Lymphoma is the most common haematopoietic tumour of cats [1-6], and feline retrovirus infection is a known risk factor for the development of lymphoma [7-11]. Three retroviruses have been identified in domestic cats: Feline immunodeficiency virus (FIV), feline leukaemia virus (FeLV) and feline foamy virus (FeFV), which was previously known as feline syncytium-forming virus (FeSFV). All have a globally widespread distribution but differ in their potential to cause disease [12-15]. Feline foamy virus is a spumavirus and not associated with clinical disease, including tumour development [16].

Clinical signs in FIV and FeLV infections vary, and infection with either virus can lead to the development of tumours, haematopoietic and neurological disorders, immunodeficiency, immune-mediated diseases and stomatitis, after a long asymptomatic period [17,18]. The pathomechanism of these diseases syndroms, however, differs depending on the retrovirus involved (Table 1).

Feline immunodeficiency virus

FIV, a lentivirus, shares many properties with human immunodeficiency virus (HIV). Cats infected with FIV can develop an acquired immune deficiency syndrome, which increases the risk of tumours, secondary infections, stomatitis, immune-mediated diseases and neurological disorders [19]. In most naturally infected cats, FIV infection does not cause severe clinical syndromes, and with proper care FIV-infected cats can live many years. In fact, many FIV-infected cats die at an older age from causes unrelated to their FIV infection [17,18]. In a follow-up study in naturally FIV-infected cats, the rate of progression was variable, with death occurring in about 18% of infected cats within the first two years of observation (i.e. about five years after the estimated time of infection). An additional 18% developed increasingly severe disease, but more than 50% remained asymptomatic during the first two years [20]. FIV infection has little impact on a cat population and does not reduce the number of cats in a household [21]. Thus, overall survival time in FIV-infected cats is not shorter than in uninfected cats [21,22], and quality of life is usually fairly high over an extended period of time [23].

Pathogenesis and clinical signs

Clinical signs in naturally FIV-infected cats usually reflect secondary diseases, such as tumours and infections, to which FIV-infected cats are considered more susceptible. Rarely, some clinical signs (e.g. neurological disorders) attributable to abnormal function or inflammation of affected organs are directly caused by FIV. In experimental FIV infection, an initial stage is described, which is characterised by transient and mild clinical signs that include fever, lethargy, enteritis, stomatitis, dermatitis, conjunctivitis, respiratory tract disease and generalised lymph node enlargement [24]. However, in naturally infected cats, the acute stage is often not present or not noticed by the owners. The acute stage can...
The duration of the asymptomatic stage depends on the pathogenicity of the infecting FIV strain and subtype, exposure to secondary infectious agents and the age of the cat at the time of infection [25]. In the final symptomatic stage (‘AIDS phase’) of infection, the clinical signs are a reflection of secondary infections, neoplasia, stomatitis, immune-mediated diseases and neurological disorders. Although secondary infections are common, specific opportunistic infections or acquired immunodeficiency virus- (AIDS-) defining infections, such as those that occur in HIV, are not commonly reported in FIV-infected cats [17,18], and staging in FIV infection is not as clear-cut as it is in humans with HIV infection.

Table 1. Comparison of clinical syndromes and their main pathomechanism in feline leukaemia virus- (FeLV-) infected and feline immunodeficiency virus- (FIV-) infected cats

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>FeLV</th>
<th>FIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumours</td>
<td>62 times as likely as in non-infected cats, direct role of FeLV, mainly T-cell lymphoma</td>
<td>5 times as likely as in non-infected cats, indirect role of FIV, mainly B-cell lymphoma</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>common, anaemia, thrombocytopenia, neutropenia or pancytopenia, primary infection of bone marrow precursor cells and stroma cells</td>
<td>rare, mainly neutropenia, soluble factors inhibiting bone marrow function</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>rare, direct influence of the virus, lymphoma and neurotoxic effects (of FeLV envelope glycoprotein)</td>
<td>rare, direct influence of the virus (specific FIV strains), impairment of astrocyte function</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>common, several mechanisms, e.g. replication of virus in all bone marrow cells (including neutrophils), changes in cytokine pattern</td>
<td>common, several mechanisms, e.g. decrease in CD4+ cells, changes in cytokine pattern</td>
</tr>
<tr>
<td>Immune-mediated diseases</td>
<td>rare, e.g. immune-mediated haemolytic anaemia</td>
<td>occasional, hyperglobulinaemia common with immune complex deposition leading to e.g. glomerulonephritis and uveitis</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>common, multi-factorial disease</td>
<td>very common, multi-factorial disease</td>
</tr>
</tbody>
</table>

