**Canine Lymphosarcoma: Clinical Features**

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**ABSTRACT:** Canine lymphosarcoma (LSA) is among the most commonly treated disseminated malignant diseases in companion animals. Although there is a level of uniformity in the clinical presentation among dogs with LSA, there is a great deal of heterogeneity noted in the biologic behavior, histologic subtype, immunophenotype, therapeutic response, and outcome. This article reviews the biology, classification, prognostic factors, etiopathogenesis, and clinical features of LSA.

Today, the potential for complete cure of lymphosarcoma (LSA) exists for both humans and companion animals. LSA is a clonal proliferation of malignant lymphocytes in solid tissues, such as lymph nodes, bone marrow, and visceral organs. Canine LSA is a spontaneous, naturally occurring neoplasm that is similar to non-Hodgkin's lymphoma (NHL) in humans. Canine LSA responds well to treatment but is rarely curable. Combination chemotherapy with antineoplastics results in a high rate of initial remission, and a median survival of 8 to 12 months can be anticipated in most cases. The greatest clinical challenges include reinduction of remission in patients that have relapsed after complete remission and induction of remission in patients with primary refractory LSA. This article discusses the incidence, cause, pathophysiology, and clinical features of various anatomic forms of canine LSA. Biologic behavior and molecular pathogenesis and prognostic factors are also presented, including a brief discussion of treatment options available to the practicing clinician.

**INCIDENCE**

Lymphoma accounts for approximately 7% to 24% of all canine neoplasms and is the third most frequently encountered malignancy in canine patients. It is the most common hematopoietic tumor seen in dogs: 83% of all canine hematopoietic malignancies are lymphomas. The annual incidence is estimated to range between 13 and 24 per 100,000 dogs at risk. A review of the veterinary

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*A companion article on diagnosis and treatment appears on p. 584.*
medical database program (maintained at Purdue University) indicated an increase from 0.75% to 2% in canine LSA patients presented to 20 veterinary institutes from 1987 to 1997. No breed predilection is reported; however, the following breeds were affected most often: golden retriever, German shepherd, Labrador retriever, cocker spaniel, rottweiler, and Shetland sheepdog.

CAUSE
The exact cause of LSA is unknown in virtually all cases. Postulated causes include viral infection, herbicide exposure, chromosomal aberrations, genetic predisposition, and exposure to electromagnetic radiation.

Viruses
Retroviruses have been described as an etiologic factor for canine LSA on the basis of findings of viral particles with retrovirus type C morphology in ultrathin sections of the canine lymphoma cell line DLC 01 and DLC 02 cell pellets. However, retroviral infection has not yet been conclusively documented in spontaneous cases of canine LSA.

Chemicals
An association between the risk for canine malignant lymphoma and exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) herbicides was reported. Other studies did not confirm a dose–response relationship between 2,4-D exposure and canine LSA, and the association of canine LSA with the use of 2,4-D was disputed. Residency in industrial areas and exposure to environmental pollutants, such as paints and solvents, were positively associated with canine LSA. Human malignant lymphoma samples have a detectable mutation in the c-N-ras oncogene. The frequency of gene mutation in naturally occurring LSA derived from 20 dogs with known exposures to 2,4-D and from eight dogs with no known exposure to the herbicide was evaluated. This study demonstrated that, unlike the case in humans, gene mutations are uncommon in dogs with malignant lymphoma and that there is no association between 2,4-D exposure and activation of the c-N-ras oncogene in dogs.

Molecular Aberrations
Chromosomal aberrations have been identified in dogs with malignant LSA. In 1994, Hahn et al reported that dogs with trisomy of chromosome 13 as a primary chromosomal aberration had a significantly longer first remission than those with other primary chromosomal aberrations. Teske et al studied DNA ploidy and the cell kinetic characteristics of canine malignant lymphoma by flow cytometry and concluded that nonneoplastic tissues were diploid, whereas 74 of the 94 lymphomas evaluated were diploid or near-diploid and 20 were aneuploid. The frequency of DNA aneuploidy in canine malignant lymphoma was thus found to be similar to that seen in human NHL. In contrast to findings in human NHL, however, there was no relationship between DNA ploidy or cell kinetic features and histomorphology or prognosis.

