Comparing Human Breast Cancer with Canine Mammary Cancer

13

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Abstract

Tumors arising spontaneously in human and canine mammary gland tissue appear to have many common clinical features. This book chapter gives an overview of the incidence, risk factors, histological appearance, tumor genetics, biological behavior, molecular targets, and treatment responses in human breast cancer patients and dogs with mammary carcinomas. In both species, malignant tumors of the mammary gland are the most frequent neoplasms in females. Accordingly, the sexual steroid hormones, estrogen and progesterone, are considered not only to play a major role in the development of normal but also of neoplastic mammary gland tissue in both species. While most of the tumorigenic mutations arise during the life span of the affected individual, hereditary mutations like BRCA1 and BRCA2, p53, and PTEN are detectable in dogs and humans. Many diagnostic procedures, classification systems, and numerous prognostic features are similar in human and canine patients, though veterinarians tend not to have the same standardized procedures mostly due to the owners' financial limitations. Nonetheless, spontaneous mammary tumors in dogs provide important proof-of-concept models to support preclinical transgenic or xenograft rodent models in the development of new treatment strategies for human and consequently also canine patients.

13.1 Introduction

Human breast cancer (HBC) is a neoplastic disease of the epithelium of mammary glands that occurs mostly, though not only, in females. In this chapter, we will describe and compare the development, clinical symptoms, and treatment of breast cancer and mammary carcinoma in humans and dogs, respectively.

Taking into consideration that cancer is an acquired genetic disease, the decoding of the dog genome in 2005 and finding that the genome has high homology to its human counterpart were major breakthroughs for comparative oncology (Lindblad-Toh et al. 2005). In contrast to many chapters of this book, we will not include a separate chapter for horses, as mares do not tend to develop mammary carcinoma. Up to date, only few case reports on mammary carcinoma in horses have been published; therefore no epidemiologic or etiologic data is available. Similarly, data about cats with mammary carcinoma is rare to date, which makes the comparison with dogs and human mammary gland tumors inconclusive. However, the comparative analysis of the feline and canine genome, which was published just recently, will provide the key for researchers to explore and collect data on feline mammary tumors in the near future (Montague et al. 2014).

412,258 female patients suffered from breast cancer across Europe in 2012 (Ferlay et al. 2015), making this type of cancer the most common cancer in women. It is estimated that men have a 150-fold lower risk of developing breast cancer; thereby there were about 2500 men suffering from breast cancer in Europe in 2012. Similarly, mammary gland tumors are the most common neoplasms in intact female dogs, although reported data varies depending on the origin of the study. In general, open population-based or insurance-based studies may underestimate the natural

incidence of mammary carcinoma in dogs, although an open population-based study from the UK describes an annual incidence rate of 205 mammary tumors (malignant and benign) per 100,000 dogs (Dobson et al. 2002).

During the last decade, three main risk factors for canine mammary tumors (CMT) have been identified: breed, age, and hormone exposure (Perez Alenza et al. 2000; Sleeckx et al. 2011). Studies on mammary tumors have shown that certain breeds are more likely to develop mammary tumors than others, suggesting a genetic influence. Purebred and smaller dogs such as poodles, dachshunds, Maltese, Chihuahuas, Yorkshire terriers, and cocker spaniels are predisposed to mammary tumors (Schneider 1970). Nevertheless, larger dog breeds like boxers, English setters, pointers, Brittany and English springer spaniels, Dobermans, and German shepherds are also at an increased risk. While mutations in breast cancer genes (BRCA1) and (BRCA2) account for 5–10 % of all human breast cancers, data from canine BRCA mutation studies is limited at present (Rivera and von Euler 2011; Enginler et al. 2014). Interestingly, a recent study in English springer spaniels showed a significant correlation between germ line mutations in BRCA1 and BRCA2 and mammary carcinoma (Rivera et al. 2009). Usually, mammary tumors affect middle-aged and older dogs, the mean age for malignant mammary tumors being 9–11 years, while benign tumors occur at a mean age of 7–9 years. Though humans and dogs have different life expectancies, their biological age at onset of mammary tumors is approximately the same. Human patients have a reported peak incidence at the age of 50–58 years, which coincides with the age at peak incidence in dogs after converting "dog years" to "human years" by multiplying with an average factor of five.