Last several days to a few weeks and is followed by an asymptomatic period that usually lasts many years. The duration of the asymptomatic stage depends on the pathogenicity of the infecting FIV strain and subtype, exposure to secondary infectious agents and the age of the cat at the time of infection [25]. In the final symptomatic stage (‘AIDS phase’) of infection, the clinical signs are a reflection of secondary infections, neoplasia, stomatitis, immune-mediated diseases and neurological disorders. Although secondary infections are common, specific opportunistic infections or acquired immunodeficiency virus- (AIDS-) defining infections, such as those that occur in HIV, are not commonly reported in FIV-infected cats [17,18], and staging in FIV infection is not as clear-cut as it is in humans with HIV infection.

Feline Leukaemia Virus

FeLV, an oncornavirus, is more pathogenic than FIV. Historically, FeLV was thought to account for more disease related deaths and clinical syndromes than any other infectious agent. It was proposed that approximately one third of all tumour-related deaths in cats were caused by FeLV, and an even greater number of cats died of FeLV-related anaemia and infections secondary to bone marrow suppression and immunosuppression [42]. The prevalence and importance
of FeLV have decreased, mainly because of testing and eradication programs and the use of FeLV vaccines \[^{[43]}\]. However, if present in closed households with other viruses, such as feline coronavirus (FCoV) or FIV, progressive FeLV infection has the greatest impact on survival \[^{[21]}\]. The death rate of progressively FeLV-infected cats in multi-cat households has been estimated at approximately 50% in two years and 80% in three years \[^{[44,45]}\], but survival time is considered higher today, at least for cats that are well taken care of and that are kept strictly indoors. A survey in the United States compared the survival of more than 1,000 progressively FeLV-infected cats with that of more than 8,000 age- and sex-matched uninfected control cats and found that in progressively FeLV-infected cats, median survival was 2.4 years compared with 6.0 years for control cats \[^{[46]}\]. In a long-term follow-up study of cats experimentally infected with FeLV, progressively infected cats lived an average (median) of 3.1 years (range 0.6 to 6.5 years) \[^{[47]}\]. Thus, progressive FeLV infection leads to a decrease in life expectancy \[^{[21, 22]}\]; however, with appropriate care, many FeLV-infected cats can live for many years with a fairly good quality of life \[^{[23]}\].

**Pathogenesis and clinical signs**

There are three major outcomes of FeLV infection: Progressive infection (antigen-positive, provirus-positive cats), regressive infection (antigen-negative, provirus-positive cats) and abortive infection (antigen-negative, provirus-negative, but antibody-positive cats) \[^{[12,23,48]}\]. Differentiation of these three outcomes is done through testing for antigen, proviral DNA and antibodies (Table 1). The outcome of infection depends on the immune function of the cat and the amount of infecting virus. In addition to these three outcomes, so-called focal infections have been described as rare events in which FeLV infection is restricted to certain tissues, such as spleen, lymph nodes, small intestines or mammary glands \[^{[49,50]}\]. However, these focal infections probably do not play an important role in naturally infected cats.

In the past, it was assumed that most cats would clear the virus from the body after a period of transient viraemia. However, the development of more sensitive PCR assays has revealed that most (or even all) cats remain infected for life \[^{[47]}\].

