [105]. Similarly, other imaging methods like CT or MRI cannot provide a secure diagnosis; however, in case of canine prostatitis, the CT findings correlated well with the CT outcome [68]. When using CT, the age of the dog must be considered since the normal CT findings change in the aging dog. The prostate growth shows three phases [106]: during the first phase (1–5 years), the gland reaches normal morphology; in the second phase (6–10 years), first hyperplastic changings occur; and in the third phase (≥11 years), senile involution is typical. These changings can be observed in the CT pictures as well [67].

As described in the chapter BPH, the echostructure analysis revealed typical findings in case of prostatitis; homogeneity was significantly decreased in comparison to BPH [62]. Further investigations are necessary to prove these first results.

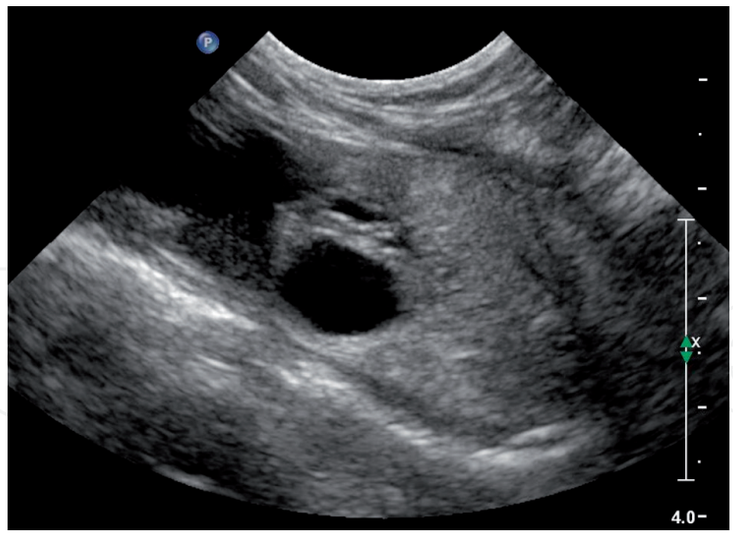

Figure 7.
Sonography of a prostate gland with acute prostatitis. Prostate gland of a 12-year-old dog with fever, apathia, urine loss, obstipation, and a painful abdomen. The prostate gland was painful upon digital-rectal palpation. The gland was high-grade enlarged and the structure was inhomogenous. An intraprostatic cyst, 1,5x2 cm in size, was visible. The urine was examined bacteriologically and Streptococcus canis +++ was found. The dog received effective antibiotics according to the resistency test for 6 weeks and the antiandrogen cyproterone acetate (3 mg/kg SID, s.c.). A sonographical control 2 weeks later showed that the cyst had diminished.

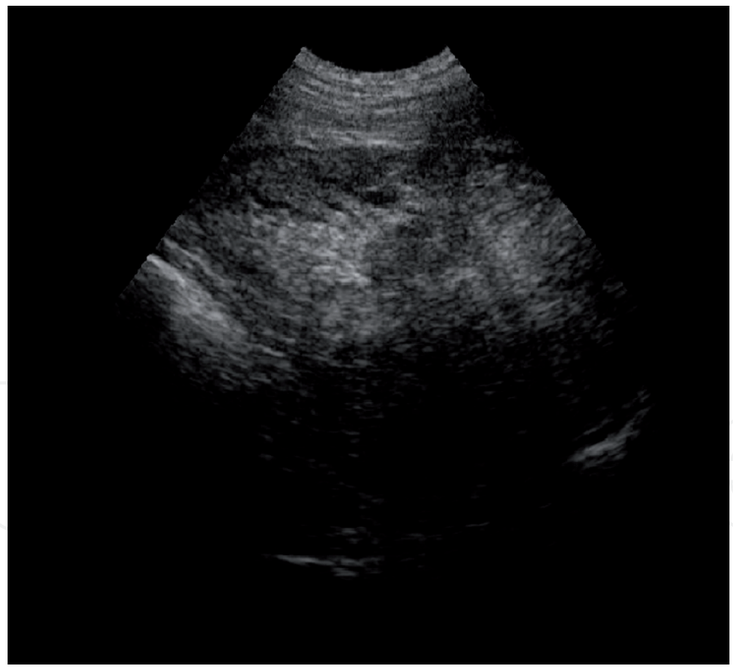

Figure 8.
Sonography of a chronical prostatitis. The gland was high-grade enlarged and the structure was inhomogenous, mainly most areas hyperechoic. Very small cysts were visible. The dog showed chronic recurrent bloody preputial discharge, dyschezia, and obstipation. The semen was examined bacteriologically and ++ E. coli was isolated.