The role of sexual steroid hormones has been well described, although a recent meta-analysis has found only a weak correlation between early castration and the development of mammary carcinoma (Beauvais et al. 2012). Nevertheless, the incidence of CMT in countries with the common practice of early castration of female dogs (before the first or second heat cycle), such as the USA and some countries in Western Europe, is significantly lower than it is in countries such as Spain, Italy, and Scandinavia, where most of the dogs are intact.

Interestingly, obesity increases the risk of developing mammary tumors and influences their behavior in humans and dogs alike. Studies in human and canine mammary cancer patients have identified hormones and cytokines and their receptors (insulin, aromatase, leptin, IL-6, insulin-like growth factor-1 (IGF-1), and its receptor (IGF-1R) secreted by the fatty tissue as potential risk factors (Lim et al. 2015).

13.2 Breast Cancer in Human Patients

13.2.1 Clinical Problem

Breast cancer, as the most common cancer in females in Western countries, represents a tough challenge for oncologists treating these neoplasms (Rahman and Hasan 2015). Nevertheless, during the last decades, significant progress was made

to establish improved diagnostic methods and therapies, followed by significant increase in patients' survival time after diagnosis. Today, diagnosis and therapy of breast cancer is a multidisciplinary issue involving gynecology, oncology, surgery, radiology, obstetric medicine, pathology, and several additional disciplines (Ueno and Mamounas 2016).

13.2.2 Pathophysiology

The human body consists of approximately 4×10^{13} cells (Bianconi et al. 2013). Various, entangled mechanisms are responsible for regulation of their growth and death, thereby preventing uncontrolled proliferation. If a cell escapes these regulating mechanisms due to changes in its genome, cancer occurs (Hanahan and Weinberg 2011). Cancer cells are characterized by longer survival, formation of new cancer cells, and invasion and destruction of other tissues (Hanahan and Weinberg 2011). They are even able to remodel surrounding tissue to ensure their nutrition by formation of additional blood vessels (Nishida et al. 2006). In the pathogenesis of breast cancer, where the epithelium of the mammary gland transforms into cancer cells, hormones like estrogen and progesterone play a crucial role. They are key regulators of physiological breast development and function. Therefore, breast cancer is a hormone-driven disease, and hormone levels are the major risk factor. Women without functional ovaria and estrogen substitution almost never develop breast cancer (Yager and Davidson 2006). Additional risk factors for developing breast cancer can be divided into genetic factors, ionizing radiation exposure, obesity, smoking, and alcoholism. Only 5–10 % of all breast cancers are caused by genetic mutations, which are present at birth. The probability for developing breast cancer is 65 % for women having the breast cancer gene mutation BRCA1 and 45 % for those women having the BRCA2 mutation (Antoniou et al. 2003). Other hereditary mutations, like abnormalities in the p53 tumor-suppressor protein (Li-Fraumeni syndrome), are also associated with a significantly higher occurrence of breast cancer, but are very rare in the general population. However, in about 40 % of women with breast cancers, mutations of p53 are found. In additional 10 % of cases, the PTEN gene that also acts as a tumor suppressor is mutated. Additional 25 % of cases express the epidermal growth factor receptor family member HER2. In this case the gene is not mutated; however, the resulting gene is overexpressed (Olayioye 2001). As with many other tumors, the occurrence rate of breast cancer correlates with increasing age; however, after the menopause, the rate is lower (Adami et al. 1985). So far, three periods in the life of a woman have been shown to have a high influence on breast cancer development: the time points of the menarche, of the menopause, and of the first pregnancy. Women with a later menarche (16 vs. 12 years), but earlier menopause (42 vs. 52 years) or pregnancy (under 18 years), have a 30–60 % lower risk of developing breast cancer. These factors, especially the age at first pregnancy, could explain the high country-dependent differences in breast cancer frequency (Adami et al. 1985). Women from North America have a nine times higher risk for developing breast cancer when compared to women in Asia