In most cats, antigenaemia (presence of viral proteins in the blood) correlates with viraemia (presence of infectious virus that can be cultured from the blood) \[^{[51]}\]. Infected cats can remain viraemic and antigenaemic (progressive infection) or revert to an aviraemic state (regressive infection) in which neither antigen nor culturable virus is detected but in which FeLV proviral DNA can still be identified by PCR \[^{[48,52]}\]. A third possibility is that cats test negative in all direct virus detection methods (such as tests detecting antigen and proviral DNA), but remain antibody-positive (abortive infection). Regressive and progressive infections can be distinguished by repeated testing for FeLV antigen in serum because progressor cats remain antigen-positive, while regressor cats revert to an antigen-negative status \[^{[52]}\]. They can also be distinguished by their provirus load \[^{[47]}\]; during early infection, all cats have similar provirus loads \[^{[53]}\], but after a few weeks, the provirus load drops in regressively FeLV-infected cats, while it remains high in progressively FeLV-infected cats \[^{[48]}\].

**Table 2. Feline leukaemia virus infection status possibilities**\[^{[23,48]}\]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Soluble FeLV p27 antigen in blood</th>
<th>Proviral DNA in blood</th>
<th>Antibodies in blood</th>
<th>Replicating virus in blood</th>
<th>Viral RNA in blood</th>
<th>Viral shedding</th>
<th>FeLV-associated diseases</th>
<th>Vaccination useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive infection</td>
<td>Positive</td>
<td>Positive</td>
<td>Low or negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Yes</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Regressive infection</td>
<td>Negative</td>
<td>Positive</td>
<td>High</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
<td>Uncommon, reactivation possible</td>
<td>No</td>
</tr>
<tr>
<td>Abortive infection</td>
<td>Negative</td>
<td>Negative</td>
<td>High</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Not FeLV-infected</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Role of Retroviruses in Feline Lymphoma

Progressive infection
In progressive infection, insufficient FeLV-specific immunity results in extensive virus replication that occurs first in the lymphoid tissues and then in the bone marrow. Spread to mucosal and glandular tissues and excretion of infectious virus occurs simultaneously with bone marrow infection. The number of cats that will develop progressive FeLV infection depends mainly on infection pressure and varies from 3% (after single contact with an FeLV-shedding cat) to 30% (when living together for several weeks with a shedding cat). Progressively infected cats are persistently antigenaemic, continuously shed the virus, frequently succumb to FeLV-associated diseases within a few years and have a decreased life expectancy.

Regressive infection
In regressive infection, an effective immune response limits virus replication prior to or at the time of bone marrow infection. In recent studies, 2 to 10% of FeLV-antigen-negative cats were found to be positive for FeLV provirus by PCR and thus were characterised as regressively infected. In these cats, FeLV antigen is sometimes detectable in peripheral blood within two to three weeks after virus exposure but then disappears two to eight weeks later or, in rare cases, even after several months. Some infected cats fail to ever develop detectable antigenaemia. Cats with regressive infection have persistent integration of FeLV DNA in their genome. In a recent study, complete clearance of FeLV viral RNA or provirus was not detected in cats with regressive infection, even up to 12 years after exposure. Regressively infected cats only rarely develop FeLV-associated diseases, such as lymphoma or bone marrow disorders. Even though viral shedding does not occur, it is possible that cats with regressive infection transmit FeLV via blood and tissue donation because provirus is infectious. It is also possible that the regressive state can convert to a progressive state (reactivation). This is more likely to occur soon after exposure to FeLV, but has been described in cats that were antigen-negative for many years. In a long-term follow-up study on experimentally infected cats, five of 10 regressively infected cats had reactivation of infection and became antigen-positive at different time points over a period of up to 8.5 years after infection.

Abortive infection
In abortive infection, cats are negative for culturable virus, antigen, viral RNA and proviral DNA, but remain antibody-positive. Recent studies suggest that abortive infection is more common than previously estimated. These cats are assumed to have life-long protection against new infection.

