Mammary Tumours in Dogs and its Treatment Option- A Review

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ARTICLE INFO

Received: September 11, 2020
Published: September 22, 2020

Citation: Haben Fesseha. Mammary Tumours in Dogs and its Treatment Option- A Review. Biomed J Sci & Tech Res 30(4)-2020. BJSTR. MS.ID.004980.

Keywords: Neoplasm; Tumor Disease; Hyperplastic Lesions; Mammary Adenoma; Fibrothecoma; Glandular Epithelium

ABSTRACT

Mammary tumors are the most common type of tumors in intact female dogs. Several epidemiologic studies have been conducted over the years and provide an estimate of the incidence of canine mammary gland tumors. This type of treatment recommendation may also be made in dogs based on recognized, well-accepted prognostic factors such as tumor size, stage, type, and histologic differentiation. Based on the limited clinical information available in veterinary medicine, the drugs that are effective in human breast cancer, such as cyclophosphamide, 5-fluorouracil, and doxorubicin, may also have a role in the treatment of malignant mammary gland tumors in dogs. The treatment of canine mammary gland tumors will be based on the individual oncologist's understanding of tumor biology, experience, interpretation of the available studies, and a little bit of gut-feeling. Randomized prospective studies are needed, however, to evaluate the efficacy of chemotherapy in dogs with high-risk mammary gland tumors and to determine which drugs and protocols are the most efficacious.

Abbreviations: PTHrP: Parathyroid Hormone-Related Protein; ER: Estrogen Receptor; SNP: Single Nucleotide Polymorphism

Introduction

A tumor is an abnormal mass of tissue resulting from autonomous, progressive, excessive proliferation of body cells not integrated into normal tissue and exhibit varying degrees of fidelity to their precursors [1]. In oncology, the expression of tumor disease, cancer disease, and the term neoplasm are used. The term neoplasm is composed of the prefix neo, which comes from the Greek neos (new) and plastic (formation) [2]. Non-neoplastic tumors are defined as neoplastic-like lesions without an inflammatory component whereas masses with inflammatory infiltrates with or without an intralesional etiologic agent were defined as inflammatory lesions [3]. A tumor may be classified by their primary site of origin, grade, stage (tumor size (T), the degree of regional spread or node involvement (N), distant metastasis (M) (TNM staging), and their histological or tissue types. However, the commonly used and most useful classification of tumors is histogenetic, that is, the tumors are named according to the tissues from which they arise and of which they consist [4]. According to their histological structure, tumors can be grouped in the following main categories: epithelial tumors, of ectodermal and endodermal embryonic origin; mesenchymal or connective tumors, of mesodermal origin; neuroectodermal tumors, hematopoietic tissue tumors, multiple tissue tumors, and pseudotumors or hyperplastic lesions [2,5].

The most frequent tumors in domestic animals include squamous cell carcinoma, papilloma, equine sarcoid, fibroma, fibrosarcoma, leiomyoma, leiomyosarcoma, lipoma, hematopoietic/lymphopoietic tumor (lymphoma, leukemia, hemangioma, hemangiopericytoma, and hemangiosarcoma), melanoma, osteosarcoma, basal cell carcinoma, mammary adenocarcinoma, mammary adenoma, cutaneous mast cell tumor, transmissible venereal tumor, histiocytoma, malignant fibrous histiocytoma, Sertoli cell tumor, seminoma, Leydig cell tumor, thymoma, fibrothecoma, hepatoid gland adenoma, and malignant peripheral nerve sheath tumor [6-8]. A mammary tumor is a common type of neoplasm originating from the glandular epithelium of the mammary gland. It is a common finding in intact and older female
dogs and cats that are not spayed, but they are found in other animals as well. Therefore, these tumors represent a serious problem in veterinary medicine. Two histologic classification systems for canine mammary tumors and dysplasias have been published: the first in 1974 and modification in 1999 [9]. The frequency of mammary neoplasia in different species varies tremendously. The dog is by far the most frequently affected domestic species, with a prevalence ~3 times that in women; ~50% of all tumors in the bitch are mammary tumors. Mammary tumors are rare in cows, mares, goats, ewes, and sows. There are differences in both biologic behavior and histology of mammary tumors in dogs and cats. Approximately 45% of mammary tumors are malignant in dogs, whereas ~90% are malignant in cats, and dogs have a much higher number of complex and mixed tumors than do cats [7,10].

According to several surveys and studies, canine mammary gland tumors are widespread in different parts of the world. Besides, different evidences showed that the incidence is higher in intact female dogs than spayed or neutered dogs. [11]. The incidence of canine mammary gland tumors in the United States, however, has been reduced significantly since that time because of the common practice of performing ovariohysterectomy (OHE) at an early age. Mammary gland tumors are much more common in many European countries where ovariohysterectomy is not routinely performed [12]. The cause of mammary tumors is unknown in any species except mice, in which an oncornavirus is causative in certain inbred strains. Hormones play an important role in the hyperplasia and neoplasia of mammary tissue, but the exact mechanism is unknown. Estrogen and progesterone play a major role in normal mammary gland development, but these hormones have also been implicated in tumor development [13]. Estrogens are promoters of initiated cells in addition to regulating the transcription of several nuclear protooncogenes [14]. Mammary gland tumors, both benign and malignant, express Estrogen Receptors (ERs). In addition to being involved in the initial malignant transformation, the ER may also represent a rational therapeutic target in canine mammary gland tumors [15]. Moreover, Estrogen or progesterone receptors (or both) have been reported on mammary tumor cells in animals; these may influence the pathogenesis of hormone-induced mammary neoplasia as well as the response to hormone therapy [11].

