GUIDELINE for Feline Injection-Site Sarcoma

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Key points

- In cats, invasive sarcomas (mostly fibrosarcomas), so called “feline injection-site sarcomas” (FISS), are the most serious adverse effects following vaccination. These tumours develop at sites of vaccination or of injection of other substances. They have characteristics that are distinct from those of fibrosarcomas in other areas and behave more aggressively. The rate of metastasis ranges from 10% to 28%.
- The pathogenesis of these sarcomas is not yet fully understood. There is neither definitive causal relationship that explains their occurrence nor a direct link with vaccination. The most widely accepted hypothesis suggests that chronic inflammatory reaction at the site of injections provides a trigger for subsequent malignant transformation.
- Aggressive, radical excision is required to avoid tumour recurrence.
- The prognosis improves if additional radiotherapy and/or immunotherapy and/or chemotherapy are used in addition to surgical excision.
- To prevent FISS development, several recommendations should be followed:
    - Although vaccinations can be associated with FISS formation, immunisation of cats with various vaccines provides essential protection and should not be stopped because of the risk of FISS. It is important to realize that vaccines are not the only injectable medical products associated with FISS.
    - However, an individually tailored vaccination schedule is important for each cat. Cats should be vaccinated only as often as necessary in accordance with current guidelines.
    - Mucosal intranasal vaccines are preferred over injectable vaccines, if available.
    - Injectable vaccines should be brought to room temperature prior to administration but should not be kept unrefrigerated for hours.
    - Multi-dose vaccine vials should not be used in cats.
    - Subcutaneous injection is preferred to intramuscular injection.
    - Vaccines providing a long duration of immunity are preferred over those with a short duration of immunity.
    - Appropriate sites for injections should be selected. The interscapular region as well as the lateral thoracic wall should generally be avoided for any injection. Vaccines should be injected at sites where any subsequent mass could be easily surgically removed, preferably distally in a limb.
    - Generally, any skin or subcutaneous mass in a cat requires further diagnostics. Specifically, thorough post-vaccination monitoring should be performed considering the “**3-2-1**”-rule: Any lump at the site of injection

that is still present **three** months after vaccination, or that is larger than **2** cm in diameter, or that is increasing in size **one** month after vaccination should be surgically removed and investigated through histopathology.

- ABCD recommends that veterinarians carry out a risk–benefit analysis for each vaccine to avoid unnecessary vaccination of cats, to monitor the injection site, and to report all vaccine-associated adverse events to the manufacturer and/or to their competent authority.

- Considering injectable vaccines, there has been much discussion of whether non-adjuvanted vaccines should be generally preferred over those containing adjuvant, if available and with proven similar efficacy. However, currently, there is insufficient information to make definitive recommendations on the vaccine type. The current knowledge is as follows:
  - It is a fact that every injectable vaccine can cause FISS.
  - It is a fact that vaccines containing adjuvant cause more inflammation than vaccines without adjuvants.
  - It has been reported that inflammation might contribute to FISS development.
  - There are conflicting data on whether vaccine adjuvants truly are associated with increased risk of FISS development.
  - It is currently difficult to truly compare vaccine efficacy studies because of differences in study designs.
  - Therefore, there is insufficient information to make definitive recommendations on the vaccine type and it is important to consider efficacy data. Where efficacy studies have shown higher protection rates in cats vaccinated with adjuvanted vaccines versus non-adjuvanted vaccines, the former are preferable in cats at high risk of infection. Otherwise, given the current state of knowledge, if vaccines without adjuvants have been proven to be equally effective as adjuvant-containing ones, it is reasonable to suggest that vaccines without adjuvants should be preferred, at least until the pathogenesis of FISS is better understood.

Epidemiology

Vaccination of cats always has received scientific and public attention following the supposition that a range of rare vaccine-associated adverse events (VAAEs) can arise following vaccination (Moore and HogenEsch, 2010). In cats, the most serious of these adverse consequences is the occurrence of invasive sarcomas (mostly fibrosarcomas), so called “feline injection-site sarcomas” (FISS), that can develop within the skin at sites of previous vaccination (Fig. 1 and 2) (Hosie et al., 2013; Hartmann et al., 2023; ABCD Guideline for Adverse Reactions to Vaccination). A task force has been instituted and is regularly updated in the USA to help veterinarians understand, manage, and prevent these tumours (Morrison and Starr, 2001; Vaccine-Associated Feline Sarcoma Task Force, 2005). In fact, it was mainly the occurrence of FISS that increased the concern among cat owners about the safety of vaccines in general and rekindled the discussion on VAAEs in cats. Despite extensive research on the pathogenesis of these sarcomas, there is neither proof of definitive causal relationship that explains their occurrence nor of a direct link with vaccination. The most accepted hypothesis suggests that chronic inflammatory reaction at the site of injection provides a trigger for subsequent malignant transformation (Hartmann et al., 2015).