4.3.4 Differential diagnoses

BPH and neoplasia of the prostate gland have to be considered.

4.3.5 Therapy

In acute canine prostatitis, typically, high-grade disturbance of the general conditions occurs; furthermore, acute urination and defecation problems require emergency measures. The rapid reduction of the prostate gland size is important, in addition to effective treatment of the infection. Intravenous infusions of physiological solutions are necessary for treatment of circulatory disturbances. Drugs against pain and inflammation such as NSAID and/or morphine derivates should be given (for example Carprofen 4 mg/kg SID i.v. or Buprenorphin 0.01–0.02 mg/kg every 6–8 h i. v.). In case of vomiting, metoclopramide injections are useful (0.5–1 mg/kg, BID-TID, s. c., i. m., i. v.) or maropitant (1 mg/kg SID s. c., i. v.). Dogs should be In-patient while treated until improvement.

Antibiotics have to be chosen according to a resistance test and according to the ability to penetrate the diseased tissue. In acute cases, the blood-prostate barrier is ruptured; therefore, each broad-spectrum antibiotic can be applied when effective according to the resistance test [97, 107]. Meanwhile, it is important to not only examine for bacteria but also for mycoplasms (M.) and ureaplasma (U.) inclusive specification and quantification; *M. canis*, *M. cynos,* and *U. canigenitalium* were isolated in semen, prostate secretions and urine of dogs with prostatitis. Even though it is not proven that they are causative agents, high-grade monocultures should be treated according to a resistance test [97, 99, 108]. Acute symptoms may be treated with broad-spectrum antibiotics before the resistance test is available [7]. In these cases, fluoroquinolones (for example Enrofloxacin s. c, i. v. SID or SOD 5–10 mg/kg) or erythromycins (for example Azithromycin 5–10 mg/kg SOD) can be given. These antibiotics are also effective against mycoplasms and ureaplasma.

In chronical canine prostatitis, the blood-prostate barrier is intact; therefore, antibiotics must be chosen according to the resistance test and the ability to penetrate the tissue. The latter is possible by using weak alkaline medicaments with a high pKa-value (acid-dissociations constant), good fat solubility, and weak protein binding [97]. In these cases, fluoroquinolones and erythromycins are good options as well, furthermore clindamycin and chloramphenicol.

In both acute and chronical prostatitis, the duration of treatment is important; in chronical cases, 4–6 weeks and up to 8–12 weeks are recommendable in dogs [19, 107]. One week after the end of the antibiotic treatment, another bacteriological examination should be done [19].

In dogs, prostate abscesses can be punctured and emptied; for this measure, a mild sedation is required. The needle should be carefully placed under sonographical control and samples for cytological and bacteriological examination obtained (**Figure 6**); sometimes one to four repetitions are required and in some cases, operative removal of the abscess is necessary [93]. Operative treatment is possible by marsupialization, a Penrose drain, or partial prostatectomy [109–112]; a further method with low recidivism rate is the operative drainage of the abscess cavity and consecutive filling with omentum (omentalization) [112]. The prostate has to be pulled out of the abdomen; the contents of the abscess are sucked off (**Figure 9a** and **b**), then the opening is enlarged and the cavity flushed. Another opening is cut into the opposite side of the gland (**Figure 9c**) and the omentum is pulled into and through the cavity. The omentum is fixed with a suture on the opposite side of the gland. Additional application of antiandrogens and antibiotics according to a resistance test are necessary measures.

