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Mammary Tumours in Dogs and its Treatment Option- A Review

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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, thecoma, 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 aromatases. 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

compared with the others, and the advantages of the simpler procedures are obvious [13,14].

Furthermore, ovariectomy before the first estrus reduces the risk of mammary neoplasia to 0.5% of the risk in intact bitches; ovariectomy after one estrus reduces the risk to 8% of that in intact bitches. Bitches neutered after maturity have generally been considered to have the same risk as intact bitches. However, questions remain regarding the impact of ovariohysterectomy at the time of tumor excision. Questions also remain about the timing of such surgery relative to survival. In one study, dogs spayed <2 yr before tumor excision lived 45% longer than either intact dogs or those spayed >2 yr before tumor excision [4,8]. The prognosis is based on multiple factors. In dogs, most mammary tumors that are going to cause death do so within 1year. Sarcomas are associated with shorter survival times than carcinomas. Other factors, including the size of the tumor, lymph node involvement, and nuclear differentiation, also affect the prognosis [6,18,19].

Etiology

The exact causes for the development of canine mammary tumors are not fully understood. However, hormones of the estrous cycle seem to be involved. Female dogs who are not spayed or who are spayed later than the first heat cycle are more likely to develop 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]. Sorenmo 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 dog s with mammary gland tumor s 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 dog s 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 ed. 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].

Histological Grade

Mammary tumors can be benign or malignant. Unfortunately, the distinction between the two can be considerably less clear-cut than one would like. Mammary tumors are classified first according to their tissue of origin and whether they are benign or malignant. Originating tissues include glandular (adenoma/adenocarcinoma), ductular (papilloma/carcinoma), myoepithelial, and pluripotential (mixed) 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 histogenic 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 s 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].All 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, close 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 tumours 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].

Mammectomy

Mammectomy 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].

Mastectomy

Unilateral mastectomy involves the removal of all mammary tissue on one side of the midline. The mammary tissue extends from midline to the nipple line plus an equal distance lateral to the nipple line. Make an elliptical incision from the most cranial nipple to the most caudal nipple so that the medial extent of the ellipse is at midline and the lateral extent of the incision is equidistant on the lateral side of the nipple line. Remove all skin, mammary tissue, and fat down to the rectus fascia. Besides, the rectus fascia or muscle should not be removed [9,35].During caudal dissection, ligate the caudal superficial epigastric artery and vein to prevent excessive bleeding. These vessels run cranially under the mammary glands medial to the inguinal ring and anastomose with the cranial superficial epigastric vessels. The superficial inguinal lymph node is typically contained within the fat underlying the inguinal mammary tissue. If possible, dissect this node and submit it separately for histologic evaluation to help further determine the disease stage [12].Unilateral mastectomy can be combined with lumpectomy on the opposite chain. If both mammary chains require mastectomy because of multiple masses, remove the side with the most disease first. Then remove the second mammary chain 2-4 weeks later. This will result in minimal complications related to skin tension [11]. Bilateral mastectomy performed as a single procedure can often result in unacceptable skin tension and possible respiratory compromise (especially in cats) and has a high complication rate. Staged unilateral mastectomy is recommended when the disease extent requires removal of both mammary chains [6,18,35].

Radical Mastectomy

Radical mastectomy involves the removal of the mammary tissue and underlying rectus fascia, muscle, or body wall. It is indicated for mammary tumors fixed to the underlying body wall. In general, removal of fascia or partial-thickness body wall does not require body wall reconstruction. If full-thickness body wall resection is required, reconstruction methods need to be followed to prevent herniation of abdominal contents [11,17]. In cats, the mammary tissue extends to the skin overlying the caudal thorax. It is difficult to avoid penetrating the thoracic cavity in cats when partial-thickness body wall resection is attempted during radical mastectomy of the cranial mammary glands [11,43].

Laser therapy

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_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].

Prognosis

Benign mammary tumors should be cured by simple surgery. However, it is important to emphasize that histological evaluation of an excised specimen may not identify a microscopic nest of malignant cells within an otherwise benign nodule, resulting in a misdiagnosis. For malignant mammary tumors, the prognosis is related to the histological grade and clinical stage [28,42].

Histological 'stage 1' tumors are likely to be cured following complete surgical removal although cases that subsequently develop a metastatic disease are recognized; in these cases, it must be assumed that histological evaluation failed to reveal malignant tissue [18].

Histological 'stage 2' tumors have a median survival time of a year following surgery. In these cases, re-evaluations are recommended and consideration should be given to adjuvant chemotherapy or surgery if the progressive disease is recognized. Monitoring evaluations are suggested after six, 12, and 18 months [42].

For 'stage 3' tumors, further monitoring or therapy should be considered quarterly if the further intervention will be offered if the progressive disease is identified. With current knowledge and treatments, if adjuvant chemotherapy can be justified at all, it is for patients exhibiting stage 3 tumors [4,28,29].

Despite the poor prognosis described for patients with metastatic disease, occasionally those with regional lymph node metastases do still enjoy a prolonged period of a normal quality of life. Lymph node removal can be performed, but in nearly all cases the tumor has progressed beyond the limits of the lymph node capsule rendering simple lymphadenectomy useless; advanced surgical techniques are therefore required in this situation. Inflammatory carcinoma carries a poor prognosis with most patients succumbing to their illness within four to eight weeks. Preliminary data have demonstrated improvements in clinical signs with the administration of COX inhibitors, in particular the COX-2 selective antagonist firocoxib [24].

Follow-Up

After the diagnosis of a malignant mammary tumor, consideration should be given to the indications or otherwise for further monitoring or therapy. Since chemotherapy has largely proved to be unrewarding, my recommendation instead is that patients that have been diagnosed with a high-grade mammary tumor undergo serial monitoring using thoracic radiography and abdominal ultrasonography on a regular, initially quarterly, basis. Accurate recording of lymph node size and definition of the state of the hepatic and splenic parenchyma allow early changes due to the development of metastatic disease to be recognized. At this time, surgery may be indicated. Alternatively, chemotherapy can be

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 mammae, 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].

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