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PERSPECTIVES FOR DIAGNOSIS, PROGNOSIS AND TREATMENT OF MAMMARY NEOPLASMS IN DOGS

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Introduction
Mammary tumors are the most frequent neoplastic processes of the female dog and represent a problem of large impact in veterinary medicine. In this context, many efforts are being directed towards adopting criteria towards standardizing diagnosis, understanding behavior and tumor evolution and evaluating prognostic factors such as: morphology, oncogenes expression and genetic alterations. Knowledge and adoption of these parameters are fundamentally important for choice and success of therapies that promote reduction of tumoral recurrence and increase survival. In addition, mammary tumors of the female dog present epidemiological (HÉLLMEN, 1993), clinical (MILLER, 1991; LAS MULAS et al., 2005), biological (GERALDES et al., 2000; DUTRA et al, 2004) and genetical (LEE et al., 2004) similarities with mammary neoplasms of women, therefore considered to be important models in comparative studies.

Diagnosis
Initial diagnosis of mammary neoplasms is performed based on age, reproductive history and clinical signs such as existing mammary mass, regional lymph node volume augmentation.

Histopathological exam of incisional or excisional biopsies is the safest diagnostic method. Besides facilitating injury classification, histopathological exams allows to evaluate: infiltration of skin, soft tissue and surrounding vessels, histomorphological details of the tumor (presence or absence of pleomorphism, differentiation grade, mitotic index, presence or absence of necrosis); and excision precision.

In diagnostic criteria of mammary carcinoma of women, evaluating the integrity of the myoepithelial/basal layer is an important tool for differential diagnosis between in situ and invasive malignant lesions, mainly assisting the detection of microinvasion foci (STERNLICHT et al., 1997; YAZIJI et al., 2000). In veterinary medicine, myoepithelial markers such as smooth muscle alpha-actin, S-100 protein (DESTEXHE et al., 1993), calponin (LOS MONTEROS et al., 2002), p63 (GAMA et al, 2003) and maspin (LOS MONTEROS et al, 2005) have been used mainly in researches directed towards determination of tumoral histogenesis. However, their use as an assistant tool in determining invasion is yet limited and few studies approached this aspect (BERTAGNOLLI et al, 2009).

Although some authors consider cytological diagnosis of mammary tumors of the female dog as poorly accurate, its use in small animal clinical practice is increasing and substantial levels of cytohistopathological agreement has been described (CASSALI et al, 2007). However, caution in obtaining adequate samples and training the cytologist, that should have experience in histopathology, is very important. This certainly is one of the limiting factors to promoting the use of FNA in veterinary medicine (CASSALI et al, 2007).

Mixed Tumors
Approximately 50% of mammary tumors that affect female dogs are benign and among them, benign mixed tumors are the most frequent (MISDORP et al, 1999). In a recent survey of diagnosis of the Laboratory of Comparative Pathology – Department of General Pathology
(ICB/UFMG/Brazil), from 1040 examined mammary “tumors”, 209 (20.096%) were benign mixed tumor and 264 (25.38%) were carcinoma in mixed tumor.

Benign mixed tumors are rare in the human mammary gland, though the most frequent type in salivary glands where are denominated pleomorphic adenomas (VOZ, 2000). These tumors are characterized by a complex phenotypical and biological heterogeneity and are capable of becoming malignant.

The malignant transformation of these neoplastic processes may occur, which is correlated with advanced age and larger tumor size (MOULTON 1990). In both species, histogenic origin of its heterologous elements, as well as characteristics that determine its malignant evolution continues unclear (GARTNER et al, 1999; BERTAGNOLLI et al, 2008).

Data referring to the frequency of benign mixed tumors are imprecise, especially due to difficulty in comparing different studies. According to Misdorp et al (1999) the benign mixed tumor is “a tumor composed of benign cells morphologically resembling epithelial components (luminal and/or myoepithelial) and mesenchymal cells that have produced cartilage and/or bone and/or fat eventually in combination with fibrous tissue”. In our laboratory, we consider as benign mixed tumor when there is myoepithelial cell proliferation associated to presence of myxoid matrix. Erdélyi et al (2005) show the cartilagenous differentiation of complex tumors and myoepitheliomas and indicate that myxoid tissues and myoepithelial-like cell proliferations are the precursor tissues of the ectopic cartilage in mixed tumors. They suggest that cartilage formation in canine mammary tumors is a result of (myo)epithelial to mesenchymal transition.

Despite the increased frequency of carcinomas in mixed tumors in the canine specie, there is little information regarding mechanisms related to the progression of these lesions (GENELHU et al., 2007; BERTAGNOLLI et al, 2009).