In dogs, one Single Nucleotide Polymorphism (SNP) in exon 9 of BRCA1 and one SNP in exon 24 of BRCA2 was found to be significantly associated with canine mammary tumors. It has been demonstrated that the consumption of red meat, obesity at 1 yr. of age, and obesity a year before diagnosis are associated with an increased risk of mammary gland tumors in intact or ovariohysterectomized dogs. Obesity is thought to mediate breast cancer risk in postmenopausal women by increasing circulating free estrogen levels as well as through increased local estrogen production by aromatastes. Obesity may increase the risk of mammary tumors through similar mechanisms in dogs [15,16].

On clinical presentation, the two posterior mammary glands are involved more often than the three anterior glands. Grossly, tumors appear as single or multiple nodules (1-25 cm) in one or more glands. The cut surface is usually lobulated, gray-tan, and firm, often with fluid-filled cysts. Mixed mammary tumors may contain grossly recognizable bone or cartilage on the cut surface. More than 50% of canine mammary tumors are benign mixed tumors; a smaller percentage of malignant mixed tumors are seen. In the latter, epithelial or mesenchymal components, either singly or in combination, may produce metastases [13,16]. Histologically, canine mammary gland tumors have been classified by the World Health Organization as carcinomas (with six types and additional subtypes), sarcomas (four types), carcinosarcomas (mixed mammary tumors), or benign adenomas. This classification scheme is based on the extent of the tumor, involvement of lymph nodes, and presence of metastatic lesions (TNM system); it includes unclassified tumors and benign dysplasias. In addition to tumor size and the status and timing of neutering, special stains (including those for the KIT receptor and AgNOR) may have prognostic value [17,18].

A mammary tumor is usually suspected of the detection of a mass during physical examination. The length of time the mass has been present is usually unknown, but the rate of growth may help to determine prognosis. The palpation of the regional lymph nodes can help determine the extent of spread. Thoracic radiographs, preferably three views (a ventral-dorsal and two laterals), should be taken to detect pulmonary metastases. Fine-needle aspirates may differentiate between inflammatory and neoplastic lesions but may lead to erroneous conclusions and delay of surgery. The diagnosis is determined by histopathology and is important in defining treatment and prognosis [6,15]. Accurate identification of the source of the tumor depends not only on the location but also on a morphologic resemblance to a normal tissue despite the histologic divergence of tissue they are originated from [1]. Some of the histologic features of the tumor cell include high cellularity, cellular enlargement, increased nuclear/cytoplasmic ratio, nuclear hyperchromasia, discohesiveness of cells, prominent and large nucleoli, abnormal distribution of nuclear chromatin, increased mitotic activity, and especially the presence of abnormal ones, nuclear membrane abnormalities, cellular and nuclear pleomorphism, and background tumor necrosis (also known as tumor diathesis) [1,2].

Mammary tumors are treated surgically, although there is no consensus as to the best procedure. Removal of the tumor alone (lumpectomy), simple mastectomy (removal of the affected gland only), modified radical mastectomy (removal of the affected gland and those that share lymphatic drainage and associated lymph nodes), and radical mastectomy (removal of the entire mammary chain and associated lymph nodes) all have their proponents. In dogs, the more involved procedures have not prolonged survival
This model is derived from a prospective study of canine mammary characteristics of malignancy increased with increasing tumor size. An otherwise benign tumor. The proportion of tumors exhibiting development in which the malignant phenotype develops within recently, a marked correlation has been noted between mammary shown to be higher than normal mammary tissue [23] and, more raises the risk of the development of neoplasia. The earliest study of these growth pathways, it makes biological sense that increased mutation has not been identified [21]. Physiological mammary development of canine mammary tumors but a specific genetic multiple. The average age of dogs with mammary tumors is ten to heat cycle have 8 percent of this risk [20]. The tumors are often mammary tumors. Dogs have an overall reported incidence of mammary tumors of 3.4 percent. Dogs spayed before their first heat have 0.5 percent of this risk, and dogs spayed after just one heat cycle have 8 percent of this risk [20]. The tumors are often multiple. The average age of dogs with mammary tumors is ten to eleven years old [10]. Obesity at one year of age and eating red meat have also been associated with an increased risk for these tumors, [4] as has the feeding of high-fat homemade diets [8]. There are several hypotheses on the molecular mechanisms involved in the development of canine mammary tumors but a specific genetic mutation has not been identified [21]. Physiological mammary development occurs under the influence of the somatotrophic and gonadal hormones. Since cancer arises through subversion of some of these growth pathways, it makes biological sense that increased or prolonged exposure to growth-promoting hormonal influences raises the risk of the development of neoplasia. The earliest study to recognize an increased risk of mammary neoplasia associated with remaining sexually entire was performed [13,22]. Mammary tumor tissue prolactin concentrations have been shown to be higher than normal mammary tissue [23] and, more recently, a marked correlation has been noted between mammary tumor tissue prolactin concentration and survival [24]. Sorensen et al. [25] have proposed a model of canine mammary neoplasia development in which the malignant phenotype develops within an otherwise benign tumor. The proportion of tumors exhibiting characteristics of malignancy increased with increasing tumor size. This model is derived from a prospective study of canine mammary tumors that is currently incomplete. The model is supported by other studies, which demonstrate a compelling association between the size of the primary tumor and overall survival [26,27].