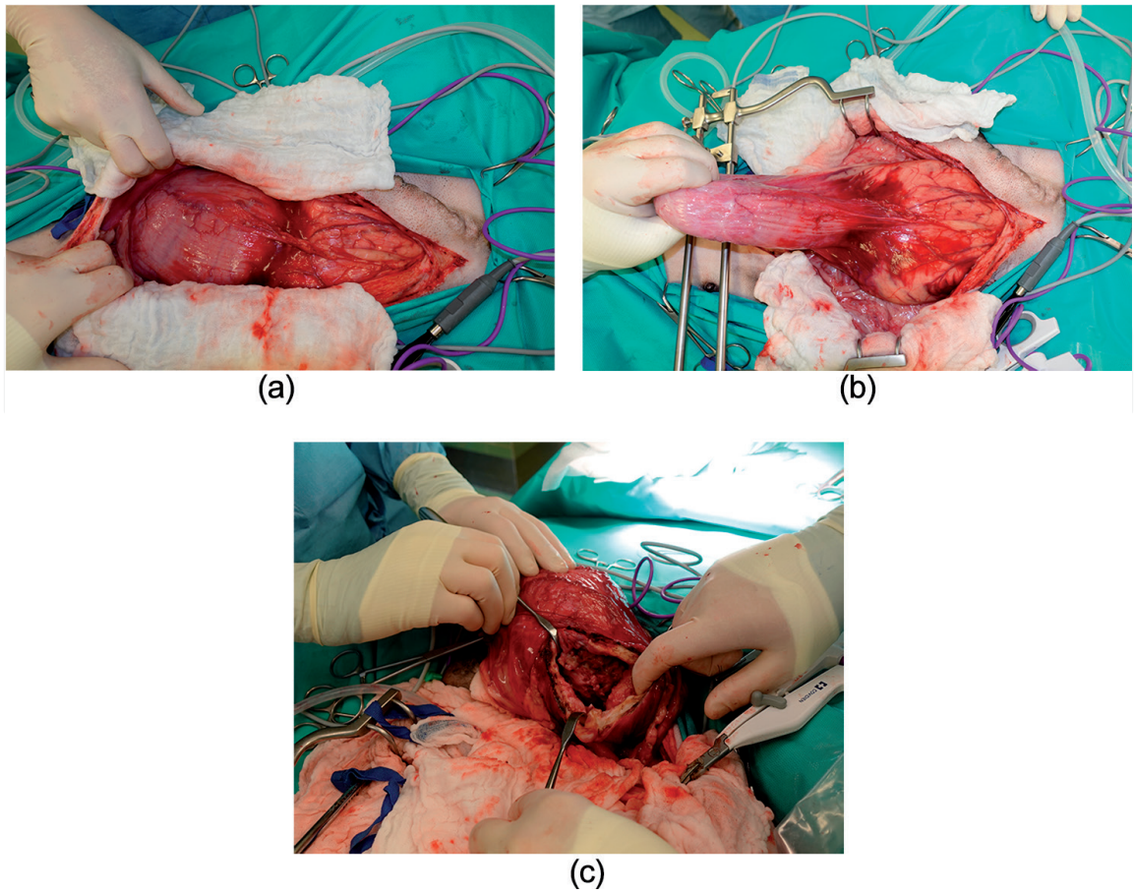

Figure 9.
Omentalisation of a paraprostatic cyst (a); The huge paraprostatic cyst was situated behind the urinary bladder (to the right, black arrow). The wall was high grade thickened. (b) The urinary bladder was emptied and the prostate cyst was pulled out of the abdomen (c) After puncture of the cyst the contents were sucked off, then a large piece of the wall was removed on both sides of the cyst by using a sealing device (LigaSure™, Medtronic, Vienna, A). The omentum was pulled into the cavity and fixed on both sides of the cyst by using resorbable material.

4.3.6 Prognosis

The clinical symptoms can be effectively treated in both acute and chronical cases; however, the course of the disease is recurrent. Fertility prognosis is good when treated in time, with well-chosen medicaments, and over a sufficient period.

4.3.7 Prophylaxis

Regular clinical and sonographical examinations, starting when the dog reached 40% of the estimated life expectation, are recommendable [18].

4.4 Squamous metaplasia

Squamous metaplasia develops because of an endocrine active testicular tumor, secreting androgens and causing hyperestrogenemia, but in addition because of exogenous estrogens [113]. The metaplasia causes a morphological change in the gland, sonographically resembling an inflammation; sometimes cysts occur.

The disease is a side effect of hyperestrogenemia since this problem causes the clinically relevant changes in the blood picture and causes organ damages. Typical

symptoms are alopecia, hyperpigmentation of the abdomen and inguinal region, gynecomastia, and in severe cases anemia.

The diagnosis can be made with FNA; however, rapid diagnosis and treatment of the hyperestrogenemia are more important. Mostly castration will solve the problem. However, it is important to know that the hyperestrogenemia can persist for months after the removal of the testicular tumor. Recurrence of the problem after castration may point toward metastasis.