The outcome of FeLV infection and the clinical course are determined by a combination of viral and host factors. Some of the differences in outcome can be traced to properties of the virus itself, such as the subgroup that determines differences in the clinical picture (e.g., FeLV-B is primarily associated with tumours, whereas FeLV-C is primarily associated with non-regenerative anaemia). One study found that high levels of circulating FeLV-specific effector cytotoxic T-lymphocytes (CTL) appear before virus-neutralizing antibodies in cats that have recovered FeLV viraemia. In contrast, progressive infection with persistent viraemia has been associated with a silencing of virus-specific humoral and cell-mediated immunity host effector mechanisms. Probably the most important host factor that determines the clinical outcome is the age of the cat at the time of infection. Neonatal kittens develop marked thymic atrophy after infection (“fading kitten syndrome”), resulting in severe immunosuppression, wasting and early death. As cats mature, they acquire progressive resistance. Older cats that become infected tend to have abortive or regressive infections or if progressive infection occurs, they have milder signs and a more protracted period without clinical signs.

Clinical syndromes associated with FeLV infection can be classified as tumours, immunosuppression, haematologic disorders and other syndromes including neuropathy, reproductive disorders and fading kitten syndrome. Most FeLV-infected cats are taken to the veterinarian for anaemia or immunosuppression rather than tumours. Of 8,642 FeLV-infected cats presented to North American veterinary teaching hospitals, various co-infections (including FIV infection, feline infectious peritonitis (FIP), upper respiratory infection, haemotropic mycoplasmosis and stomatitis) were the most frequent findings. The most common FeLV-associated disorders are lymphoma and leukaemia, while other haematopoietic tumours and other malignancies (including neuroblastoma, osteochondroma and others) are much rarer. The exact role of FeLV in the genesis of these other tumours is unclear.
Virus-induced fibrosarcomas are very unique neoplasms caused by feline sarcoma virus (FeSV), a recombinant of FeLV that develops de novo in FeLV-infected cats by recombination of the infective FeLV genome with cellular oncogenes. Through a process of genetic recombination, FeSV acquires one of several oncogenes, such as fes, fms or fgr. As a result, FeSV is an acute transforming (tumour-causing) virus, leading to polyclonal malignancy with multifocal tumours arising simultaneously after a short incubation period. Strains of FeSV identified from naturally occurring tumours are defective and unable to replicate without the presence of FeLV-A as a helper virus that supplies proteins (such as those coded by the env gene) to FeSV. With the decrease in FeLV prevalence, FeSV has also become less common. FeSV-induced fibrosarcomas are multicentric, usually occur in young cats and tend to grow rapidly, often with multiple cutaneous or subcutaneous nodules that are locally invasive and metastasize to the lung and other sites. Fibrosarcomas caused by FeSV are different tumours and should not be mixed up with solitary fibrosarcomas that are classified as feline injection site sarcomas (FISS) caused by the granulomatous inflammatory reaction at the injection site, commonly occurring after inoculation of adjuvant-containing vaccines. Neither FeSV nor FeLV play a role in the development of FISS [73].

**Lymphoma**

FeLV can act as a major oncogene in cats [6-11,23,74-76] and progressively FeLV-infected cats have a 62-fold increased risk of developing lymphoma [11]. Lymphoma can affect up to 25% of cats with progressive FeLV infection, usually within two years after diagnosis of the infection. FeLV-induced lymphomas are mainly T-cell lymphomas [73]. Multicentric and mediastinal lymphoma are the most common forms, although spinal, renal, ocular and other forms of lymphoma are occasionally reported in FeLV-infected cats.

In the past, young to middle-aged cats (median 7 years) were commonly diagnosed with lymphoma, but more recent data show that lymphoma is currently a disease of mostly older cats with a median age of 11 years [77]. This is likely a result of the decreasing prevalence of progressive FeLV infection as a contributing factor for lymphoma, as cats with FeLV-associated lymphoma are usually younger than cats with lymphoma without FeLV infection [24]. In addition, improvement in veterinary medical diagnostics, access to veterinary specialists and increased owner commitment have led to an increase in the average age of the cat population presented to veterinarians and the likelihood of diagnosing lymphoma in older cats, which also increases the median age of feline lymphoma patients. One study in North America demonstrated an approximately 20% increase in the incidence of FeLV antigen-negative lymphoma compared with the general feline caseload [78].