**Clinical Presentation**

Dogs with mammary gland tumors are typically older, approximately 9 to 11 years old, sexually intact, or spayed later in life [6]. Most dogs with mammary gland tumors are clinically healthy when they initially present for evaluation of their tumors. The duration of the clinical signs also varies greatly from just a few days to many months. Several studies have found that dogs with shorter duration of clinical signs have more aggressive tumors and a worse prognosis than dogs with longer clinical histories [18,19,25]. The tumor(s) may have been found by the owner or maybe an incidental finding during a routine physical exam. Depending on the tumor type and how soon it is detected, the tumors may be small, large, ulcerated, fixed, well-circumscribed, or involving only one or multiple glands. The caudal 4th and 5th mammary glands are more commonly involved than the more cranial glands, but location does not appear to affect prognosis [28,29]. It is not uncommon to find more than one tumor in different glands; more than 60% of the cases have more than one tumor. All of the individual tumors should be biopsied because they may be of different histopathologic types [30,31]. Multiple tumors do not necessarily imply a worse prognosis. Rather, the prognosis is influenced by the size, type, and differentiation of the individual tumors. The regional lymph node(s) may be normal or palpably enlarged. Previous reports have found that 10% to 50% of dogs with mammary gland tumors have enlarged lymph nodes [32,33].

Dogs with advanced metastatic disease or inflammatory mammary carcinomas typically have systemic signs of illness when they are diagnosed. Dogs with metastatic disease may present with non-specific signs such as fatigue, lethargy, and weight loss. The severity of these signs depends on the extent and location of the metastases. Dogs with metastases may or may not have obvious mammary gland tumors, depending on whether they have had previous surgical resection of primary tumors. Most mammary gland tumor metastases occur within 1 year of the initial surgery [12,17]. Dogs with inflammatory mammary gland carcinoma present with more dramatic clinical signs. Typical clinical signs include extensive inflammation of the involved mammary glands with edema and pain. These dogs therefore may be misdiagnosed as having mastitis. They are often in poor clinical condition and have generalized weakness, weight loss, polyuria and polydipsia, and a high incidence of metastatic disease, both to the regional lymph nodes and lungs. Prognosis is extremely poor with a mean survival of 25 days from diagnosis [13,28].

Mammary neoplasia can be presented as a solitary mammary mass or, frequently, as multiple lesions. A common scenario is an old dog, with multiple masses, which has finally been presented for
veterinary attention because the largest of her mammary tumors now drags on the floor, or has spontaneously ulcerated due to its enormous size. In situations where previous advice may have been to simply monitor a mass because it had been behaviourally benign, or because an owner would simply not have accepted alternative management, it is important to remember that mammary tumor behavior can change over time [7,17,34]. Mammary tumors primarily undergo metastasis to the regional lymph nodes or the lungs. The primary lymph node beds (lymphocentra) are the superficial inguinal and the axillary sites. Examination of the lymph nodes is mandatory in the physical examination of a patient. Inflammatory carcinoma is an unusual manifestation of mammary neoplasia typified by large erythematous and painful mammary swellings, frequently occupying all of the mammary tissues. Sometimes these lesions will spontaneously discharge a serous exudate. Patients are typically extremely depressed [4,26,27].

**Diagnosis**

The appearance and location of the tumor is enough to identify it as a mammary tumor. A biopsy will give the type and invasiveness of the tumor. Besides, newer studies showed that certain gene expression patterns are associated with the malignant behavior of canine mammary tumors [6,19,35]. All resected tissue should be submitted for histopathologic analysis. Multiple masses should be submitted in separate containers and clearly labeled. Both malignant and benign masses may be present in the same patient [18,35]. A surgical biopsy, typically an excisional biopsy, is recommended as the initial diagnostic approach to dogs with mammary gland tumors. This biopsy will provide tissue for histopathologic diagnosis and be therapeutic for dogs with benign tumors. Dogs with small, well-differentiated malignant tumor(s) may be cured by excisional biopsy if the surgical borders are complete. Fine needle aspirates may not always accurately differentiate between malignant and benign epithelial tumors [4,10]. Complete staging requires blood work including Complete Blood Count (CBC), serum chemistry profile, and urinalysis. Evaluation of the primary tumor, including size, type, and histologic differentiation; assessment of the regional lymph nodes; and three-view thoracic radiographs, generally completes the staging evaluation. The purpose of the staging is to evaluate general health and to determine the extent of the tumor. Results from staging assessment provide important prognostic information, which may affect the owner’s decision to treat. Besides, staging is also necessary for treatment planning [8,28].

Blood work is normal in most dogs with mammary gland tumors unless they have other concurrent medical problems or nonspecific age-related changes. A recent study evaluated hemostatic changes in dogs with malignant mammary gland tumors and found that two-thirds of the dogs had one or more hemostatic abnormalities, with an increased incidence in dogs with stage III and IV disease. Of these, dogs with distant metastasis, invasive or fixed tumors, severe tumor necrosis, and inflammatory carcinomas were more likely to have coagulopathies [25,36]. The clinical significance of these abnormalities is not clear; however, this paraneoplastic manifestation may be caused by osteolytic bone metastases or the production of Parathyroid Hormone-Related Protein (PTHrP) by the tumor cells. This finding is rare in dogs with mammary carcinoma, however. The status of the regional lymph node has a strong impact on survival in dogs with mammary gland tumors [29,37]. Therefore, the regional lymph nodes should be evaluated in all dogs with malignant tumors, so that systemic treatment may be initiated in cases with regional lymph node metastasis. The methods for assessing the regional lymph nodes include palpation, fine needle aspirates, or whole lymph node excision [11,31,35]. A study in veterinary medicine compared the sensitivity and specificity of these four methods of evaluating lymph nodes in patients with various types of solid tumors and found similar results. Palpation was inaccurate in predicting lymph node metastasis, whereas cytology provided an accurate method of assessing the draining lymph nodes, with a sensitivity of 100% and a specificity of 96% [25,38].