4.4.1 Prognosis

When the dog is castrated, the estrogen concentration slowly decreases over weeks and months. During this time, infections frequently occur. Dependent on the degree of anemia and organ damage, a careful prognosis is appropriate. In case of low-grade changings and correct treatment, the prognosis is good.

4.5 Tumors of the prostate gland

4.5.1 Causes

Prostate gland tumors are seldom in dogs (<1%, [16, 114] and mostly malign adenocarcinomas or transitional cell carcinomas and seldom lymphomas [41]. The cells of origin sometimes are not identified [15, 115]. They are more frequently diagnosed in castrated than in intact dogs, the growth is not androgen-dependent [[14, 15, 116]. Other diseases of the prostate gland are not predisposing [19]. It is not known, whether the age at castration plays a role [16]. However, the age itself is an important factor, since the disease mainly is diagnosed in dogs aged > 8 years [51, 117–119]. Medium to large size breeds are more frequently concerned than smaller or toy breeds [14, 114]. A breed disposition is not proven; however, a higher risk/odds ratio was found for Shetland Sheepdog, Scottish Terrier, Bouvier des Flandres, Doberman, and mongrels [9, 14, 120].

Recent studies investigated changes in the prostate gland during cancer development at the molecular level. A lack of androgen receptor and the overexpression of P-glycoprotein (P-gp) was described, indicating that androgens do not play an important role in pathogenesis [116]. P-glycoprotein regulates the influx and efflux of testosterone in prostatic cells. New findings suggest NF-kb dysregulation as a probable factor contributing to oncogenesis; chronic inflammations may trigger the change in precancerous cells causing DNA and epigenetic damage [121]. NF-kb is an inducible cytoplasmic transcription factor, able to activate genes for inflammatory cytokines, adhesion molecules, enzymes related to inflammation (such as cyclooxygenase-2), telomerase, antiapoptotic proteins, and cell cycle-regulatory genes [121].

The growth is most aggressive with an invasion of surrounding tissues and high metastatic potential. The incidence of metastases varies between 16% and 80%, dependent on age [119, 122]; the sites of metastasis are primary the lung, then regional lymph nodes, liver, urethra, spleen, colon and rectum, urinary bladder, bones, heart, kidney, and adrenal gland, but also the skin [123]. Metastases are mostly already present at the time of diagnosis of the prostate gland tumor [19].

4.5.2 Clinical symptoms

The symptoms vary independently on castration status; in some dogs, gastrointestinal symptoms are predominant (defecation problems, tenesmus), in others,

symptoms of the urogenital tract occur first (stranguria, hematuria, incontinence, dysuria, pollakisuria, and polydipsia). Enlargement of the gland was observed in only 45% of cases [119]. In some dogs, lameness, loss of weight, and abdominal pain become obvious, especially, when metastases occur [9, 114].

Since the symptoms are unspecific, a prostate gland tumor must be considered in aged dogs with severe symptoms of a disease of the urogenital tract and gastrointestinal symptoms [16].

4.5.3 Diagnosis

Prostate gland tumors are frequently diagnosed too late when the aggressive invasive growth already caused massive tissue damage and metastases. Accompanying inflammation and secondary infections of the urogenital tract complicate the diagnosis. However, early detection is an important factor for survival.

Digital rectal palpation may reveal an uneven surface, immobility, asymmetry, and/or painfulness. A blood picture can show neutrophilia, leucocytosis and in 70% an increase in alkaline phosphatase concentration. Pyuria and hematuria are possible; in the sediment, tumor cells can be detected [119].

However, cytological examination of urine or prostate secretion sediment is unreliable, even when the cytobrush method was used. For the final diagnosis, a biopsy and histological examination of the tissue are obligatory. Transcutaneous FNA has a sensitivity of 80% [119], which can be increased to 89% by punch-biopsy or excisional biopsy [102, 103, 124]. For punch-biopsy or excisional biopsy, total anesthesia is required. The gland has to be pulled forward to be able to perform the biopsy on the ventrolateral surface. The wound is closed with single sutures, including the capsule and parenchyma [125]. Histologically, a prostatic adenocarcinoma can be differentiated from a prostatic carcinoma, urothelial, and tumors of mixed morphology [124, 126]. A possible side effect is the spread of tumor cells [103].