The association between FeLV and lymphoma has been clearly established: Lymphoma can be induced in kittens through experimental FeLV infection [68,69,71]; cats naturally infected with FeLV have a higher risk of developing lymphoma than uninfected cats [68,79]; and in the past, when the prevalence of FeLV was higher, most cats with lymphoma had progressive FeLV infection. These old studies showed that up to 80% of feline lymphomas and leukaemias were FeLV-related [7,8,74,80], and from the 1970s to the early 1990s, more than 80% of cats with lymphoid malignancies had progressive FeLV infection [7-11]. However, the prevalence of progressive FeLV infection in the general cat population is decreasing and has been recently determined to be only 1 to 5% e.g. in cats in Germany [22,81-83]. The prevalence of progressive FeLV infection is also decreasing in cats with lymphoma worldwide and is now reported to be not more than 21% [62,78,84,85]. The decrease in the prevalence of FeLV has led to a decrease in the incidence of FeLV-associated lymphoma [22,77,78,86-89], and the decrease in prevalence of FeLV infection in cats with lymphoma or leukaemia also indicates a shift in tumour causation. A study conducted at a veterinary teaching hospital in Germany showed that from 1980 to 1995, 59% of all cats with lymphoma were FeLV antigen-positive, but from 1996 to 1999, only 20% were FeLV antigen-positive [77]. This finding confirms results of other recent studies worldwide, in which progressive FeLV infection in cats with lymphoma is far less common than reported in earlier studies and occurs in only 0 to 21% of feline lymphoma cases [28,62,78,84,85,80].

In a recent study in the Netherlands, only four of 71 cats with lymphoma were FeLV-positive, although 22 of these cats had mediastinal lymphoma, which previously was reported to be strongly associated with FeLV infection [85].

FeLV infection can cause tumours indirectly by immunosuppression or more importantly by directly by activating proto-oncogenes or disrupting tumour suppressor genes at or near the sites of feline leukaemia proviral DNA integration (insertional mutagenesis [23,41,91]).
This leads to disruption of the molecular regulatory circuits of cell physiology, the basic principle of tumour development. The most important mechanism for the development of malignancy is insertion of the FeLV genome into the cellular genome near a cellular oncogene (most commonly myc). This results in activation and over-expression of that gene and uncontrolled proliferation of these cells (clone). FeLV can also incorporate the oncogene to form a recombinant virus (e.g. FeLV-B, FeSV) containing cellular oncogene sequences that are then rearranged and activated. When they enter a new cell, these recombinant viruses are oncogenic. Thus, FeLV-induced neoplasms are caused, at least in part, by somatically acquired insertional mutagenesis. In a study of 119 cats with lymphoma, transduction or insertion of the myc locus had occurred in 38 cats (32%) [92]. Another study suggested that the U3-LTR region of FeLV transactivates cancer-related signalling pathways through production of a non-coding 104 base RNA transcript that activates NF kappaB [93]. Twelve common integration sites for FeLV associated with lymphoma development have been identified in six loci: c-myc, flvi-1, flvi-2 (contains bmi-1), fit-1, pim-1 and flit-1 [41]. Oncogenic association of the loci is based on the fact that c-myc is known as a proto-oncogene, bmi-1 and pim-1 have been recognized as myc-collaborators, fit-1 appears to be closely linked to myb and flit-1 insertion was shown to be associated with over-expression of cellular genes, e.g., activin-A receptor type II-like 1 (ACVRL1) [41]. Flit-1 seems to play an important role in the development of lymphoma and appears to represent a common novel FeLV proviral integration domain that can promote lymphomagenesis by insertional mutagenesis. Of 35 FeLV-related tumours, 5 of 25 thymic lymphomas demonstrated proviral insertion within fit-1 locus, whereas 0 of 4 alimentary lymphomas, 5 of 5 multicentric lymphomas and 1 of 1 T-lymphoid leukaemia had rearrangements in this region. Expression of ACVRL1 mRNA was detected in the two thymic lymphomas with fit-1 rearrangement, whereas normal thymuses and seven lymphoid tumours without fit-1 rearrangement had no detectable ACVRL1 mRNA expression [94]. Some studies also show that variations in the FeLV surface glycoprotein can determine the development of tumours [95].