This study included dogs with many different types of tumors, but it seems reasonable to assume that cytology would have similar accuracy in dogs with mammary gland tumors. Fine needle aspirates are usually easy to perform, are non-invasive, do not require sedation of the patient, and provide quick and reliable results. Cytologic evaluation of the regional lymph nodes should therefore be performed as the initial screening in all dogs with malignant tumors. If the cytology is positive or questionable, complete excision of the involved lymph node may be considered. It is controversial whether removing metastatic lymph nodes in cancer patients significantly improves survival, but node resection may improve regional tumor control and prevent signs associated with progressive lymph node enlargement [38,39]. The 1st and 2nd cranial mammary glands drain to the axillary lymph node on the ipsilateral side, and the 4th and 5th glands drain to their respective superficial inguinal lymph nodes. The lymphatic drainage of the 3rd mammary gland is most commonly to the axillary lymph node, but this gland may also drain to the inguinal lymph node. Both sites should be aspirated, therefore, in dogs with tumor(s) involving the 3rd gland [18,29,40].

All dogs with malignant mammary gland tumors should have three-view thoracic radiographs taken. Radiography is still the standard diagnostic method for evaluating veterinary patients for metastatic lung disease. Conventional radiography may detect lung lesions ranging from 6 to 8 mm in diameter. The ability to detect early metastasis can be improved by using CT for metastasis as small as 4 mm in diameter. Early detection and treatment of metastatic disease may have an impact on response and outcome in human patients, and CT has become the standard method of evaluating human cancer patients for lung metastasis [25,32,40].
and form solid sheets. Anaplastic mammary gland carcinomas are differentiated; these tumors have lost the tubular/ductal structures of the normal mammary gland. The solid carcinomas are less retained some of the original ductal or tubular morphology type of mammary gland tumors in the dog; these tumors have ducts or lobules [21,22,25]. These lesions are often multicentric and can grow in pre-existing differentiation. Carcinoma in situ is an epithelial tumor with are often classified according to histopathologic borders and few tumors are of purely mesenchymal origin. Epithelial tumors and myoepithelial tissue, with areas of cartilage and bone, and however, can have mixed histology consisting of both epithelial and myoepithelial cells, though some uncertainty about the histogenetic origin of many mammary tumor types remains [17]. In addition to the histogenetic and benign/malignant classification, additional descriptive terms can be used. The distinction between tumors demonstrating tubular/papillary differentiation and those exhibiting solid/anaplastic histology is considered to be prognostically significant. In the entire bitches, the ratio of benign: malignant tumors is approximately 50:50. Neutering, however, appears to preferentially reduce the incidence of benign mammary neoplasia. Therefore, while the overall incidence of mammary cancer is considerably less in neutered bitches, the likelihood of malignancy is greater than 50 percent [7,18]. Multiple strategies for assigning a histological grade to canine mammary tumors have been presented [6,41,42]. Features considered relevant to tumor grade include indicators of cellular differentiation; nuclear pleomorphism; and degree of invasiveness. It is important to note that the inflammatory carcinoma does not fit into other histological grading schemes and should be regarded as a separate entity in this context [25,43].

Though canine mammary gland tumors may be benign or malignant, approximately 40% to 50% of these tumors are malignant [30,38]. Further classification may be performed according to the tissue of origin (epithelial, myoepithelial, or mesenchymal tissue), descriptive morphologic features, and prognosis. The World Health Organization International Histological Classification of Mammary Tumors of the dog and the cat combines histogenetic and descriptive morphologic classification, incorporating histologic prognostic features that have been associated with increasing malignancy [7,35]. Most mammary gland tumors are of epithelial origin. Some, however, can have mixed histology consisting of both epithelial and myoepithelial tissue, with areas of cartilage and bone, and a few tumors are of purely mesenchymal origin. Epithelial tumors are often classified according to histopathologic borders and differentiation. Carcinoma in situ is an epithelial tumor with malignant features that has not invaded the basement membrane. These lesions are often multicentric and can grow in pre-existing ducts or lobules [21,22,25].

Tubular carcinomas (adenocarcinoma) are the most common type of mammary gland tumor in the dog; these tumors have retained some of the original ductal or tubular morphology of the normal mammary gland. The solid carcinomas are less differentiated; these tumors have lost the tubular/ductal structures and form solid sheets. Anaplastic mammary gland carcinomas are undifferentiated, pleomorphic, and infiltrative epithelial tumors that are not classifiable in any of the other categories of carcinomas [44]. Inflammatory mammary gland carcinomas are anaplastic carcinomas with characteristic clinical and histopathologic features such as involvement of the overlying skin with edema and pain, extensive inflammatory cell infiltrate, malignant epithelial cells in the dermal lymphatics, and a rapid clinical progression [42]. The histopathologic differentiation of epithelial mammary gland tumors has an impact on prognosis, with a worsening of prognosis associated with loss of differentiation. Carcinoma in situ and adenocarcinomas have the best prognosis, and anaplastic and inflammatory carcinomas have the worst prognosis [17]. Malignant myoepithelium as, or spindle cell carcinomas, are malignant tumors arising from the myoepithelial cells of mammary tissue, and they are quite rare in dogs. Differentiating between malignant myoepitheliomas and fibrosarcomas often requires immunohistochemical stains. Primary mammary gland sarcomas are not common and are thought to arise from pre-existing benign mixed tumor s by malignant transformation or to arise from the interlobular stroma. The most common primary mammary gland sarcomas include osteosarcomas and fibrosarcomas. Other mammary gland sarcomas occasionally encountered are chondrosarcomas and liposarcomas [45,46].