(Son et al. 2015). This correlates with lower estrogen levels in Asian women. These differences seem not to have a genetic background, as the estrogen levels of Asian women who immigrate to North America tend to adjust to those of Caucasian women born in North America. If the diet has an influence on the rate of breast cancer is currently discussed controversially (Lelievre and Weaver 2013). Studies have shown that a high calorie and fat intake increases the risk for breast cancer. However, so far, no correlation between the source of fats has been shown (Escrich et al. 2014). Tobacco and alcohol consumption are also associated with a higher breast cancer risk (Adami et al. 1985). Exogenous supply with hormones, for example, by hormonal birth control, seems to slightly increase the risk for premenopausal breast cancer. In contrast to hormonal birth control, the hormone replacement therapy, if given over a period of 6–7 years, doubles the risk for breast cancer. Due to studies performed by the Women's Health Initiative, the prescription rate of hormone replacement therapies has been reduced, followed by a reduction in breast cancer incidence (Collaborative Group on Epidemiological Studies of Ovarian Cancer et al. 2015).

Breast cancer is a very heterogeneous disease, ranging from indolent cancers that may never be diagnosed to malignant cancers that progress fast and have a grave prognosis. Due to improvements in screening procedures, the majority of breast cancers are detected in an early stage. This early diagnosis is the main reason for improved survival (Saadatmand et al. 2015).

13.2.3 Diagnosis

The definitive diagnosis of human breast cancer is usually made by a biopsy of the mammary tissue. Nevertheless, the routinely performed palpation of the breast is the first step in the diagnostic procedure. Some studies suggest that the self-examination does not increase survival in breast cancer and advise against it, as the false-positive rate is quite high. The German S3-guideline for breast cancer recommends that every woman should be aware of the changes of her body and that every woman above 30 should be offered with a manual examination of the breasts at least once per year (Albert 2008). In addition, not only the gynecologists but also general practitioners should perform breast examinations, as an early tumor recognition improves the rate of survival significantly. The procedure of the examination includes the palpation of the breast and of the armpit (axillary) region. Several methods for performing the examination are described, but a specific one is not recommended. It is helpful, if the same method is used all the time. Findings, like an irregularly defined, hard, and relocatable lump, can indicate a malignancy; however, the final diagnosis can only be made by a biopsy. If a woman performs self-examination regularly, she should do it always at same stage of the menstrual cycle in order to prevent hormonal influences to the texture of the tissue (Oeffinger et al. 2015).

According to the S3-guideline, women between the age of 50 and 70 should have a mammography every second year, as this is the only effective screening method

for early stage carcinoma. In the age group of 40–49, a mammography can increase the early recognition rate and survival; however, the false-positive rate is higher when compared to the age group of 50–70. Therefore, women younger than 50 years should undergo a routine mammography only if they have known risk factors for breast cancer (e.g., BRCA1 or BRCA2 mutations). Women with BRCA mutations or other risk factors should be examined in a center that specializes in breast cancer, as they need intensive, continuous monitoring starting at an earlier age (30 years). For those women with a high density of the breast, an additional sonography is recommended in order to increase the limited sensitivity of the mammography. Women above 70 can also be offered regular mammography screens depending on present risk factors, fitness, and life expectation. In women with a high risk for breast cancer development (e.g., BRCA1/BRCA2 mutations are present), contrast-enhanced magnetic resonance imaging should be used in addition to mammography. Despite the occurrence of false-positive and false-negative results, mammography is recommended as a tool for reducing mortality caused by breast cancer, and the benefits prevail the risks resulting from the exposition to radiation. Its sensitivity can be increased by up to 10 % if two radiologists analyze the same picture. However, in contrast to sensitivity, a second opinion does not increase the specificity. If a suspicious formation is present, several different imaging methods can be applied in order to improve the assessment of the risk for malignancy. They include magnified and spot-compressed views, oblique imaging, and sonography. If the risk of malignancy is still considered low (<3 %), a follow-up examination should be performed after 3–6 months. If the risk is higher than 3 %, additional examinations are necessary (Albert 2008).