When lymphoma is caused by FeLV, it is usually because of progressive infection. However, regressive FeLV infection also can be involved in tumour formation, and the prevalence of lymphoma caused by FeLV might be higher than indicated by conventional antigen testing of blood [94]. Cats from FeLV cluster households have a 40-fold increase in FeLV-negative lymphoma compared with cats from the general population. FeLV proviral DNA was detected in lymphomas of FeLV antigen-negative cats [94], and lymphomas have occurred in FeLV antigen-negative laboratory cats known to have been infected previously with FeLV [79]. This suggests that the virus might be associated with a larger proportion of lymphomas than previously thought. FeLV has been shown to incorporate cellular genes, and several such transduced genes, that have been implicated in viral oncogenesis, are also present in regressively infected cells [76,91,97]. The incidence of lymphoma caused by regressive FeLV infection under natural conditions is highly controversial. Two studies reported that regressive FeLV infections occurred in 50 to 52% of antigen-negative lymphomas in older cats (> 7 years) [96,98], while other groups found evidence of provirus in only 1 of 22 [77], in 1 of 10 [99] and in 0 of 50 FeLV antigen-negative lymphomas [61] suggesting that regressive infection is only rarely involved in tumour development.

Several studies have compared differences in presentation and outcome of lymphoma in FeLV antigen-negative and FeLV antigen-positive (progressively infected) cats, and the results of a recently published large cohort study are shown in table 3 [77]. In that study, no breed predisposition was found, which is in contrast to the results of other studies in which there was a relatively high incidence of mediastinal lymphoma in young, FeLV antigen-negative Siamese-type cat breeds [78,85,100,101]. These breeds have a predisposition for intestinal lymphoma [102], which suggests that breed predisposition or genetic factors play a role in lymphoma pathogenesis.

The predominant anatomical locations of lymphoma in cats are alimentary (approximately 50%) and extranodal (approximately 25%), mainly kidney and nasopharyngeal [77,78,85,90,103]. The majority of cats with alimentary and extranodal lymphoma are FeLV antigen-negative (96% and 89%, respectively) [77], which indicates a shift from progressive FeLV infection as causative agent to other multifactorial aetiologies, such as chronic inflammation or environmental and genetic factors. The feline gastrointestinal tract, kidneys and nasopharyngeal region are sites where chronic lymphocytic or lymphoplasmacytic inflammation occurs frequently (e.g. inflammatory bowel disease (IBD), dietary allergy, tubulointerstitial nephritis,
chronic rhinitis). In cats, chronic inflammation, such as IBD or dietary allergy, is thought to be a precursor of intestinal low-grade lymphoma [104,105] and progression of IBD to lymphoma is reported [106]. This suggests that cats might be predisposed to the development of cancer at or near sites of chronic inflammation. In the past, renal and multicentric lymphomas were frequently associated with progressive FeLV infection; several decades ago, 25 to 31% of renal lymphoma cases were associated with FeLV infection [8,103,107] compared with 0 to 6% in more recent studies [28,77,85,108]. A similar situation is seen in cats with multicentric lymphoma; in the 1980s and 1990s, up to 69% of all lymphomas were multicentric, and 31 to 65% of the cats had progressive FeLV infection [8,96,103] compared with 0 to 13% of cats in more recent studies [28,77,85,90]. Mediastinal lymphoma is uncommon today (10%) [77], but many affected cats have progressive FeLV infection with a prevalence ranging from 19 to 73%.