The mammary gland is the most common site of extraskeletal soft tissue osteosarcoma according to a recent study [47]. The mammary gland osteosarcomas behave as the appendicular osteosarcomas do, and they are associated with early hematogenous metastasis and short survival. Mixed mammary gland tumors consist of both ductal and myoepithelial cells with areas of cartilage and bone. The origin of the cartilage or bone in these mixed tumors is controversial and may include metaplastic changes in the epithelial cells, myoepithelial cells, or interstitial stromal cells. Malignant mixed tumors, also called carcinosarcomas, are uncommon tumors in the dog and are composed of both malignant epithelial cells and malignant connective tissue elements. These tumors are most often a combination of carcinoma and osteosarcoma [12,48]. The prognosis for dogs with malignant mixed tumors is poor, and most dogs develop metastasis within the first year [49]. Malignant mammary gland tumors have the potential to metastasize. The metastatic risk and pattern are influenced by tumor type, histologic differentiation, and several clinical prognostic factors. In general, malignant epithelial tumors metastasize via the lymphatics to the regional lymph nodes and the lungs, whereas the mesenchymal tumors typically metastasize by the hematogenous route directly to the lungs [17].

Dogs with malignant mammary gland tumors have a significantly shorter survival time than dogs with benign tumors. The overall 2-year survival has been reported to be between 25% and 40% with a mean survival time ranging from 4 to 17 months, but the survival is influenced by multiple factors, and it can vary
significantly depending on histologic type and differentiation, stage of the disease, and type of treatment [6]. Dogs with small, well-differentiated malignant epithelial tumors may have an excellent prognosis with surgical resection alone, and dogs with more undifferentiated, advanced tumors have a guarded prognosis and may require adjuvant therapy. There are currently no accepted guidelines or recommendations for dogs in the latter group, however, and there are few reports regarding the effectiveness of adjuvant therapy in such dogs [25,50].

Clinical Stage Determination

In oncology, the definition of the clinical-stage, or the anatomic extent of disease, is critical to good decision making. Since mammary tumors are recognized to be associated with metastasis in several cases, simple evaluations to define the clinical-stage are advised before performing invasive surgery. Therefore, dose examination for multiple mammary masses and fine-needle aspirates of enlarged regional lymph nodes must be performed [28,40]. Thoracic radiography is recommended for all but the smallest lesions. Abdominal ultrasonography allows the evaluation of the deep inguinal lymph nodes and the parenchyma of the abdominal viscera. For small lesions (<1 cm diameter) it would be hard to justify the expense of radiography or ultrasonography, as the likelihood of malignancy is so low. The clinical-stage also defines local invasiveness. Increasing tumor size is known to be associated with an increasing probability of significant local invasion. In canine mammary tumors, the TNM classification separates tumors, where T relates to tumor size and whether it has invaded nearby tissue, N describes the involvement of regional lymph nodes and M describes metastasis. In a survey of 54 cases, two-year survival percentages were 62% for T1 tumors and 23% for T2 and T3 tumors [41,51-53].

Management

The mainstay of management for canine mammary tumors is surgery, but chest x-rays should be taken first to rule out metastasis. Removal should be with wide margins to prevent a recurrence, taking the whole mammary gland if necessary. Because 40 to 50 percent of dog mammary tumors have estrogen receptors, spaying is recommended by many veterinarians. A recent study showed a better prognosis in dogs that are spayed at the time of surgery or that had been recently spayed [35,46]. However, several other studies found no improvement in disease outcome when spaying was performed after the tumor had developed. Chemotherapy is rarely used [37]. In dogs, 50% of mammary tumors are benign. The history of a benign mammary tumor does not indicate that subsequent tumors will also be benign. Dogs with a history of benign mammary tumors have a higher chance of developing malignant masses. Approximately 50% of malignant mammary masses in dogs will metastasize. Therefore, all suspected or confirmed mammary tumors should be thoroughly staged for evidence of metastatic disease. Following physical examination, staging tests should include CBC, serum biochemistry profile, urinalysis, 3-view chest radiography for metastasis check, evaluation of peripheral lymph nodes, and abdominal ultrasonography. Although cytology is not useful for distinguishing benign from malignant tumors, it will help identify other tumor types (e.g. mast cell tumor) that can occur in the same location [6,10,25].

Mammary tumors in dogs should be removed by the simplest method that removes all diseases with clean margins. Often, combinations of techniques are used to address disease on opposite mammary chains and when multiple tumors exist. Once the patient is anesthetized and the surgical area is clipped, it is common to find additional mammary tumors that were not readily palpable with the dog awake. Pet owners must be informed that a revised surgical plan may be required if additional mammary masses are discovered. It is important to obtain owner permission for additional surgery [6]. Prophylactic surgery using a bilateral mammary strip can, of course, prevent mammary neoplasia from developing in the future. This is, however, an extremely invasive surgical procedure with significant scope for the development of perioperative complications. These risks can be avoided by regular re-examination and prompt intervention if a new mass is recognized. There are no data to suggest that a history of malignant mammary neoplasia exposes a bitch to a higher risk that subsequent de novo mammary masses will be malignant. Chemotherapy use has been described sporadically in the management of canine mammary neoplasia but the results have, historically, been disappointing. Drugs used include doxorubicin, epirubicin, cyclophosphamide, and 5-fluorouracil [54].