Genetics
Possible genetic predisposition as a cause of canine malignant lymphoma was also suggested by Teske et al, who reported a clustering of generalized malignant lymphoma in a single household of rottweilers (i.e., in both parents and three of four siblings in one litter). In addition, malignant lymphoma of the myocardium was found in three directly related otterhounds (i.e., the sire and two sibling offspring). Clustering in households could, of course, be confounded by environmental factors, such as exposure to viruses and carcinogens. Breed predisposition is also widely recognized by veterinary oncologists.

Miscellaneous Factors
Lantinga van Leeuwen et al demonstrated that canine lymphoid tissue is an extrapituitary site of growth hormone gene expression. However, expression of the growth hormone gene in canine lymphoma cells appeared to be low, which indicated that lymphoid growth hormone is probably not a major factor in the development or progression of canine lymphoma. Enteric lymphocytic-plasmacytic inflammation has been suggested as a probable prelymphomatous change in the gastrointestinal (GI) tract. This type of inflammation can be seen both adjacent to and distant from sites of primary LSA.

Role of the Immune System
Increased information about immune-mediated and malignant diseases has revealed a potential association between autoimmunity or the immune system and hematopoietic neoplasia in dogs. Autoimmune diseases and neoplasia have occurred simultaneously in individuals. Keller showed that dogs with immune-mediated thrombocytopenia had a greater occurrence of lymphoma than dogs without this disorder. In one report, a dog developed multicentric LSA 7 months after initial diagnosis of cutaneous pemphigus foliaceus. Day et al described the presence of birefringent crystalline material, such as silicon, sulfur, copper, calcium, and aluminum, within lymph nodes of dogs with a range of systemic illness and granulomatous lymphadenopathy.
Similar crystalline material was found in the lymph nodes of dogs with LSA. The authors of this study proposed that the inflammatory response induced by the presence of these minerals within lymphoid tissue may trigger altered immunoregulation, which would lead to development of LSA or other diseases. An association between autoimmune hemolytic anemia and subsequent appearance of lymphoproliferative disorders has been postulated in humans. In another study, 4.3% of humans with chronic lymphocytic leukemia developed autoimmune hemolytic anemia, and such an occurrence did not appear to have a negative impact on survival.

**CLASSIFICATION**

Several classification schemes exist for canine LSA. The oldest one characterizes LSA by anatomic site. In this system, LSA is classified as multicentric (80% to 85% of cases), alimentary (7%), cutaneous (6%), mediastinal or thymic (3%), or extranodal (central nervous system, spinal, and rarely skeletal). Involvement of bone marrow or peripheral blood by neoplastic lymphoid cells is called leukemia. The anatomic forms of LSA are discussed in detail later (see Clinical Signs section). In general, canine LSA resembles human NHL. A solitary case of canine Hodgkin-like lymphoma was reported in Japan; tumor infiltration in lymph nodes and multiple visceral organs was detected. Histopathologic examination revealed a large number of typical Reed-Sternberg cells with symmetrically arranged nuclei, the so-called mirror-image cells, intermingled with various numbers of inflammatory cells and globule leukocytes.

Lymphoma is now classified by means of three histologic nomenclature systems: the Rappaport scheme, the National Cancer Institute Working Formulation (NCI-WF) scheme, and the Kiel classification. The NCI-WF classifies LSA into low, intermediate, and high grades and is the most commonly accepted classification in veterinary clinical medicine. Regardless of the histologic nomenclature system used, most dogs have intermediate- to high-grade LSA. In both the NCI-WF scheme and the Kiel classification, only a minority of lymphomas (i.e., 16.4% and 12.0%, respectively) were classified as low-grade malignancies. Large cell lymphomas and centroblastic lymphomas were the most frequently encountered in the NCI-WF scheme and the Kiel classification, respectively.

