

Canine Mammary Tumor Diagnosis and Treatment: Current and Emerging Advances

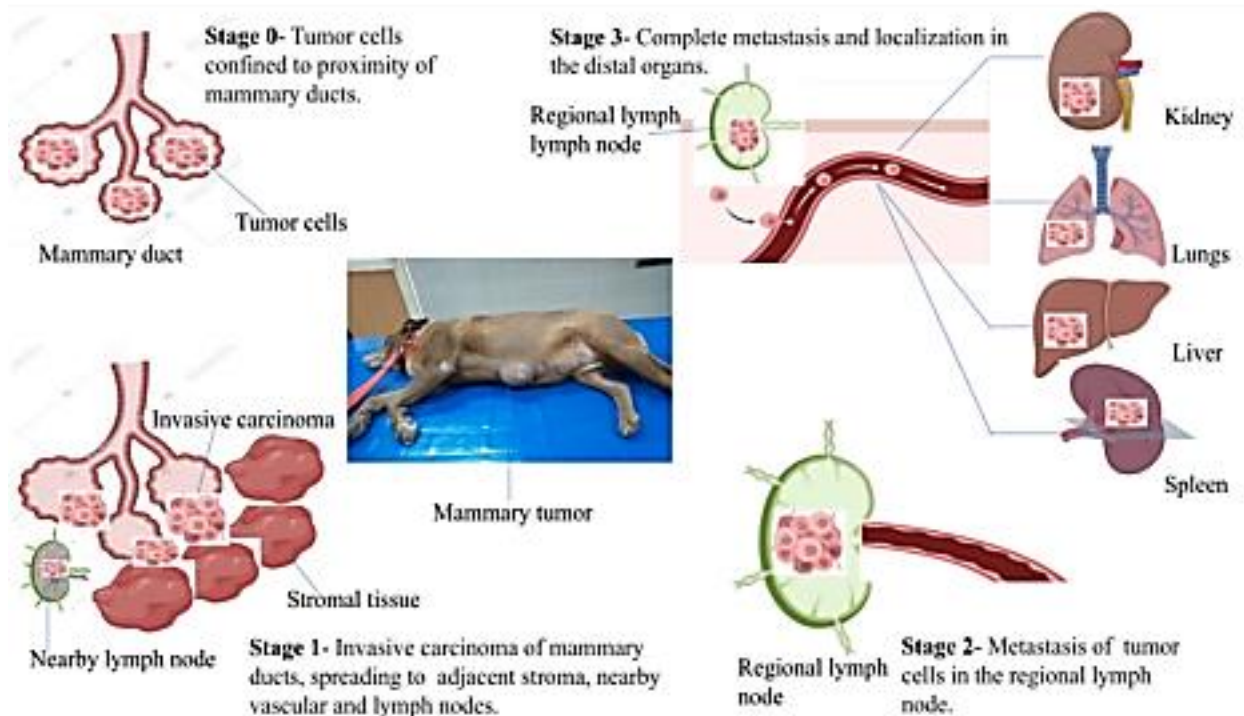
Priyanka Malakar¹, Kanchan Singh¹, Karuna Irungbam¹, Mohini Saini¹, Mukesh Kumar^{1*}

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The most frequent malignant tumor in female dogs, mammary tumors make for around half of all neoplasms (Dileep Kumar *et al.*, 2014). Canine mammary tumor (CMT) is a tumor outgrowth that occurs inside or outside of the mammary glands, mostly in the female dogs (Zheng *et al.*, 2017). CMT can be benign or malignant. Many studies show that almost 50% of the CMT could be malignant tumors that can be fatal because of their invasiveness and metastasis property which can disseminate to other parts of the body (Valdivia *et al.*, 2021 ; Nosalova *et al.*, 2024). CMT is a chronic inflammatory disease where cell division becomes aberrant that leads to tumor outgrowth. Metastasis, cell invasiveness and chemotherapeutic resistances are the cardinal features responsible for making this disease difficult to treat (de Souza *et al.*, 2009). Lack of specific treatment regimen against the CMT is also a great issue in their treatments. Making a good companion of a human, dogs can be exposed to all the nutritional and environmental factors which a human faces which makes spontaneous cancer in dogs could be the best model to study human cancer (Khanna *et al.*, 2006). Understanding and knowledge generated in the CMT can be used to understand human cancer as well as to identify the suitable treatment regimen. In our present article we discuss the etiology, epidemiology prevention and treatments as well as recent advances in research and diagnosis aspects of the CMT (Kwon *et al.*, 2023)

Etiology : Dogs possess five pairs of mammary glands. Mostly the 4th to 5th pair of mammary glands are more prone for CMT. This tumor occurs due to mutations induced alterations in the structural and functional properties of molecular, cellular and biological machinery confined nearby the mammary glands. These mutation occurrences increased due to imbalanced life styles, elevated pollutants, increased exposures of insecticides and carcinogens in the food stuff. Dogs are more likely to be exposed to the carcinogens and pollutants that might cause canine mammary cancers since they are excellent companions, live closer to humans, and depend on human food (Carvalho *et al.*, 2023 ; Takeshima *et al.*, 2019 ; Gray *et al.*, 2020). As per the GILBERTSON *et al.* (1983), the CMT can be categorized into four stages. The stage 0 where tumor cells are confined to the proximity of mammary ducts, (*carcinoma in situ*); **Stage1 indicates invasive carcinoma, spreading to the adjacent stroma, nearby** vascular and lymph nodes. Stage 2 refers to the metastasis of the tumor cells in the regional lymph node and stage 3 is the complete metastasis and localization in the distal organs (Baba *et al.*, 2007).