Lumpectomy

Lumpectomy is used to remove small, BB-pellet-sized (<5 mm in diameter), freely movable masses that are not located directly under a nipple. Remove a small cuff of normal tissue around the mass to ensure all tumor cells are extracted [55].

Mammmectomy

Mammmectomy is the removal of a single mammary gland, including the nipple and skin overlying the gland. It is a good choice when the mammary mass is directly under the nipple or is fixed to the overlying skin. It should not be used for masses fixed to the underlying rectus fascia. The mammary tissue (M) is superficial to the ventral fascia of the rectus muscle and typically has a layer of fat directly under the glands as well as remove all tissue down to the rectus fascia to ensure the removal of the mammary gland. Besides, the rectus fascia or muscle should not be removed [35].

Regional Mastectomy

Regional mastectomy is indicated when a mammary mass is located between 2 glands or when multiple small tumors are present in a section of the mammary chain. This technique should not be used for masses fixed to the underlying rectus fascia and remove the skin, mammary tissue, and underlying fat. Besides, the rectus fascia or muscle should not be removed [12,40].
Laser techniques are alternatives to traditional methods for the surgical management of tumors. Tumors of the skin and subcutaneous tissue are the largest group of canine neoplasms. Total excision is still the most effective method for the treatment of these skin tumors. For its universal properties, the carbon dioxide (CO\textsubscript{2}) laser appears to be an excellent surgical instrument in veterinary surgery. Non-contact mode of excision with laser can reduce intraoperative wound contamination by tumor cells [56].
justified once the presence of the gross disease has been confirmed, as a response to therapy can then be quantified.

**Complications**

As noted above, not all mammary tumors that are considered to be benign based on histological evaluation subsequently demonstrate benign behavior. The best histological service is obtained by providing your laboratory with all of the clinical detail that they might require. Remember that by the time a mass arrives at the laboratory, it bears little or no resemblance to the lesion as it appeared in situ. If you have concerns about the proximity of the tumor to a surgical margin, mark this margin in a manner that makes it clear to your histopathologist that you are concerned about this specific site. Similarly, if you feel that a part of the tumor appears more abnormal than the rest, mark this part and express your concerns in your detailed laboratory submission. There is no substitute for open communication between you and your histopathologist [50]. The surgical margins obtained are typically defined by the surrounding mammary anatomy rather than by oncological principles. Many mammary tumors would be appropriately managed by a skin incision reaching 1-2 cm from the apparent edge of the tumor. If you are presented with a mass that appears to require skin resection that reaches some distance from the anatomical limit of the mammas, then it may be best to assume that surgical removal has a high risk of proving incomplete. In this situation, it may be better to perform an incisional biopsy first and to discuss the case with an oncologist or a surgical specialist before proceeding with definitive mass removal [35,36].

The fibrous sheath of the rectus abdominis muscle presents a reasonably good barrier to deeper tumor invasion. Prior to embarking upon surgical resection of a mammary mass, the clinician should first ensure that there is no evidence of deep invasion of the underlying abdominal wall by grasping the mass and wobbling it (the ‘wobble test’) [28,29]. Masses exhibiting any degree of fixation to the underlying tissues will not be completely removed by simple surgery and advanced imaging should be considered mandatory before a radical or compartmental surgical excision is considered. Some mammary masses exhibit intramuscular invasion despite a negative wobble test; this only becomes evident during surgery. In these cases, abdominal wall resection is required to achieve complete local tumor eradication as the first surgery will inevitably have introduced tumor into deeper tissue planes. This should be regarded as a specialist procedure that requires advanced imaging once again as part of treatment planning [14,35]. Tumors that appear superficial but affect a surprisingly broad area of tissue are often highly invasive and require wide and deep surgical margins to achieve a local cure. Once the underlying fascia has been disturbed, the magnitude of any subsequent surgery is significant and may, in fact, be prohibitive. It is, therefore, best not to disturb the fascia of the rectus abdominis when performing simple mammary surgery [18].

Histologically confirmed complete resection of canine mammary tumors should only be regarded to be likely to be predictive of clinical cure in cases of benign or histological stage 1 malignant case. In all other cases, consideration should be given to embarking upon a course of subsequent monitoring and/or adjuvant therapy. There is little or no value in subsequent monitoring if no further action would be taken if the progression of the disease (recurrence or metastasis) is recognized [6,57].