The morphologic cell type classification used in the NCI-WF scheme includes low-grade LSA (i.e., small lymphocytic, follicular small cleaved cell, and follicular mixed small cleaved cell), intermediate-grade LSA (i.e., follicular large cell, diffuse small cleaved cell, diffuse mixed small and large cell, and diffuse large cell), and high-grade LSA (i.e., diffuse immunoblastic, diffuse lymphoblastic, diffuse small noncleaved cell). Similarly, the Kiel classification system defines canine LSA as low-grade LSA (i.e., lymphocytic, lymphoplasmacytic, centrocytic, centroblastic-centrocytic) and high-grade LSA (i.e., centroblastic, lymphoblastic T, lymphoblastic B, immunoblastic). A lower incidence of low-grade malignancy in dogs is one of the striking features when the canine classification is compared with the human counterpart. Some pathologists have recognized a histiocytic form of LSA.

Non-Hodgkin’s LSA is categorized in the Rappaport classification as lymphocytic well differentiated, lymphocytic poorly differentiated, mixed lymphocytic-histiocytic, histiocytic, or undifferentiated. The current classification system defines histiocytic LSA as large-cell LSA.

Genetic analysis has demonstrated that the B cell immunophenotype is the one most often observed in dogs; only 20% to 30% of LSAs have a T cell origin. Teske et al reported that, in contrast to the distribution pattern of human NHL in Western countries, there is a high percentage of T cell lymphomas (37.9%) in the canine population.

**BIOLOGY**

This section focuses on the molecular pathogenesis of LSA and the clinical significance of peripheral lymph nodes. The pathology and natural behavior of canine LSA for each anatomic site are detailed later (see Clinical Signs section); molecular markers that have been studied in canine LSA are also discussed later (see Prognostic Factors section). The molecular etiopathogenesis of canine LSA is still largely unknown. However, the histogenesis of lymphoma in humans has been clarified considerably in the case of lymphomas derived from B cells, whereas it is still poorly understood for lymphomas originating from T cells. B lymphocytes arise from the pluripotent stem cells in the bone marrow as a result of a multistep differentiation process and then migrate to secondary lymphoid organs, such as lymph node follicles and Peyers’s patches in the GI tract. Malignant transformation of these cells involves a complex cascade of molecular events, including gene alterations. Complete discussion of these molecular pathways is beyond the scope of this article. However, the fundamental theory of lymphoid neoplasia is that disorders of lymphoid cells represent arrested maturation at various stages in the normal differentiation scheme. Readers are advised to consult a molecular oncology textbook (e.g., The Molecular Basis of Cancer, edited by Mendelsohn and colleagues; The Basic Science of Oncology, edited by Tannock and Hill) for more in-depth information.
A variety of cellular antigens can be detected at different stages of B cell or T cell development, and most are referred to by CD (cluster of differentiation, or cluster designation) numbers. In simple terms, CD can be defined as a uniform nomenclature system that identifies a particular lineage or differentiation stage of a lymphocyte. A particular differentiation stage has a defined structure and is recognized by a group (cluster) of monoclonal antibodies. As for most cancer types, the pathogenesis of lymphoma represents a multistep process involving the progressive and clonal accumulation of multiple genetic lesions affecting protooncogenes and tumor suppressor genes.

Various naturally developing tumors in dogs often have inactivation of the p53 tumor suppressor gene, which may be one of the multiple step-wise genetic changes during tumorogenesis.48 Aberrations of the p53 gene and loss of chromosomal heterozygosity have been demonstrated in dogs with malignant lymphoma, monocytic leukemia, rhabdomyosarcoma, colon cancer, and osteosarcoma.48,49 However, similar to the situation in human disease, mutations of the p53 gene are found in only a small number of canine cases.41,50,51 It is now apparent that the clinical heterogeneity of B cell LSA may be related to heterogeneity in histogenesis of the LSA itself.46 Recent advances in molecular biology and cellular immunology have led to development of comprehensive profiles of DNA alterations found in many forms of human cancer.52 It is hoped that such profiles will provide invaluable insight into the pathogenesis of specific tumor types and eventually enable us to cure patients.52–53

Mantle cell lymphoma is a low-grade lymphoma entity that is now being recognized in canine patients. Mantle cell lymphoma is a relatively rare B cell lymphoma in humans.54 It originates from the mantle zone surrounding follicular centers of the lymph node.54 Veterinary literature currently lacks any reports of this histologic category of LSA.