Sonography is not useful to differentiate between inflammation and neoplasia; however, can be helpful [45, 63]. With B-mode, the gland appears inhomogeneous, with hyperechoic areas; mineralizations are frequent and the borders in > 80% of cases appear irregular and diffuse against the rectum, and sometimes even rupture. In many cases, the regional lymph nodes are changed [119]. (**Figure 10**)

Some imaging methods were improved. With contrast-enhanced-Doppler sonography it is possible to visualize the perfusion in the normal prostate tissue and to compare it with prostate neoplasia; in case of adenocarcinoma, the perfusion was significantly higher [81]. Elastography was used in one Labrador dog with prostatic adenocarcinoma, and the histological result of the FNA correlated well with the findings of the elastography [121]. A new experimental method is a combination of simultaneous magnet-resonance spectroscopy (MRS), positron-emission-tomography (PET), and multiparametric magnet-resonance (mpMR). In one study, the results were compared with findings from transrectal sonography and prostate biopsy. In 3/3 dogs, tumor growth was diagnosed by using the combined method; the diagnosis was verified by biopsy [71].

An X-ray of thorax and abdomen should be done to diagnose metastases in the lymph nodes, pelvic bones, and the lung [11, 41].

Recent studies focus on the detection and development of biomarkers for canine prostate cancer [126, 127]. Markers are not easy to find in case of canine prostate cancer since the tumor growth is aggressive and the pattern variable, the basal cell layer is discontinuous and markers are frequently absent. A combination of markers might

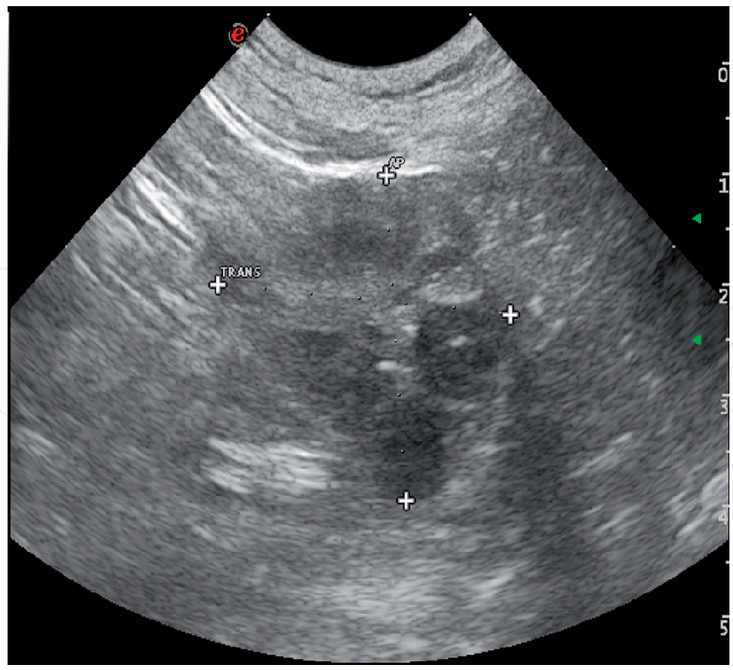

Figure 10.
Sonography of a carcinoma of the prostate gland (B-mode). The male dog showed chronical prostatitis, loss of weight, and a matt coat. The prostate gland was only low-grade enlarged, but high-grade inhomogeneous, with mineralizations. The margin was not well defined and could not be separated optically from the wall of the rectum. Small intraprostatic cysts were visible. FNA of the gland was performed and revealed the diagnosis of prostate carcinoma.

increase the diagnostic accuracy [127]. For a precise immunohistochemical analysis, different markers are necessary to differentiate between urethral, glandular, or ductal origin of the tumor, which is possible in human medicine but not sufficiently investigated in the dog. In dogs, the prostate cancer most probably originates mainly from collecting ducts [128]. In one study, qPCR revealed increased expression of PSMA in all cancer tissues [128].

In dogs, both urothelial carcinoma of the lower urinary tract and prostate cancer may occur. In both cancer types, *canine (c) BRAF V595E* gene mutations were found. The *BRAF* genes belong to the *RAF* gene family known to contribute to the MAPK pathway; mutations promote growth of cancer cells during oncogenesis [129]. *Canine(c)BRAF V595E* gene mutations were recently detected by means of droplet digital PCR (ddPCR) in approximately 80% of urogenital cancer in dogs. The *cBRAF* mutation was detectable in urine samples with the same sensitive assay and in 75% of the cancer patients [129, 130]. However, since in approximately 20% of canine urogenital cancer the *cBRAF* mutation is not detectable, the sensitivity of the ddPCR assay does not exceed 80%.