Stages of Canine Mammary Tumor



Risk factor: Female dog mammary tumors can be influenced by hormones like estrogen and progesterone. More exposure to these hormones, especially during heat cycles, can raise the chances of developing these tumors. Dogs spayed prior to their first heat cycle have a very low risk (0.5%) of mammary tumors. Removing ovaries reduces hormone levels that can stimulate tumor growth (Nosalova *et al.*, 2024). Substances like insulin-like growth factor 1 (IGF-1) and compounds released by fat cells like aromatase, leptin, and cholesterol, can also affect tumor growth (Lim *et al.*, 2015).

Epidemiology: The CMT is mostly affected to the female old dogs aged between 8-12 years (Dolka *et al.*, 2024 ; Dhama *et al.*, 2010). Certain breeds of dogs are more prone for CMT such as Spitz, German shepherd, Pomeranian boxers, cocker spaniels, English springer spaniels and dachshunds. In many studies, incidence rates increase as the dog age increases. Canine mammary tumor incidence was higher in non-spayed dogs (23/30, 76.67%) than in spayed dogs (3/30, 23.33%). According to Dhama *et al.* (2010), the incidence of canine mammary gland in Gujarat was 0.75 percent (63/8337) of all canine cases. In a second study, the incidence of mammary tumors was 0.48% among all canine cases and 24% (12 out of 50) among the various tumors. The Annual incidence of canine mammary tumors (CMT) was 205 per 10,000 female dogs (Dobson *et al.*, 2002).

Clinical signs: Mammary tumors typically appear as firm, well-defined nodules that vary in size and can appear in multiple glands simultaneously. They may have different types and grades. Caudal abdominal glands are more commonly affected (up to 60% of cases) and can cause skin changes like ulcers or trauma in advanced cases. Multiple tumors can also occur within the same gland (Baba *et al.*, 2007; Vazquez *et al.*, 2023)

Treatments: The treatment of canine mammary tumor is surgical resection, followed by combining certain chemotherapy drugs like cyclophosphamide with 5-fluorouracil or with mitoxantrone and vincristine has increased survival time in dogs with mammary tumors (Nosalova et al., 2024). Carboplatin and gemcitabine together resulted in a 13% response rate. Side effects were generally mild, like gastrointestinal or hematological issues (Dominguez et al., 2009). Other treatments like gemcitabine alone or certain combinations didn't show significant improvements in survival or time to metastasis. The Ovarian hormones like progesterone and estrogens are linked to the development of mammary tumors in dogs. Targeted therapies, such as hormone receptor inhibitors, may be used to treat these tumors (Kwon et al., 2023; Nosalova et al., 2024). Drugs like goserelin and aglepristone have shown promise in reducing tumor size, but more research is needed. Tamoxifen, commonly used in humans, has not been effective in dogs and can cause side effects. Overall, hormonal therapy has potential but requires further study for effectiveness and safety in treating canine mammary tumors (Valdivia et al., 2021; Nosalova et al., 2024).



Recent advances in Canine Mammary Tumor (CMT) research: In recent years, advancements in both the treatment and diagnosis of canine mammary tumors (CMT) have led to a renewed sense of optimism (Zuccari et al 2024). Promising therapies include oncolytic virotherapy (Shoj et al 2016) and the use of agents such as melatonin, alpha-fetoprotein-derived peptides, and the bevacizumab biosimilar MB02(Zuccari et al 2024). The combination of carboplatin with low-dose cyclophosphamide has also been explored for CMT treatment. Additionally, the advanced histopathological classification of CMT (Goldschmidt et al 2011) and the identification of molecular markers like E-cadherin, N-cadherin, vimentin, HER-2, CEA, CA15-3, Foxp3+, Sirtuin-1, and SF have enhanced diagnostic and prognostic capabilities, offering new pathways for improving treatment outcomes (Zuccari et al 2024).

Prevention : However, CMT is highly unpredictable like another type of cancer and difficult to prevent, however better health care and management practices can reduce the risk of occurrence in female dogs. Better care and management of dogs in terms of regular health checkup, hygienic and nutritious diets, less exposure to the household and stray garbage containing pollutants, all these could reduce the risk for the CMT.

Conclusion:

Canine mammary tumors (CMT) are a major health problem in female dogs, accounting for a sizable proportion of neoplasms. Specifically, increased environmental pollution and changes in people's lifestyles cause hormonal imbalances, genetic mutations, environmental contaminants, and food carcinogens, all of which eventually contribute to cancer in dogs. Understanding CMT is crucial not just for better canine treatment and preventive techniques, but also for learning about human breast cancer due to the parallels in tumor behavior between species. Surgical surgery and chemotherapy are now the primary therapeutic choices, although obstacles persist due to the disease's complexity and the need for new effective targeted medicines. Preventative strategies,



while difficult owing to the unpredictable nature of CMT, can be improved with adequate canine care, frequent veterinarian check-ups, and limiting exposure to probable carcinogens. One method we may prevent CMT is to reduce human exposure to pollution and carcinogens. More rigorous study is required to discover better therapeutic techniques and treatment regimens that will enhance the prognosis for afflicted canines.

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