Another term now commonly used by veterinary pathologists is large granular lymphocyte (LGL) leukemia. LGL leukemia involves a lymphoid subset that makes up 10% of peripheral blood mononuclear cells, and these cells are characterized by abundant basophilic cytoplasm containing distinct granules of variable size and number.12,55 The clinical course of LGL leukemia has been evaluated in three dogs.56 Similar to humans with the disease, dogs with LGL leukemia have a heterogeneous clinical progression. One dog in this report had a long-term remission, whereas the other two dogs exhibited a more progressive clinical course.56

Another pathogenic condition that is often noted in routine clinical settings is progression of LSA in a solitary site to a generalized multicentric form of LSA. Humans have shown progression from a local LSA to clinically diffuse disease. This pattern was reported in one dog in which an orbital T cell–rich B cell lymphoma progressed to a diffuse B cell lymphoma.57

### Clinical Signs

In most cases, LSA at diagnosis is characterized clinically as a disseminated disease.58 Very rarely is a dog diagnosed with a single involved node, indicating clinical stage I disease. LSA can be classified on an anatomic basis as multicentric, GI, central nervous system, cutaneous, hepatic, splenic, mediastinal or pulmonary, and ocular. In addition, specific clinical signs may relate to dysfunction of an involved nonlymphoid organ system.

### Multicentric Disease

Clinical features of multicentric lymphoma usually include painless, generalized peripheral lymphadenopathy, with or without hepatosplenomegaly.5,59 Lymph nodes are a major site for immunologic recognition in a host, and they respond to various pathologic processes, such as infection, inflammation, neoplasia, and immune disorders. Lymphadenopathy is defined clinically as an increase in the size of lymph nodes. This size increase is primarily due to hyperplasia or nodal infiltration by inflammatory or neoplastic cells.59 Reactive nodal hyperplasia is often caused by antigenic stimulation and is characterized cytologically by proliferation of lymphocytes (B and T subtypes), reticuloendothelial cells (macrophages), and plasma cells.60 Neoplastic lymphadenopathy in lymphoma is due to partial or complete replacement of normal nodal architecture by malignant lymphocytes. In the canine patient, enlarged peripheral lymph nodes that can easily be palpated on physical examination include mandibular, prescapular, popliteal, and inguinal nodes.

Bone marrow infiltration may be present with or without associated signs of bone marrow dysfunction.61–63 These signs may include myeloproliferative disorders, such as leukemia, which are distinguished by a marked neoplastic lymphoid infiltrate, reduced number of erythroid precursors, and reduced myeloid activity with normal maturation; also, the number of megakaryocytes can be reduced in dogs with LSA, but this sign is more often noted in dogs with leukemia.62,63 Raskin and Krehbiel62 reported that 28% of cases were diagnosed as leukemic on the basis of peripheral blood smear evaluation, whereas bone marrow assay indicated that 57% were leukemic.

Non-specific clinical signs include lethargy, fever, anorexia, weight loss, abdominal distension, and poly-
uria/polydipsia\textsuperscript{3,60} as well as others related to dysfunction of nonlymphoid organ systems.

**Alimentary System**

The GI form of LSA is an uncommon clinical presentation in dogs, usually representing 5\% to 7\% of all canine lymphomas.\textsuperscript{64} Dogs with GI LSA may exhibit signs such as vomiting, diarrhea, weight loss, and malabsorption. Lymphocytic-plasmacytic enteritis can be detected adjacent to or distant from the primary tumor. It may be difficult for the pathologist to differentiate low-grade GI LSA from lymphocytic-plasmacytic enteritis.\textsuperscript{24} A syndrome of immunoproliferative intestinal disease, clinically resembling lymphocytic-plasmacytic enteritis, was described in Basenji dogs that subsequently developed GI LSA.\textsuperscript{25} Dogs that present with mesenteric lymphadenopathy and primary hepatic, splenic, or gastric LSA are often classified as having alimentary LSA.