**References**

1. Rubin R (2008) Rubin's pathology: clinicopathologic foundations of medicine. Lippincott Williams & Wilkins.
2. Baba A I, Cátoí C (2007) Epithelial and melanocytic tumors of the skin. In Comparative Oncology, The Publishing House of the Romanian Academy.
3. Morrison W B (2012) Inflammation and cancer: a comparative view. Journal of veterinary internal medicine 26(1): 18-31.
4. Joshi S, Bhaduria RS, Gunjan Jadon, Diwaker AK (2012) Introduction to neoplasms: ‘tumor classification’ a review article. International Journal of Advanced Research in Pharmaceutical & Bio Sciences 1(3): 227-264.
5. Birbrair A, Tan Zhang, Zhong Min Wang, Maria Laura Messi, John D Olson (2014) Type-2 pericytes participate in normal and tumoral angiogenesis. American Journal of Physiology-Cell Physiology 307(1): C25-C38.
6. Dantas Cassali G, Angélica Cavalleiro Bertagnoli, Enio Ferreira, Karine Araújo Damasceno, Conrado de Oliveira Gamba, et al. (2012) Canine mammary mixed tumours: a review. Veterinary medicine international 2012: 1-7.
7. Haziroglu R, B Yardimci, S Aslan, M Z Yıldırım (2010) Cytological Evaluation of canine mammary tumours with fine needle aspiration biopsy. Revue Méd Vét 161(5): 212-218.
8. Kimura K C, A P Gárate, Maria Dagli (2012) Retrospective study of neoplasms in domestic animals: A survey between 1993 and 2002 of the service of animal pathology, department of pathology, school of veterinary medicine and animal science, University of Sao Paulo, Southeast Brazil. Brazilian Journal of Veterinary Pathology 5(2): 66-69.
9. Tran C, A S Moore, AE Primiberger (2016) Surgical treatment of mammary carcinomas in dogs with or without postoperative chemotherapy. Veterinary and comparative oncology 14(3): 252-262.
10. Morrison W B (2002) Cancer in dogs and cats: medical and surgical management. Teton New Media.
11. Kamble M, S S Dhakate, S V Upadhye, S B Akhare (2016) Surgical management of mammary tumor in a dog. Intas Polivet 17(1): 196-197.
12. Goldschmidt M, Hendrick M (2002) Tumors of the skin and soft tissues. Tumors in domestic animals 45-117.
13. Ali M R, Ibrahim M Ibrahim, Hala R Ali, Sahab A Selim, Mostafa A El Sayed (2016) Treatment of natural mammary gland tumors in canines and felines using gold nanorods-assisted plasmonic photothermal therapy to induce tumor apoptosis. International journal of nanomedicine 11: 4849-4863.
14. Garden O, S W Volk, N J Mason, J A Perry (2018) Companion animals in comparative oncology: One Medicine in action. The Veterinary Journal 240: 6-13.
15. Canadas Sousa A, Marta Santos, Bárbara Leal, Rui Medeiros, Patricia Dias Pereira (2019) Estrogen receptors genotypes and canine mammary neoplasia. BMC veterinary research 15(1): 325.
16. Cassali G D, Lidianne Narducci Monteiro, Conrado de Oliveira Gamba, Karine Araújo Damasceno, Cecília Bonolo de Campos (2015) Cytologic analysis of the mammary papillary discharge in a canine micro-papillary carcinoma. Veterinary clinical pathology 44(3): 448-451.
17. Goldschmidt M, L Peña, R Rasotto, V Zappulli (2011) Classification and grading of canine mammary tumors. Veterinary pathology 48(1): 117-131.
18. (2018) Mammary Tumors in Dogs Clinical Oncology Service Ryan Veterinary Hospital of the University of Pennsylvania.
19. Alenza M P L, Peña, N del Castillo, A I Nieto (2000) Factors influencing the incidence and prognosis of canine mammary tumours. Journal of Small Animal Practice 41(7): 287-291.
20. Klopfleisch R, H von Euler, G Sarli, S S Pinho, F Gartner, et al. (2010) Molecular Carcinogenesis of Canine Mammary Tumors: News From an Old Disease. Veterinary Pathology 48(1): 98-116.
21. Marconato L, Giorgio Romanelli, Damiano Stefanello, Claudio Gabrion (2009) Prognostic factors for dogs with mammary infiltrative carcinoma: 43 cases (2003-2008). Journal of the American Veterinary Medical Association 235(8): 967-972.
22. Shafee R, Jawd Javanbakht, Nasib Atayi, Pegah Kheradmard, Danial Kheradmard, et al. (2013) Diagnosis, classification and grading of canine mammary tumours as a model to study human breast cancer: an Clinico-Cytohistopathological study with environmental factors influencing public health and medicine. Cancer cell international 13: 79.
23. Queiroga F, Pérez Alenz, G Silvanc L Peña, C Lopes (2005) Role of steroid hormones and prolactin in canine mammary cancer. The Journal of steroid biochemistry and molecular biology 94(1-3): 181-187.
24. Queiroga F (2008) Serum and tissue prolactin levels in canines with malignant mammary tumours by ELISA assay: clinical and prognostic implications. In Proceedings of 18th ECVIM-CA Congress 4-6.
25. Sorenmo K (2003) Canine mammary gland tumors. Veterinary Clinics: Small Animal Practice 33(3): 573-596.
26. Chang S C, Chao Chin Chang, Tien Jye Chang, Min Liang Wong (2005) Prognostic factors associated with survival two years after surgery in dogs with malignant mammary tumors: 79 cases (1998-2002). Journal of the American Veterinary Medical Association 227(10): 1625-1629.
27. Philibert J C, Paul W Snyder, Nita Glickman, Larry T Glickman, Deborah W Knapp, et al. (2003) Influence of host factors on survival in dogs with malignant mammary gland tumors. Journal of Veterinary Internal Medicine 17(1): 102-106.
28. Kudnig S T, Séguin B (2012) Veterinary surgical oncology. John Wiley & Sons.