Table 3. Comparison of FeLV antigen-positive (progressively infected) cats with lymphoma and FeLV antigen-negative cats with lymphoma in a study including 156 cats with lymphoma (percentages in parentheses indicate percentages of all cats (%) and percentages of cats within the FeLV antigen-positive and -negative group [%], respectively). [27]

<table>
<thead>
<tr>
<th>Variable and category</th>
<th>All cats evaluated</th>
<th>FeLV antigen-positive cats</th>
<th>FeLV antigen-negative cats</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = number of cats</td>
<td>156</td>
<td>20 (13%) [100%]</td>
<td>136 (87%) [100%]</td>
<td></td>
</tr>
<tr>
<td>Median age (years) [range]</td>
<td>3.7 [0.8–13.5]</td>
<td>11.3 [0.7–18]</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>94</td>
<td>13 (14%) [65%]</td>
<td>81 (86%) [60%]</td>
<td>0.642</td>
</tr>
<tr>
<td>Female</td>
<td>62</td>
<td>7 (11%) [35%]</td>
<td>55 (89%) [40%]</td>
<td></td>
</tr>
<tr>
<td>Breed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domestic shorthair</td>
<td>127</td>
<td>17 (13%) [85%]</td>
<td>110 (87%) [80.9%]</td>
<td>0.379</td>
</tr>
<tr>
<td>Mix</td>
<td>7</td>
<td>1 (14%) [5%]</td>
<td>6 (86%) [4.4%]</td>
<td></td>
</tr>
<tr>
<td>Norwegian Forest</td>
<td>3</td>
<td>0 (0%) [0%]</td>
<td>5 (100%) [3.7%]</td>
<td></td>
</tr>
<tr>
<td>Half Angora</td>
<td>3</td>
<td>1 (33%) [5%]</td>
<td>2 (67%) [1.5%]</td>
<td></td>
</tr>
<tr>
<td>Maine Coon</td>
<td>2</td>
<td>0 (0%) [0%]</td>
<td>3 (100%) [2.2%]</td>
<td></td>
</tr>
<tr>
<td>Domestic longhair</td>
<td>2</td>
<td>1 (50%) [5%]</td>
<td>2 (100%) [1.5%]</td>
<td></td>
</tr>
<tr>
<td>Balinese</td>
<td>2</td>
<td>0 (0%) [0%]</td>
<td>1 (50%) [0.7%]</td>
<td></td>
</tr>
<tr>
<td>Russian Blue</td>
<td>2</td>
<td>0 (0%) [0%]</td>
<td>2 (100%) [1.5%]</td>
<td></td>
</tr>
<tr>
<td>Siamese</td>
<td>1</td>
<td>0 (0%) [0%]</td>
<td>2 (100%) [1.5%]</td>
<td></td>
</tr>
<tr>
<td>Somali</td>
<td>1</td>
<td>0 (0%) [0%]</td>
<td>1 (100%) [0.7%]</td>
<td></td>
</tr>
<tr>
<td>Ragdoll</td>
<td>1</td>
<td>0 (0%) [0%]</td>
<td>1 (100%) [0.7%]</td>
<td></td>
</tr>
<tr>
<td>Anatomical location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicentric</td>
<td>15 (10%)</td>
<td>2 (13%) [10%]</td>
<td>13 (87%) [10%]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>80 (51%)</td>
<td>3 (4%) [15%]</td>
<td>77 (96%) [57%]</td>
<td></td>
</tr>
<tr>
<td>Mediastinal</td>
<td>16 (10%)</td>
<td>8 (50%) [40%]</td>
<td>8 (50%) [6%]</td>
<td></td>
</tr>
<tr>
<td>Extranasal</td>
<td>36 (23%)</td>
<td>4 (11%) [20%]</td>
<td>32 (89%) [23%]</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>4</td>
<td>1 (25%) [5%]</td>
<td>3 (75%) [2%]</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>16</td>
<td>1 (6%) [5%]</td>
<td>15 (94%) [11%]</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal</td>
<td>7</td>
<td>0 (0%) [0%]</td>
<td>7 (100%) [5%]</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>6</td>
<td>0 (0%) [0%]</td>
<td>6 (100%) [4%]</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td>2 (100%) [10%]</td>
<td>0 (0%) [0%]</td>
<td></td>
</tr>
<tr>
<td>Retrobulbar</td>
<td>1</td>
<td>0 (0%) [0%]</td>
<td>1 (100%) [1%]</td>
<td></td>
</tr>
<tr>
<td>Lymphoid leukaemia</td>
<td>9 (6%)</td>
<td>3 (33%) [15%]</td>
<td>6 (67%) [4%]</td>
<td></td>
</tr>
<tr>
<td>Overall response to therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (complete remission)</td>
<td>23/72 (32%)</td>
<td>6/7 [86%]</td>
<td>17/65 [26%]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PR (partial remission)</td>
<td>14/72 (19%)</td>
<td>0/7 [0%]</td>
<td>14/65 [22%]</td>
<td></td>
</tr>
<tr>
<td>Median survival time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cats: days [range]</td>
<td>2 [1 – 77]</td>
<td>5 [1 – 1156]</td>
<td>0.131 \ 0.271</td>
<td></td>
</tr>
</tbody>
</table>
Role of Retroviruses in Feline Lymphoma