**Mediastinum**

Dogs with the mediastinal form of LSA may present with dyspnea, cough, weight loss, polyuria/polydipsia, and hypercalcemia. Mediastinal LSA can also manifest clinically as precavai syndrome, which is characterized by pitting edema of the anterior cervical and facial regions and thoracic limb area.\textsuperscript{3}

**Skin**

Cutaneous LSA can be generalized or multifocal.\textsuperscript{65,66} Lesions can occur as nodules, plaques, ulcers, generalized erythematous erosive dermatitis, scaling, alopecia, crust, and pruritus. The differential diagnosis for cutaneous lymphoma should include cutaneous histiocytosis, allergic dermatitis, discoid lupus erythematosus, and nodular dermatofibrosis.\textsuperscript{67,68} In most cases, the canine cutaneous LSA is the T cell subtype and responds poorly to chemotherapy.\textsuperscript{3,68} Canine cutaneous LSA can be classified as nonepitheliotropic or epitheliotropic.\textsuperscript{69} Lesions such as erythema, plaques, and nodules can also be found at mucocutaneous junctions.\textsuperscript{70} Progression of the disease can be particularly rapid in the buccal forms.\textsuperscript{3} Adenopathies noted at the time of diagnosis or during the course of progression are often accompanied by peripheral lymphocytosis (Sézary syndrome) and organ infiltration. Metastasis to the central nervous system from primary cutaneous epitheliotropic T cell LSA was reported in a German shepherd.\textsuperscript{71}

Canine epitheliotropic T cell lymphoma and mycosis fungoides (MF) are spontaneous neoplasms of skin and mucous membranes that occur in old dogs (mean age: 11 years) and have no breed predilection. Canine MF has been documented as a T cell lymphoma in which epitheliotropic lymphocytes consistently expressed CD3 and CD8.\textsuperscript{72,73} The pathogenesis of canine MF is not completely understood. In human cases, lymphocyte adhesion to keratinocytes appears to be significant; however, similar correlation between epithelial lymphocyte infiltration and keratinocytes does not appear to be significant in canine MF.\textsuperscript{72,74–76}

**Nervous System**

Dogs with primary central nervous system LSA may present with neurologic signs, such as seizures, paresis, paralysis, locoregional neuropathy, behavior change, and circling. Primary central nervous system LSA may show local solitary involvement, primary central nervous system disease, or multifocal involvement; central nervous system LSA may also be metastatic from other primary sites.\textsuperscript{77–79}

**Eyes**

Ocular LSA is characterized as bilateral uveitis, hypHEMA, hypopyon, synchiae, complete bulbar detachments, exophthalmos, and secondary glaucoma.\textsuperscript{57,80,81} (Figure 1). Ocular lesions may be primary or may represent extension of advanced-stage systemic involvement.

**Other Anatomic Sites**

Rarely, lymphoma lesions have been documented at other anatomic sites in dogs: skeletal muscle,\textsuperscript{82} penis,\textsuperscript{83} urinary bladder,\textsuperscript{84} skeletal involvement at multiple locations,\textsuperscript{85} and nasal area.\textsuperscript{86}

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**Figure 1**—A 4-year-old spayed female rottweiler diagnosed with recurrent conjunctival T cell LSA. Note the profound hyperemic chemosis. Approximately 14 weeks earlier, the mass had been surgically excised. (Courtesy of Dr. Kristina Burling, staff ophthalmologist, Animal Eye Specialists of San Jose, CA)
PARANEOPLASTIC SYNDROMES