The next step in the diagnostic procedure is a tissue biopsy. The method of the triple diagnosis, including palpation, mammography, and fine-needle aspiration, is not recommended, as the cytological examination requires extensive experience of the pathologist. The tissue biopsy, where not only cells themselves but also the coherent tissue is excised, obliterates the 1 % risk of malignancy that remains when fine-needle aspiration is used. Several methods of biopsy exist and are used depending of the position, size, texture, and chance of malignancy. Stereotactic biopsy, an image-guided intervention, is especially helpful if small, probably benign lesions are present. It is a less invasive method when compared to open excisional biopsy, which should be used only if an image-guided intervention is not possible. The benefit of the excisional biopsy is that the tumor is usually remove in total, and no further interventions are needed if tumor-free surgical margins have been achieved. In the presence of suspect lymph nodes within the axillary region, a biopsy of these nodes should be performed too. This can reduce unnecessary axillary surgeries (Albert 2008).

The biopsy material is evaluated for the type of cancer and for the maturity (differentiation) of the neoplastic cells. In general, better differentiated neoplastic cells tend to have a lower proliferation- and metastasis rate and thereby a better prognosis. Immunostaining for estrogen receptors, progesterone receptors, and HER2 is performed and provides a rationale for systemic treatment options. Molecular analysis for the presence of genetic aberrations also provides important information about prognosis and treatment options (Albert 2008).

A vital part of the diagnostic procedure in locally progressed carcinoma or suspicious clinical symptoms is the evaluation of the stage of progression. X-ray imaging of the chest and abdomen, sonography of the liver, scintigraphy of the bones, and additional imaging using computed tomography can reveal presence of metastasis and indicate for an additional, systemic therapy (Albert 2008).

Breast cancer staging uses the "TNM" system of the World Health Organization (WHO), where T refers to the primary tumor in the breast; N refers to progression into regional lymph nodes; and M refers to distant metastasis. A higher stage is associated with a less favorable prognosis. Lower stages as 0, I, and II, as well as many stage III cancers, are considered to be curable. Therefore, the primary treatment option is surgery. In higher stages, a systemic treatment is the first approach, followed by secondary surgery if reasonable (NCCN clinical practice guidelines in oncology: breast cancer).

13.2.4 Therapy in human breast cancer

As mentioned above, surgery is the method of choice for lower-stage carcinomas and can be curative. In smaller tumors, where at least 1 cm difference between the tumor and the healthy tissue can be achieved, a lumpectomy can be performed. This is a breast-conserving method, and it may be as effective as a complete removal of the breast (mastectomy) (Albert 2008). Due to cosmetic and psychological issues, this method is increasingly utilized. However, in large tumors, in low-differentiated tumors with a high risk of recurrence, or in presence of more than one tumor, a mastectomy may be indicated. The aim is to achieve tissue margins clear of tumor cells for complete tumor removal. In order to do so, sometimes additional tissues, like parts of breast muscle, have to be removed too. Additional tissues that are sometimes removed are the axillary lymph nodes (Albert 2008). Today, the so-called sentinel lymph node (SLN) dissection is used most often. In contrast to previous methods, which included removal of up to 40 axillary lymph nodes, the SLN dissection utilizes tracing of the specific lymph nodes responsible for tumor drainage by dye staining or radioactive tracing. Removal of only few lymph nodes can prevent problems with the lymph drainage of the affected arm with only low risk of increased recurrence and decreased survival (Kuehn et al. 2005).

Radiation therapy is frequently used in combination with surgery. It is primarily applied after a lumpectomy in order to remove eventual residual neoplastic cells from the breast tissue and prevent local recurrence of the tumor (Anderson et al. 2009). A lumpectomy combined with a radiation therapy has the same low recurrence rate as a radical mastectomy. However, radiation can be also used if the complete removal of the tumor by mastectomy was not possible. Radiation can be applied externally using high-energy X-rays or internally by placing the radiation source directly at the site of surgery (brachytherapy) (Albert 2008). Radiotherapy destroys both normal and tumor cells; therefore, it is usually given over a longer period (up to 10 weeks) of time, so that the normal tissue has the chance to recover, whereas tumor cells often lack the necessary repair mechanisms. Most common method of applying radiation is a linear accelerator, and the treatment is planned

using computed tomography. The radiation itself is performed from several angles, all focusing on the breast, so that the highest dose can be delivered to the former tumor site with reduced stress to the other organs. In patients with metastasized carcinoma, radiation therapy is applied only in a palliative setting in order to reduce pain and other symptoms (Albert 2008).