Clinical Staging and Grading
Clinical staging of cancer is based on the size of the primary tumor (T), in the extent of its dissemination to regional lymph nodes (N) and presence or absence of distant metastasis (M). Classifying each case according to the TNM system (Tumor, Lymph Node, Metastasis), proposed by the World Health Organization (OWEN, 1980), allows: to establish prognosis and plan a treatment, to precisely indicate to anatomopathologists about the material sent to analysis and compare clinical observations from different sources.

Grading a cancer is based on the grade of tumoral cell differentiation and number of mitoses present in the tumor, supposedly correlated to the aggressiveness of the neoplasm. Therefore, cancers are classified into grades I to III, with increasing anaplasia. Grading criteria of mammary tumors are poorly utilized in veterinary medicine. Lagadic et al. (1990) used the same histologic criteria described by Bloom & Richardson (1957) for tumors affecting women (tubular differentiation, nuclear pleomorphism and number of mitoses) and found similar results regarding biological behavior, i.e., longer survival time for tumors with low malignity.

Dutra et al (2008) emphasize the importance of mitotic count and histological grade and type for assessing the prognosis of canine mammary tumors and indicates that criteria used for this assessment should be well standardized and controlled. In contrast to the MIB-1 index, mitotic count per 10 HPF is less expensive, requires no additional technology, applies to most histological types, and can be carried out on formalin-fixed tissue sections.

Prognostic
Patient’s prognosis is directly related to factors such as: tumor size, lymph node involvement, presence of distant metastasis, histologic type, histologic grading, nuclear differentiation level, invasion level, intravascular growth and presence of estrogen receptors. Large tumors (larger than 3.0 cm) with lymph node metastasis indicate worse prognosis, approximately 80% of patients
show recurrence after six months of treatment, leading to short overall survival and disease-free survival (WITHROW & MAC EWEN, 2001; CAVALCANTI, 2006; CAVALCANTI & CASSALI, 2006).

Prognostic and predictive markers established in the human area as hormonal receptors (Estrogen Receptor, Progesterone Receptor), rate of cellular proliferation (MIB-1, PCNA), presence of oncogene products (c-erbB2) and tumor suppressor gene (p53), have been currently studied in veterinary medicine. Although some markers present a correlation with behavior (benign or malignant), histologic grading or the evolution of neoplasms, their applicability is yet restricted, especially due to high costs of exams (CASSALI, 2002).

**Treatment**

Surgery remains the treatment of choice for female dogs with mammary gland tumors, except those with inflammatory carcinomas or distant metastasis. The type of surgery depends on the extent of disease, injury size and location and lymphatic drainage (WITHROW & MAC EWEN, 2001). Lesions smaller than 2 cm can be treated with lumpectomy (nodulectomy). Other lesions are removed through mammectomy or mastectomy, either regional or radical, depending on the lymphatic drainage of the affected mammary gland (BRODEY et al, 1983). Lymph nodes altered in size and consistency should be removed and submitted to histological analysis for metastasis research (MORRISON, 1998).

Chemotherapy is not commonly used and no adjuvant protocol has been effective. Protocols proposed by the literature consist on the use of doxorubicin in combination with cyclophosphamide or use of cisplatin or carboplatin as a single agent, although additional studies are necessary to determine an efficient protocol for canine mammary tumors. Some authors recommend the use of tamoxifen associated to diets with higher protein levels and less fat (OGILVE & MOORE, 1996; MORRISON, 1998; WITHROW & MAC EWEN, 2001).

Our group studied side effects of oral administration of tamoxifen in spayed and intact bitches and verified similar side effects to those observed in women with breast cancer treated with this medication. Considering the limited therapeutic resources in mammary neoplasms of the female dog, the confirmed benefits of tamoxifen in human mammary tumors and the insufficient data on the canine species, justifies performing studies that addresses criteriously the additional effect of this drug in veterinary medicine.

Patients suffering from mammary tumors with advanced clinical staging were studied. Analyzing the overall survival of animals treated only with surgery compared to those complementarily treated with carboplatin and Cox-2 inhibitors, the benefit of these patients from complementary therapy was verified. Carboplatin as an only drug was indicated for treating mammary tumors of female dogs in advanced clinical staging, with minimal side effects and easy administration.

**Conclusion**

The existing literature and data obtained in our group’s routine indicate that the use of clinical staging TNM criteria and evaluating classic morphologic prognostic factors (tumor size, mitotic count, histologic grade and type and lymph node involvement), well established for the human species, are useful in the prognostic evaluation of female dogs suffering from mammary carcinomas. Consequently we need to improve and standardize diagnostic criteria and continuing to invest in the study of prognostic and predictive markers so these factors can be routinely employed by veterinary pathologists and provided to clinics and surgeons so that new treatment options and longer survival can be established for these patients.

**References:**