Tumors may produce signs at sites distant from the primary tumor or its metastases, and these are referred to as paraneoplastic syndromes.\(^{67}\) The syndromes may be due to production of substances by a tumor that directly or indirectly causes distant signs; depletion of normal substances that leads to a paraneoplastic manifestation; or a host response to the tumor that results in the syndrome.\(^{67,87}\) Tumor-derived proteins responsible for paraneoplastic syndromes have been identified and include various growth factors and cytokines, such as interleukin-1 and tumor necrosis factor.\(^{87,88}\)

Paraneoplastic syndromes that have commonly been reported in association with canine LSA include hypercalcemia; normocytic, normochromic nonregenerative anemia; hemolytic anemia; thrombocytopenia; monoclonal gammopathy; neuropathy; myasthenia gravis; and cancerous cachexia.\(^{61,89–92}\)

Hypercalcemia of malignancy is the most frequently reported paraneoplastic syndrome associated with LSA. Other malignancies, both epithelial and mesenchymal in origin, can also induce hypercalcemia. In LSA, hypercalcemia is likely due to humoral hypercalcemia of malignancy or to local resorption of bone induced by LSA.\(^{93}\)

A parathyroid hormone–related peptide has been identified in most cases as the cause of hypercalcemia of malignancy.\(^{94}\) Serum levels of parathyroid hormone, parathyroid hormone–related peptide, and ionized calcium can be obtained for diagnosing the cause of this disorder. LSA in most dogs that are hypercalcemic because of humoral mechanisms has a T cell phenotype.\(^{95}\)

Hypercalcemia in patients with bone involvement, such as extensive osteolysis, can be due to direct bone destruction by cancer cells (i.e., local osteolytic hypercalcemia).\(^{95}\) It is now evident that hypercalcemia, even in patients with extensive osteolysis, is mediated by factors released by malignant cells in an autocrine manner,\(^{96}\) such as osteoclast-activating factor, interleukins, and prostaglandins, that ultimately act to resorb calcium from bone.\(^{92,95}\)

These soluble osteoclast-activating factors stimulate calcium resorption from the renal tubule, but this effect is secondary in importance to accelerated osteoclastic bone resorption.\(^{95}\) Elevated serum 1,25-dihydroxyvitamin D\(_3\) levels have been reported in humans with Hodgkin’s disease, NHL, myeloma, and, occasionally, solid tumors. Whether vitamin D\(_3\) plays a critical pathophysiologic role in hypercalcemia is still unclear.\(^{97}\) Prostaglandins have long been implicated as circulating mediators of cancer-related hypercalcemia.\(^{98}\) Other cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor, are also potent inducers of bone resorption in vitro.\(^{99–101}\)

PROGNOSTIC FACTORS

Prognostic factors in canine LSA include age, sex, tumor stage, histomorphologic grade (Kiel classification, NCI-WF), immunophenotype (CD3 and CD79a markers), and cell proliferation indices, such as Ki-67, proliferating cell nuclear antigen, mitotic index, and argyrophilic nucleolar organizer regions.\(^{102–115}\) However, some oncologists believe that age is not prognostically significant (Table 1).

Assays of tumor cell proliferation by use of quantitative measures, such as mitotic index, immunoreactivity for proliferating cell nuclear antigen, and Ki-67, along with apoptotic index, have been evaluated in dogs with lymphoma. Of the proliferation markers, only the results of Ki-67 analysis predicted the duration of the first relapse-free interval, but they did not predict overall survival. Pretreatment apoptotic index also predicted the duration of first relapse-free interval but not overall survival.\(^{104}\)

Other kinetic parameters studied in canine LSA include potential doubling time (\(T_{pot}\)), duration of S phase (\(T_s\)), labeling index (LI), and DNA index (DI) measured by flow cytometric techniques. In this study, dogs with longer-than-median \(T_{pot}\) and \(T_s\) values and lower-than-median LI values had significantly longer remission after treatment than all other dogs in the study. The mechanisms by which kinetics are associated with response to chemotherapy are still not clear.\(^{105}\) Hahn et al\(^{106}\) demonstrated that mean plasma glutathione S-transferase concentrations were markedly increased (\(P < .05\)) at the time of relapse in dogs with LSA. It is hoped that these molecular markers will be made available through commercial reference laboratories to aid clinicians in making therapeutic and prognostic decisions.