In a study from the Netherlands, only 19% of cats with mediastinal lymphoma were progressively FeLV-infected, but of the cats with lymphoma, all progressively infected cats had mediastinal lymphoma. This most likely reflects the very low prevalence of FeLV (0.3%) among cats in this country. Thus, if a cat is progressively infected with FeLV and develops lymphoma, the tumour will most likely be in the mediastinum.

The results of studies on FeLV as a negative prognostic factor with regard to remission and survival times in lymphoma patients are contradictory. However, in a recent study, FeLV antigen-negative cats with lymphoma had significantly longer remission times (472 days) than FeLV antigen-positive cats (25 days) following treatment. In another study, the median remission and survival times for FeLV antigen-positive cats were 27 and 37 days and for FeLV antigen-negative cats, 146 and 170 days. The prognosis for lymphoma in cats with progressive FeLV infection is poor because of bone marrow suppression, which is usually exacerbated by chemotherapy and can frequently delay treatment. Immunosuppression caused by FeLV infection is also aggravated by chemotherapy, leading to secondary infections that can cause overt clinical signs and impair quality of life. Furthermore, FeLV-associated lymphomas are associated with a higher rate of mitoses, possibly indicating a more aggressive biological behaviour that negatively affects outcome. The prognosis is also guarded because of the theoretical risk of the development of additional lymphoid malignancies in cats with FeLV-associated lymphoma. During virus replication, FeLV is integrated into the host genome and recombination with endogenous FeLV-related sequences could form new and more pathogenic variants, such as FeLV-B, with the potential for new lymphoma formation at any time. Finally, owners of cats with progressive FeLV infection and concurrent lymphoma commonly do not comply with treatment and often elect euthanasia.

Conclusions

Lymphoma is a very common tumour in cats, but is only rarely caused by retrovirus infection. There are three retroviruses that have been identified in domestic cats: FeFV, which is common but not pathogenic; FIV, which is associated with an approximately five-fold increase in the risk of lymphoma; and FeLV, which can act as a major pathogen and increases the tumour risk by 62 times. However, because the prevalence of FeLV is low, so is the prevalence of progressive infection in cats with lymphoma. In addition, regressive FeLV infection is not commonly found in cats with lymphoma. Therefore, today, other factors play a much more important role in the development of lymphoma in cats than retrovirus infections.

References

Role of Retroviruses in Feline Lymphoma


66. Torres AN, K.P. OH, Larson L, Schutz RD, Hoover EA, editors. Insight into FeLV: host relationships using real-time DNA and RNA qPCR. 8th International Feline Retrovirus Research Symposium; 2006; Washington, DC.
88. Muirden A. Prevalence of feline leukaemia virus and antibodies to feline immunodeficiency virus and feline coronavirus in stray cats sent to an RSPCA hospital. The Veterinary Record. 2002;150(20):621-5.