To differentiate between urothelial and prostate carcinoma, a combination of markers will be necessary. In a recent study [131], the chemokine CCL17 was found to contribute to regulatory T cell (Treg) recruitment in prostate tumors. In dogs with prostate cancer, tumor-infiltrating Tregs were found to be associated with bad prognosis [132]. In urine samples of dogs with urothelial cancer, increased concentrations of CCL17 were found in comparison to healthy dogs. The *cBRAF* mutation is believed to induce the COX-2/PGE_2/EP2 pathway, thereby triggering the CCL17 production and the Treg infiltration in canine urothelial carcinomas; however, a direct relation between *cBRAF* mutation and prognosis was not possible [131]. Recently, the concentration of another chemokine, named CCL2, was found to be increased in urine

of dogs with urothelial carcinoma [133]. The combined measurement of CCL17 and CCL2 in urine might improve the sensitivity and specificity of each biomarker for detection of canine urothelial cancer [131].

In one study, RNA-Sequencing of canine normal prostate gland tissue and malignant tissues was performed to find differentially expressed genes (DEGs) and deregulated pathways. The detected DEGs were grouped into the superior pathways (1) inflammatory response and cytokines; (2) regulation of the immune system and cell death; (3) cell surface and PI3K signaling; (4) cell cycle; and (5) phagosome and autophagy. Meanwhile, some genes were listed in relevant databases and might improve diagnosis and therapy in future.

Furthermore, canine prostate cancer cell lines have been developed making investigation of molecular mechanisms easier [134]; one cell line expressing red-fluorescence proteins was developed to improve in-vivo imaging [135].

4.5.4 Differential diagnosis

BPH, chronical prostatitis, or other tumor diseases must be considered, especially in case of weight loss.

4.5.5 Therapy

Conservative therapy comprises chemotherapy and palliative measures and shall improve the median survival time (MST) and well-being. Surgical treatment is possible; partial and total prostatectomy followed by chemo- and radiotherapy, photodynamic therapy and COX inhibitors [15] are possible methods. Castration is not useful and should not be recommended [19, 119].

Prostate surgery is mostly recommended in case of intracapsular growth and early-stage cancer. For total prostatectomy, the prostate-inclusive prostatic urethra has to be removed; thereafter, the urethra is reconstructed. Subtotal intracapsular prostatectomy proved to prolongue the MST more than 5fold in comparison to total prostatectomy (112 ± 63.3 days vs 19.9 ± 10.67 days [136]. Most frequent postoperative complication is a permanent incontinence, occurring in 33–100% of cases; however, less frequent after subtotal intracapsular prostatectomy [136, 138]. In one retrospective study [139], the postoperative survival time (time between operation and death) was 231 days (median; range: 24–1255 days). In the evaluated studies, ureter-urethral anastomoses (14), cysto-urethral anastomoses (9), anastomoses between ureter and colon (1), and anastomoses between urinary bladder neck and pelvic part of the urethra were described (1). The dogs in addition received mitoxantrone, NSAID, metronomic thalidomide, cyclophosphamide, piroxicam, carboplatin, and/or deracoxib. In 8/23 dogs, postoperative incontinence occurred. Further complications were dehiscence of sutures, uroabdomen, and prepubic herniation. In 3/23 dogs a recidive occurred, in 4/23 metastases were diagnosed [139].

Another study compared the outcome of medical therapy (n=12) and surgery in dogs with adenocarcinoma of the prostate gland [140]. The surgery comprised total prostatectomy (TP, n=20)) and prostatocystectomy (TPC, n=9). In the surgical group, the overall MST was longer than in the medical treatment group (337 vs. 90.5 days). Within the surgical group, the postoperative MST was longer in the TP group (510 vs. 83 days). In case of aggressive prostate cancer, TPC is preferred, therefore more severe complications occur, explaining the shorter MST.

In recent years, the surgery was improved by use of Light-Amplification by Stimulated-Emission-of-Radiation (laser). Meanwhile, the method is used for prostatectomy. The laser (Diode, Nd:YAG or CO2) must be adapted to the predominating tissue, i.e. the vascularization and the pigment since the absorption spectrum can be influenced by melanin, hemoglobin, and water. For prostatectomy, the CO_2 laser in combination with electrocautery was proven advantageous [141].