29. Mc Carthy (2003) Canine mammary carcinoma. Online resources of the Department of Pathology, University of Georgia College of Veterinary Medicine.
30. Benjamin S, A C Lee, W J Saunders (1999) Classification and behavior of canine mammary epithelial neoplasms based on life-span observations in beagles. Veterinary pathology 36(5): 423-436.
31. Fowler E, G P Wilson, A Koestner (1974) Biologic behavior of canine mammary neoplasms based on a histogenetic classification. Veterinary Pathology 11(3): 212-229.
32. Sorenmo K U (2013) Tumors of the mammary gland. In Withrow and MacEwen’s small animal clinical oncology 538-536.
33. Sorenmo K, R Rasotto, V Zappulli, M H Goldschmidt (2011) Development, anatomy, histology, lymphatic drainage, clinical features, and cell differentiation markers of canine mammary gland neoplasms. Veterinary pathology 48(1): 85-97.
34. Andrade F H, Fernanda C Figureiroa, Paulo Ro Bersano, Denise Z Biscacot, Noeme S Rocha (2010) Malignant mammary tumor in female dogs: environmental contaminants. Diagnostic pathology 5: 45.
35. Fesseha H (2020) Mammary Mastectomy Due to Mammary Gland Tumors in Intact Female Dog. Biomed J Sci & Tech Res 28(1): 21224-21226.
36. Withrow S J, David Vail, Rodney Page (2007) Withrow and MacEwen’s small animal clinical oncology. Elsevier Health Sciences.
37. McEntee M C (2002) Reproductive oncology: Clinical techniques in small animal practice 17(3): 133-149.
38. Cassagi G D, Giedtice E Lavalle, Enio Ferreira, Alessandra Estrela Lima (2011) Consensus for the diagnosis, prognosis and treatment of canine mammary tumors. Brazilian journal of veterinary pathology 7(2): 153-180.
39. White R R, Wilma E Stanley, L J Johnson, Douglas S Tyler, Hilliard F Seigler (2002) Long-term survival in 2,505 patients with melanoma with regional lymph node metastasis. Annals of surgery 235(6): 879-887.
40. Glasspool R, Evans T (2000) Clinical imaging of cancer metastasis. European Journal of Cancer 36(13): 1661-1670.
41. Gilbertson S J D Kurzman, R Zachrau, A I Hurvitz, M M Black (1983) Canine mammary epithelial neoplasms: biologic implications of morphologic characteristics assessed in 232 dogs. Veterinary pathology 20(2): 127-142.
42. Karayannopoulou M, E Kaldymidou, T C Constantinidis, A Dessiris (2005) Histological grading and prognosis in dogs with mammary carcinomas: application of a human grading method. Journal of comparative pathology 133(4): 246-252.
43. (2006) Mammary Tumors: Introduction.
44. Stratmann N, Klaus Fallin, Andreas Richter, Axel Wehrend (2008) Mammary tumor recurrence in bitches after regional mastectomy. Veterinary Surgery 37(1): 82-96.
45. Mathewos M, Tilaye Demissie, Haben Fesseha, Metages Yirgalem Tindaiche, et al. (2020) Histological, Cytological Characteristics and Treatment Options on Common Skin Tumors of Domestic Animals: A Review. Int J Rec Biotech 8: 1-24.
46. Shahzamani P, Mohammad Ashrafzadeh Talakfooled, Mohammad Hadi Daneshi (2013) Phylodes Tumor of Mammary Gland in a Dog: Case Report. Global Veterinaria 10(2): 239-242.
47. Bertagnoli A C, Paul Soares, Bárbara van Asch, António Amorim, Luis Círnes (2009) An assessment of the clonality of the components of canine mixed mammary tumours by mitochondrial DNA analysis. The Veterinary Journal 182(2): 269-274.
48. Espinosa De Los Monteros, Y M Millán, J Ordás, L Carrasco, C Reynudo (2002) Immunolocalization of the smooth muscle-specific protein calponin in complex and mixed tumors of the mammary gland of the dog: assessment of the morphogenetic role of the myoepithelium. Veterinary pathology 39(2): 247-256.
49. Ferletta M, Jan Grawé, Eva Hellmén (2011) Canine mammary tumors contain cancer stem-like cells and form spheroids with an embryonic stem cell signature. International Journal of Developmental Biology 55(7-9): 791-799.
50. Sorenmo K (2011) Canine mammary tumors: treatment, prognostic factors and outcome. In Proceedings of the 36th World Small Animal Veterinary Congress WSAVA.
51. Kurzman I D, S R Gilbertson (1986) Prognostic factors in canine mammary tumors. Semin Vet Med Surg (Small Anim) 1(1): 25-32.
52. Hurley J, Jahara A (1964) Properties of “cartilage” in canine mammary tumors. Archives of pathology 77: 343-347.
53. Kawabata A, Kumioko Okano, Kazuyuki Uchida, Ryoji Yamaguchi, Toshiharu Hayashi, et al. (2005) Co-localization of chondromodulin-I and bone morphogenetic protein-6 (BMP-6) in myoepithelial cells of canine mammary tumors. Journal of veterinary medical science 67(11): 1097-1102.
54. Karayannopoulou M, E Kaldymidou, T C Constantinidis, A Dessiris, et al. (2005) Adjuvant post-operative chemotherapy in bitches with mammary cancer. Journal of Veterinary Medicine Series A 55(7-9): 791-799.
55. Rao C M, B chandra prasad, N V Hari Krishna (2011) Surgical Management of Lipoma in a Dog. Veterinary World 4(1) 34.
56. Fesseha H (2020) Laser Therapy and its Potential Application in Veterinary Practice-A Review. J Light Laser Curr Trends.

57. Eisen A, Jan Lubinski, Jan Klijn, Pal Moller, Henry T (2005) Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. Journal of clinical oncology 23(30): 7491-7496.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2020.30.004980

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