In patients with aggressive tumor types, HER2-positive tumors, with metastasizes or in young patients (<35), an additional systemic therapy is recommended. This systemic therapy can be divided in three different types: chemotherapy, immune therapy, and hormonal therapy (Albert 2008). An adjuvant (post-surgery) chemotherapy should contain a taxane and an anthracycline. The chemotherapy is cycle based, so that the normal cells have certain time periods for recovery. In case of HER2-overexpressing tumors, an immune therapy with trastuzumab (HER2-targeting antibody) should be started together with the adjuvant chemotherapy. After the completion of the chemotherapy, a hormonal therapy with tamoxifen should be given to patients with estrogen- and/or progesterone-sensitive tumors. If tamoxifen is given as a single drug, the hormonal therapy can be given over at least 5 years or until the tumor recidivates. In patients, where an adjuvant systemic therapy is indicated, it can also be given as a neoadjuvant therapy. The primary goal of a neoadjuvant therapy is to reduce the tumor size before a surgery can be conducted. However, in those tumors where surgery would be applicable as the first approach, there is no difference in survival regardless if the therapy is given pre- or post-surgery (Albert 2008).

In conclusion, many different drugs and drug combinations for treatment of breast cancer are available today. The suitable therapy is given depending on the grade and stage of the tumor, molecular and/or immune markers, age, fitness, and the hormonal status of the patient.

13.3 Tumors of the Mammary Gland in Dogs

13.3.1 Clinical Presentation

Female dogs usually have five pairs of mammary glands arranged in two mammary chains. Canine mammary tumors (CMT) are usually well palpable masses that are noticed by dog owners themselves. Alternatively, veterinarians may detect nodules in the mammary gland during a routine checkup. About half of the mammary tumors are benign and half are malignant and half of the latter metastasize to regional lymph nodes and/or lungs (Sleeckx et al. 2011). Tumors can arise in every mammary gland, though two most caudal mammary glands are most frequently affected. Whenever a dog is presented with a mammary tumor, thorough palpation of all mammary glands is recommended since 70 % of the intact dogs have more than one tumor at the time of diagnosis (Fig. 13.1). Dogs suffering from inflammatory mammary carcinoma (IMC), a rare tumor of the mammary gland, are often misdiagnosed as having mastitis due to the clinical appearance. In these cases, the entire mammary chain is swollen, warm, and painful. In most of the cases, affected patients have distant metastases and a very poor prognosis, similar to human patients with IMC (de M Souza et al. 2009).

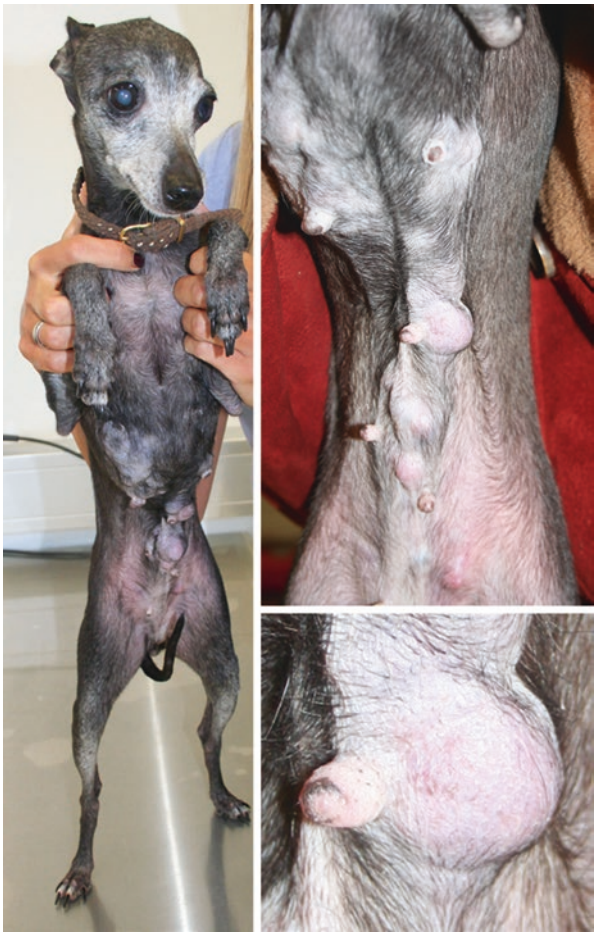

Fig. 13.1 Canine mammary cancer. Italian greyhound, female unspayed, 14 years of age with multiple tumors in both mammary chains

