

# The Diagnostic Assessment of Canine Lymphoma: Implications for Treatment

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## KEYWORDS

- Clonal antigen receptor polymerase chain reaction
- Flow cytometry • Immunohistochemistry • Lymphosarcoma
- Veterinary • WHO classification

Lymphoma in dogs is a heterogeneous cancer with highly variable prognosis. Many types of canine lymphoma have similar counterparts in the WHO classification of human lymphoid tumors. The most common variant of canine lymphoma is diffuse large B cell lymphoma, which, if treated with multi-agent chemotherapy, has a survival time of approximately 12 months. T cell lymphomas are more heterogeneous and high and low grade variants are common, which necessitates classification beyond B- versus T-cell lineage.

## EPIDEMIOLOGY, ETIOLOGY, CLINICAL FEATURES, AND GENETICS

The incidence of lymphoma in dogs appears to be relatively high, though large-scale recent epidemiologic data are lacking. In a Norwegian population study of cancer in animals, lymphoma was the most common malignancy in all dogs younger than 2 years, and second only to mast cell tumors in male and neutered female dogs younger than 6 years.<sup>1</sup> In comparable regions of Norway, among all cancers the overall incidence of lymphoma was 3.4% in dogs and 3.1% in people.<sup>1</sup> Data from

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pedigree dogs in the United Kingdom suggested a lower incidence of lymphoma at 0.8%,<sup>2</sup> but the analysis included predominantly very young (and insured) dogs. Previous surveys from North America<sup>3</sup> and the Netherlands<sup>4</sup> indicated incidence rates of 24 and 33 per 100,000 dogs, respectively. Hence, though precise and current figures on the epidemiology of canine lymphoma are incomplete, lymphoma is sufficiently common to be regularly encountered by general veterinary practitioners, and to comprise a large proportion of the caseload in specialized veterinary oncology practices.

Dogs are diagnosed with lymphoma most commonly between 6 and 9 years of age, with some variation according to breed and type of lymphoma.<sup>1,2,5,6</sup> Considering that humans live 6 to 8 times longer than dogs, the age of highest lymphoma incidence in dogs would correspond to 42 to 63 years of age in people. Breeds reported to have lymphoma at a younger age include Golden Retrievers, Bullmastiffs, and Bulldogs, but these are large dog breeds that have a naturally shorter lifespan.<sup>2,7</sup> Cutaneous epitheliotropic lymphoma is more commonly diagnosed in older dogs (mean 9–11 years), whereas thymic lymphoma is more commonly diagnosed in younger dogs (mean 5.8 years).<sup>8–10</sup>

Certain dog breeds have a higher incidence of lymphoma than others. Dogs have been selectively bred for more than 100 years to achieve breed-specific appearance and behavior, which has resulted in dramatic phenotypic variation as illustrated by the more than 80-fold difference in weight between Irish Wolfhounds and Chihuahuas. Concomitantly, breeding efforts have reduced genetic heterogeneity within breeds and have increased the incidence of breed-associated genetic conditions, including cancer susceptibility.<sup>11</sup> Breeds recognized in multiple surveys to have a significantly increased incidence of lymphoma are Boxers, Bulldogs, Bullmastiffs, Golden Retrievers, Bernese Mountain Dogs, Flat-coated Retrievers, and Rottweilers.<sup>1,2,5</sup> Conversely, breeds with a lower relative risk of lymphoma are Bichon Frise dogs, poodles, German shorthaired pointers, West Highland white terriers, and German Shepherds.<sup>1,2,5</sup> While such data may apply regionally, breed-specific epidemiologic data should be interpreted cautiously, due to global variation in breed popularity and definition. The genetic basis for breed-specific susceptibility to lymphoma is unknown.

Lymphoma in dogs is considered to be a sporadic cancer. Etiologic agents analogous to Epstein-Barr herpesvirus or T-lymphotropic retrovirus in humans have not been convincingly demonstrated in dogs, nor has immunodeficiency been identified as a contributing factor. In France, correlation of the geographic location of waste incinerators, pollution, and radioactive waste storage with the frequency of diagnosing lymphoma in dogs and people suggested significant associations with each of these environmental factors.<sup>6</sup> An increased risk for lymphoma in dogs was also reported if owners applied 2,4-dichlorophenoxyacetic acid (2,4-D) herbicide to lawns,<sup>12</sup> and if dogs resided in industrial areas or with owners who applied lawn herbicides.<sup>13</sup> However, experimental studies did not replicate genotoxicity or carcinogenesis of 2,4-D; therefore, the potential of environmental toxin exposure to cause canine lymphoma remains unclear.<sup>14</sup>

The clinical features of lymphoma in dogs (and humans) vary by the type of lymphoma. In approximately 80% of dogs, lymphoma presents as a painless enlargement of multiple peripheral lymph nodes noticed by the owner or detected on physical examination by the veterinarian. This presentation is often associated with a history of vague illness or inappetence over days or a few weeks. This multicentric type of lymphoma is of B-cell origin in 60% to 70% of cases, and of T-cell origin in 30% to 40% of cases.<sup>7,15</sup> Other types of lymphoma in dogs involve primarily the skin,

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