Immunotherapy is under intense investigation in human medicine and recently, a promising study in dogs with naturally occurring prostate cancer was published [132]. In this study, the presence and molecular mechanism of targeting regulatory T-cells (Tregs) were studied in canine cancer cells and an anti-Treg treatment (anti-human CCR4, mogamulizumab) in combination with Piroxicam tested in dogs with prostate cancer. The tumor response was evaluated according to canine response evaluation criteria [142]. The presence of tumor-infiltrating CCR4 Tregs was found to be associated with bad prognosis. The anti-CCR4 compound reduced circulating $CD4^+Foxp3^+$ Tregs and $CCR4^+$ Tregs, furthermore, the number of local CCR4 cells was reduced. The combined treatment with piroxicam better reduced the tumor size than piroxicam alone. The median progression-free survival time (PFS) was 204 (21–573) days and 57 (6–210) days in mogamulizumab/piroxicam dogs and piroxicam dogs, respectively; the respective OS time was 312 (86–1000) days and 99 (6–468) days. Observed clinical side effects were grade 1 or 2 (vomiting, anorexia, pancreatitis, urticaria, rash, and infusion reaction).

Modern studies investigate molecular targets like tight junction proteins. A recent in vitro approach used prostate adenocarcinoma (PAC) and transitional cell carcinoma (TCC) cell lines to investigate whether it is possible to destroy tumor cells by gold-nanoparticle-mediated laser perforation (GNOME-LP [143]), a noninvasive thermotherapy. The gold-nanoparticles (AuNPs) were conjugated to *Clostridium perfringens* enterotoxin (C-CPE); the latter are known to bind to claudins, which are tight junction proteins frequently expressed in tumors. They are of interest since they regulate the transfer of molecules through tight junctions and in case of deregulation because cancer might contribute to metastase spreading [144]. The targeted AuNPs enter the tumor and the laser activation leads to protein thermodenaturation. The successful laser perforation was recognized by red fluorescence signals. When the combination of functionalized AuNPs and GNOME-LP was used, cell survival was significantly reduced in comparison to non-treated control cells. The targeted treatment is a promising new approach.

In human medicine, *BRAF* inhibitors have been developed for targeted treatment of *BRAF* mutant tumors [145]; respective investigations concerning prostate cancer cell lines are ongoing in veterinary medicine [131].

Another interesting method is the prostate artery chemoembolization, causing necrosis of prostate gland and tumor tissue and a decrease in prostate volume of approximately 70% in one study [146]. The method is promising; however, since all dogs died because of metastases within 9 months, improvement of early diagnosis of the disease is most important.

4.5.6 Prognosis

The prognosis of maligne prostate cancer is poor; the median survival time (MST) is still 0–6.9 months and better in case of intracapsular growth and early-stage cancer [15, 115].

5. Conclusions

Diseases of the prostate gland are frequent disorders of the aging dogs. The symptoms sometimes are unspecific; however, in case of urination and defecation problems in older male dogs, the enlarged prostate gland must be considered. The andrological examination must include the whole urogenital tract. The Benign Prostate Gland Hyperplasia (BPH) develops slowly and mild symptoms like bloody preputial discharge are typical at the beginning. Using routine diagnostic pathways, starting with a thorough case history followed by clinical examination including digital-rectal palpation and B-mode sonography, the correct diagnosis is quickly made in most cases. Measurement of the CPSE serum concentration can be done; however, the result must be carefully interpreted, considering the age of the dog. When the well-being of the dog is disturbed or sonography of the prostate gland reveals signs of a chronical inflammation, further examinations are necessary. Semen collection with cytological and bacteriological examination of the sperm-rich fraction or prostatic secretion is one possibility. If this is not possible, transcutaneous puncture of cysts can be performed, eventually followed by FNA or biopsy of the diseased tissue. All samples should be examined cytologically and bacteriologically; cytological findings well correlate with FNA findings, and the bacteriological examination should always be combined with a resistance test, since antibiotics in chronical cases, have to be applied for weeks. Prostate gland tumors can only be diagnosed by FNA or biopsy; the search for reliable biological markers and new imaging methods is ongoing. New therapeutical methods such as immunotherapy combined with NSAIDs, targeted noninvasive thermotherapy, *BRAF* gene inhibitors or prostate artery chemoembolization are currently under investigation.

Conflict of interest

The author declares no conflict of interest

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