13.3.2 Pathophysiology

Hormone exposure is one of the main risk factors for mammary tumors in humans and dogs. Estrogens and progesterone are essential for normal mammary gland development and maturation. Historically, the tumorigenic effect of estrogens was attributed solely to the fact that their binding to the mammary gland receptors leads to increased growth factor production and therefore cell proliferation. More recent studies have detected that estrogens and their metabolites have direct genotoxic effects resulting in mutations and abnormal numbers of chromosomes in cells of the mammary gland (aneuploidy) as well. The tumorigenic effect of progesterone is caused by its stimulating of the production of growth hormone (GH) and the expression of growth hormone receptors, resulting in increased insulin-like growth factor-1 (IGF-1) levels in the mammary gland (Spoerri et al. 2015). The GH/IGF-1 axis has been identified as an important factor in tumor induction, and many studies have demonstrated elevated tissue concentrations of GH, IGF-1, progesterone, and

estrogen metabolites in malignant tumors. When comparing the hormonal etiology of CMT and HBC, the differing hormone cycles of women and female dogs as well as menopause, which dogs do not go through, must be taken into consideration.

Most dogs develop tumors at multiple sites along the mammary chains. Interestingly, tumors of different sizes and in different stages of progression – benign tumors, premalignant hyperplasia, carcinoma in situ, and malignant invasive tumors – may be found in one and the same patient (Sorenmo et al. 2009). This is called multistep carcinogenesis and is the result of the accumulation of genetic alterations like mutations in oncogenes and/or loss of tumor-suppressor genes in mammary gland cells.

Mammary cancer is a rather heterogeneous disease: mammary gland tumors may arise from epithelial, glandular, or mesenchymal tissue; some tumors remain benign, while others become malignant. However, similar to human breast cancer patients, most of the malignant tumors in canines are carcinomas of epithelial origin (Sorenmo 2003). Sarcomas are very rare tumors of the mammary gland, accounting for less than 5 % of all mammary tumors. The biological behavior of these neoplasms is highly aggressive and associated with a very grave prognosis.

The similar pathophysiology of canine and human mammary gland tumors provides unique opportunities to study risk factors, mammary carcinogenesis, and metastatic mechanisms in a comparative manner with direct implications for humans and dogs (Uva et al. 2009).

13.3.3 Diagnosis in canines

At present, the WHO international classification of mammary tumors in dogs combines their histogenetic classification, descriptive morphology, and prognostic elements (Misdorp 1976; Goldschmidt et al. 2011). While the cytological examination is a necessary initial diagnostic step to exclude differential diagnoses (e.g., abscess), it cannot be used to classify CMT. Classification and grading of the CMT must be based on the assessment of a biopsy sample or the surgically resected tumor itself (Goldschmidt et al. 2011).

In addition, 50–70 % of dogs with CMT have multiple tumors at presentation; therefore many veterinarians recommend bilateral mastectomies to remove the existing tumor and prevent new tumor formation in the remaining mammary glands. However, recent studies were not able to identify a significant difference between simple mastectomy (removal of one mammary gland) and chain mastectomy regarding disease-free interval and overall survival, but there are also studies available, which indicate that surgical extent is important. CMT are graded according to a specific scoring system from grade I (low grade) to grade III (high grade). The process of describing the severity of the patient's cancer based on the size of the tumor and whether or not cancer has spread in the body is called staging. As in human patients, CMT are staged according to the TNM system of the WHO, describing the size of the tumor as well as the presence or absence of local (lymph node) and distant metastasis (e.g. in the lungs). Staging includes a thorough history, physical