In a study of 28 dogs with LSA, the remission duration was shorter in dogs with stage IV or V disease, in dogs with pretreatment hypoalbuminemia, and in dogs that had received glucocorticoids before initiation of chemotherapy.\(^{107}\) Another retrospective study of 145 dogs diagnosed with lymphoma demonstrated that dogs with a history of certain chronic inflammatory diseases were 3.23 times more likely to have a relapse than was the overall population of LSA patients. In cases of failure of induction chemotherapy, GI toxicity from induction and clinical stage B were associated with higher relative risks of death.\(^{108}\) By means of univariate analysis, Keller et al\(^{109}\) identified sex, World Health Organization stage, and serum calcium levels as statistically significant prognostic variables for both survival and remission duration. With multivariate analysis, only stage B was a significant prognostic factor for remission duration, whereas both stage and sex were significant prognostic factors for sur-
Immunophenotype was found to be valuable for predicting duration of first remission, disease-free interval, and overall survival. In one report, dogs with T cell LSA were at significantly higher risk for relapse and early death after therapy compared with dogs with B cell LSA (52 versus 160 days, and 153 versus 330 days, respectively).  

### Table 1. Summary of Canine Lymphosarcoma Prognostic Factors

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Influence on Survival</th>
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<tbody>
<tr>
<td>Age&lt;sup&gt;115&lt;/sup&gt;</td>
<td>Some veterinary oncologists believe that young age is a negative prognostic factor.</td>
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<tr>
<td>Sex&lt;sup&gt;109, 112&lt;/sup&gt;</td>
<td>Spayed females have a more favorable prognosis.</td>
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<tr>
<td>Clinical stage&lt;sup&gt;33, 37, 107, 109,113, 116, 117&lt;/sup&gt;</td>
<td>Dogs with stage IV or V disease have a shorter DOR. Substage b indicates a negative prognostic outcome.</td>
</tr>
<tr>
<td>Anatomic site&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Shorter remission and survival occur with cranial mediastinal LSA.</td>
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<tr>
<td>Histologic grade&lt;sup&gt;33, 37, 118&lt;/sup&gt;</td>
<td>Dogs with lower-grade disease have longer survival, unless high-grade disease is treated with an aggressive anthracycline-based regimen.</td>
</tr>
<tr>
<td>Immunophenotype&lt;sup&gt;33, 37, 92, 102, 104&lt;/sup&gt;</td>
<td>Longer survivals correlate with a B cell immunophenotype.</td>
</tr>
<tr>
<td>Ki-67&lt;sup&gt;104&lt;/sup&gt;</td>
<td>Ki-67 is predictive for duration of the first relapse-free interval but not predictive of overall survival.</td>
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<tr>
<td>AgNOR&lt;sup&gt;102, 110, 111&lt;/sup&gt;</td>
<td>AgNOR has an equivocal influence.</td>
</tr>
<tr>
<td>Apoptotic index&lt;sup&gt;104&lt;/sup&gt;</td>
<td>This index is predictive of the duration of the first relapse-free interval but not of overall survival.</td>
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<tr>
<td>Potential doubling time (&lt;i&gt;T_{pot}&lt;/i&gt;)&lt;sup&gt;105, 111&lt;/sup&gt;</td>
<td>Dogs with longer-than-median values have a longer DOR after treatment.</td>
</tr>
<tr>
<td>Labeling index (LI)&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Dogs with lower-than-median values have a longer DOR after treatment.</td>
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<tr>
<td>Duration of S phase (&lt;i&gt;T_s&lt;/i&gt;)&lt;sup&gt;105&lt;/sup&gt;</td>
<td>Dogs with longer-than-median values have a longer DOR after treatment.</td>
</tr>
<tr>
<td>Hypercalcemia&lt;sup&gt;33, 90, 114, 119&lt;/sup&gt;</td>
<td>Negative prognostic factor. However, one study demonstrated that hypercalcemia was not a significant prognostic factor.</td>
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<tr>
<td>Albumin&lt;sup&gt;107&lt;/sup&gt;</td>
<td>Dogs with pretreatment hypoalbuminemia have a shorter DOR.</td>
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<tr>
<td>Prior steroid exposure&lt;sup&gt;107&lt;/sup&gt;</td>
<td>Steroid exposure has a negative influence on survival and remission duration.</td>
</tr>
</tbody>
</table>