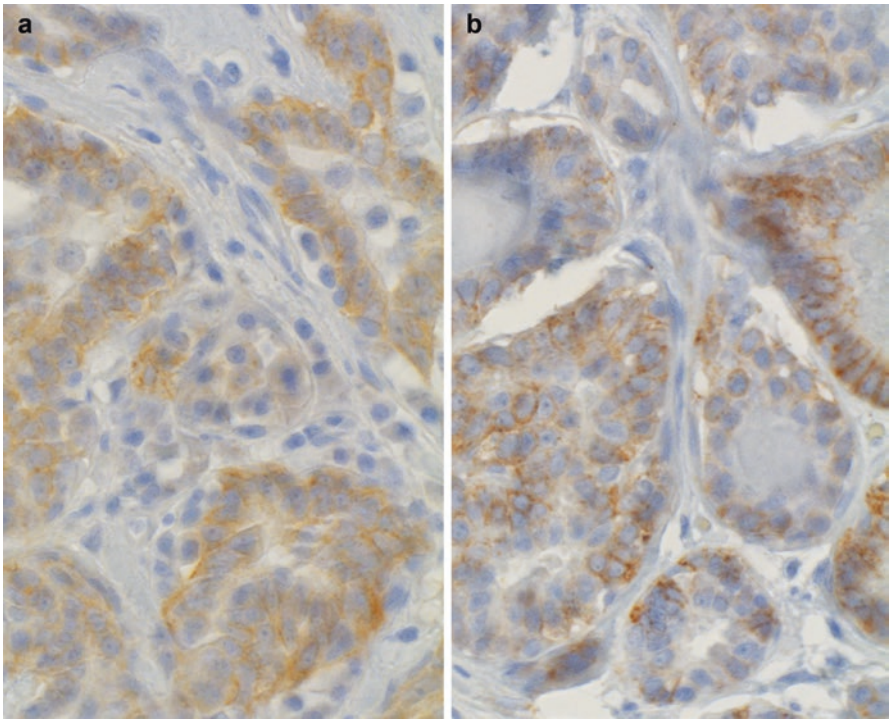

Fig. 13.2 Immunohistochemical staining of the HER2 equivalent in dogs with mammary cancer. (a) and (b) Two exemplary canine mammary carcinoma specimens showed positive staining with HercepTest™, as visible by the specific brownish color in the HER2 overexpressing cancer cells (staining kindly provided by Josef Singer, Institute uf Pathophysiology and Allergy Research, Medical University Vienna). HercepTest™ is the most routinely used immunohistochemical assay to determine HER2 protein overexpression in human breast cancer tissue. The molecular similarity (92 % amino acid sequence homology between human and canine HER2) makes the use of this test kit in canine samples thus feasible (Singer et al. 2012)

examination, complete blood work, thoracic radiographs, and abdominal ultrasound in cases of suspicious lymph node involvement. The use of additional imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI) has been evaluated in CMT, though these techniques, as well as positron emission tomography (PET), are not routinely applied in the diagnostic workup of dogs with mammary tumors. Nevertheless, a CT scan of the thoracic cavity is more sensitive for lung metastases than lung radiographs and will be increasingly established as part of routine tumor staging. As in humans, a higher stage is associated with a poorer prognosis, and the status of the local lymph nodes is highly prognostic. Additional markers, like hormone receptors (estrogen receptors (ER), progesterone receptors (PR), and other growth factors, e.g., human epithelial growth factor receptor-1 and -2; EGFR1/HER1 and EGFR2/HER2), are not part of the routine diagnostic procedures in dogs at present. Although ER and PR are usually detectable in

benign and low-grade carcinomas, high-grade carcinomas are more often negative for hormone receptors, as in humans with highly aggressive breast cancer. Interestingly, as shown in Fig. 13.2, HER2 overexpression has been detected in CMT using the same test as in human breast cancer diagnostics (Singer et al. 2012). Some studies have shown that, as in human breast cancer patients, HER2 staining significantly correlates with negative prognostic features and short survival time. However, there are also other studies with controversial results in regard to HER2 expression of CMT patients; therefore further research is warranted to confirm the species comparability in this concern (Pena et al. 2014). The p53 suppressor gene is a major regulator of cell growth after DNA damage and is able to stop tumor formation. When mutations appear in this gene, the tumor-preventive function is diminished and tumor formation and progression may occur. Mutations in this gene are detectable in about 20 % of dogs with mammary tumors and indicate a grave prognosis (Klopfleisch et al. 2011).