<sup>AgNOR</sup> = argyrophilic nucleolar organizer regions;  
<sup>DOR</sup> = duration of remission.

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**REFERENCES**


101. Barri YM, Knochel JP: Hypercalcemia and electrolyte distur-
1. Which statement concerning canine LSA is false?
   a. Peripheral lymphadenopathy is almost always diagnostic for canine multicentric LSA.
   b. LSA is the most common hematopoietic tumor seen in dogs.
   c. Immune-mediated diseases do not appear to be a risk factor for canine lymphoma.
   d. Enteric lymphocytic-plasmacytic inflammation has been suggested as a probable prelymphomatous change in the GI tract.
   e. Canine LSA is similar to NHL in humans.

2. Which of the following is not a hypothesized cause of canine LSA?
   a. viral infection
   b. herbicide exposure
   c. exposure to electromagnetic radiation
   d. chromosomal aberrations
   e. rodenticide toxicity

3. Histologic classification of LSA is complex, but for simplicity, the most commonly accepted classification system in veterinary clinical medicine is
   a. the NCI-WF scheme.
   b. the Rappaport scheme.
   c. the Kiel classification.
   d. an anatomic classification.
   e. the Moulton classification.

4. The designation CD, commonly used in immunophenotyping to indicate the cellular antigens on lymphocytes, refers to
   a. cluster of differentiation or cluster designation.
   b. cell differentiation or cell designation.
   c. cell differentiation.
   d. cell designation.
   e. cytologic differentiation.

5. Which statement about canine cutaneous LSA is false?
   a. Cutaneous LSA in dogs is generally the T cell type.
   b. In most cases, cutaneous LSA responds favorably to chemotherapy.

   c. Cutaneous LSA can be classified as nonepitheliotropic or epitheliotropic.
   d. The progression of the disease can be very rapid in the buccal forms, which are generally aggressive.
   e. Cutaneous LSA, when accompanied by peripheral lymphocytosis and lymphadenopathy, is also known as Sézary syndrome.

6. MF is a variant of
   a. canine epitheliotropic lymphoma (cutaneous LSA).
   b. multicentric LSA.
   c. mediastinal LSA.
   d. GI LSA.
   e. muscular LSA.

7. Which statement does not describe the clinical features of lymph nodes?
   a. Reactive nodal hyperplasia is cytologically characterized by proliferation of lymphocytes, macrophages, and plasma cells.
   b. Lymph nodes are a major site for immunologic recognition in a host.
   c. Lymph nodes respond to various disease processes, such as infection, inflammation, and neoplasia.
   d. Lymphadenopathy is defined clinically as an increase in the size of the lymph nodes.
   e. Reactive nodal hyperplasia is often due to neoplasia.

8. Clinical features of canine multicentric LSA may include
   a. generalized peripheral lymphadenopathy.
   b. weight loss.
   c. hepatosplenomegaly.
   d. polyuria and polydipsia.
   e. all of the above

9. The most common paraneoplastic sign reported in canine LSA is
   a. generalized peripheral lymphadenopathy.
   b. seizures.
   c. vomiting and diarrhea.
   d. hypercalcemia.
   e. pleural effusion.

10. The variables evaluated as prognostic factors and found to be significant in canine LSA include all of these except
    a. age and sex.
    b. clinical tumor stage.
    c. histomorphologic grade.
    d. breed.
    e. immunophenotype and cell proliferation indices.