Many diagnostic procedures, the classification systems, and also numerous prognostic features are similar in human and canine patients; nevertheless, veterinarians do not use the same standardized procedures mostly due to financial limitations of the dog owners.

13.3.4 Therapy in Canine Cancer

Surgical excision is the therapy of choice in all dogs with mammary tumors except those with advanced metastatic stages and IMC. Dogs with benign mammary tumors and about half of the dogs with malignant tumors will be cured after surgical resection of the neoplasms. Whether radical mastectomy (surgical removal of both mammary chains) is indicated or partial resection might suffice continues to be controversially discussed. However, a recent prospective clinical study determined that 58 % of dogs undergoing only partial mastectomy developed a new mammary tumor after surgery (Stratmann et al. 2008). Therefore, these authors recommended a more aggressive surgical approach. Furthermore, resection of the inguinal lymph nodes is indicated in all dogs due to their proximity to the caudal mammary glands. Controversy also persists regarding gonadectomy after CMT resection. Whether late castration of female dogs with CMT influences survival time is still under investigation, and further investigations are warranted. However, there is one recent report that shows a significantly longer survival time in dogs with CMT that underwent ovariectomy or ovariohysterectomy after CMT surgery (Sorenmo et al. 2000). Since the most common hormone therapy in HBC patients with ER-positive tumors, the antiestrogen drug tamoxifen is not recommended in canine mammary cancer due to its severe hormone-related side effects; gonadectomy seems to be the most practical approach in dogs.

In the last decade, clinical trials have been performed demonstrating the effectiveness of radiation therapy, hormone therapies, chemotherapy, and treatment with COX-2 inhibitors and angiogenesis inhibitors. Nevertheless, there are no established guidelines regarding additional therapies after surgical excision of CMT. For

example, while radiation therapy has long been established in HBC therapy to control local recurrence, the benefit of radiation therapy has not yet been evaluated in the course of treatment of CMT.

The efficacy of numerous cytotoxic drugs like 5-fluorouracil, doxorubicin, cyclophosphamide, paclitaxel, and gemcitabine has been evaluated in CMT patients, demonstrating clinical potency, but broader clinical trials are warranted to support evidence-based guidelines in dogs (Simon et al. 2006). Despite this uncertainty, chemotherapy is recommended for highly malignant tumors in dogs. Similarly, antiangiogenic drugs should be effective as there is strong evidence that CMT have a higher vessel density than mammary gland tissue (Madej et al. 2013). However, these drugs are very expensive and therefore not used in veterinary medicine at present. Immunotherapy against overexpressed growth factors like EGFR2 (HER2) with monoclonal antibodies is established in HBC, and there is strong evidence that this treatment may benefit dogs with HER2-positive CMT as well (Singer et al. 2012). Unfortunately, however, these antibodies are humanized and cannot be applied in dogs to date, though efforts are being made to develop caninized monoclonal antibodies against tumor-associated proteins for the treatment of CMT (Singer et al. 2014).

Mammary gland tumors are one of the major health problems in women and female dogs alike. Exposure to similar risk factors due to shared environment and life style, the fact that humans and dogs have similar genomes and gene mutations, and the high incidence of CMT in female dogs make spontaneously occurring CMT a valuable model for oncological research (Queiroga et al. 2011). As a result, canine patients benefit from new diagnostic procedures and treatment options developed for HBC patients. The one-health concept is internationally accepted in the field of comparative oncology, making many novel and highly effective targeted drugs available to canine cancer patients as well.

13.4 Synopsis

In this chapter, the incidence, risk factors, histological appearance, tumor genetics, biological behavior, molecular targets, and treatment responses of malignant neoplasms of the mammary glands are compared in humans and dogs. While breast cancer is a very heterogeneous disease, there are many similarities regarding clinical appearance, diagnostic procedure, therapeutic options, and prognostic features. Therefore, a one-medicine concept to develop new treatment strategies can benefit both human and canine mammary cancer patients.

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