Fig. 1. Cat with feline injection-site sarcoma. Provided by Tadeusz Frymus, Warsaw University of Life Sciences, Warsaw, Poland

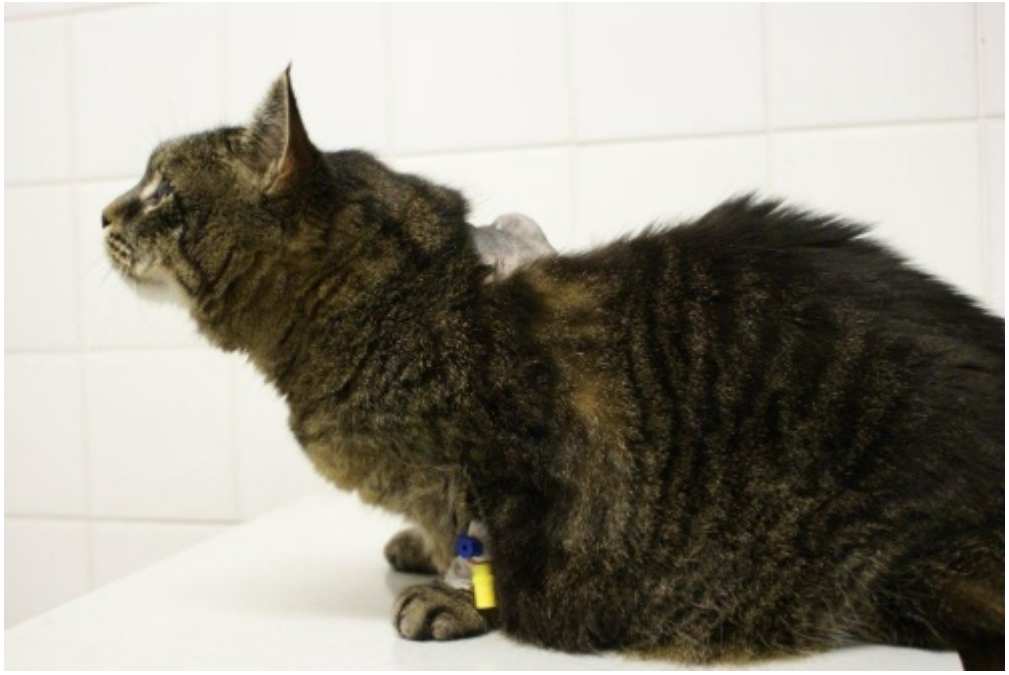

Fig. 2. Cat with feline injection-site sarcoma. Provided by Katrin Hartmann, LMU, Munich, Germany

Around 1990, an increased incidence of tumours in cats that developed at injection sites was first reported in the USA (Hendrick and Dunagan, 1991; Hendrick and Goldschmidt, 1991). This observation was connected to an increased use of rabies and feline leukaemia virus (FeLV) vaccinations (Hendrick and Goldschmidt, 1991; Kass et al., 1993). As a consequence, these tumours were first called feline "vaccine-associated sarcomas". However, the subsequent finding that other non-vaccinal injectables could also be associated with this type of tumour has led to reclassification of these neoplasms as "feline injection-site sarcomas" (FISS). It has been suggested that injections in cats induce repeated local irritation with chronic inflammation, which can act as a precursor to local neoplastic transformation of stromal cells. These tumours seem to be relatively unique to cats (Carroll et al., 2002), although comparable tumours have been reported in ferrets (Munday et al., 2003) and rarely in dogs (Vascellari et al., 2003). Still, FISS are highly similar to soft tissue sarcomas in dogs and humans, at the level of gene expression (Wei et al., 2019).

FISS occur at sites typically used for vaccination and injections, such as the interscapular region (Fig. 3), the lateral thoracic or abdominal wall, the lumbar regions, and in the area of the semimembranosus and semitendinosus muscles in the hindlimbs. FISS are most commonly located in the subcutis, but also can occur intramuscularly (Dubielzig et al., 1993; Hendrick and Brooks, 1994; Graf et al., 2018). FISS can develop as early as four months and up to two to three years after an injection (Srivastav et al., 2012).

Fig. 3. Cat with feline injection-site sarcoma. Provided by Katrin Hartmann, LMU, Munich, Germany

In the last 20 years, an epidemiological association has been demonstrated between vaccinations and the later development of FISS (Hendrick et al., 1992; Kass et al., 1993; Hendrick and Brooks, 1994; Macy, 1995; Kass et al., 2003; Dean et al., 2006). The incidence of FISS has been estimated at 1 to 4 in every 10,000 vaccinated cats in USA (Coyne et al., 1997; Gobar and Kass, 2002; Ladlow, 2013), and the ratio of injection-site to non-injection-site sarcomas increased from 0.5 in 1989 to 4.3 in 1994 (Doddy et al., 1996). In one study from 1998 to 2000 in the USA and Canada, the reported rates were 0.3 cases of FISS per 10,000 vaccines and 11.8 post-vaccinal inflammatory reactions per 10,000 vaccinations in cats (Gobar and Kass, 2002). If inflammatory reactions are a necessary prelude to FISS, then these rates suggest that 1 in 35 to 40 inflammatory reactions develop into FISS. During 2008–2013 in Poland, the prevalence of FISS was estimated to be 16 in 10,000 cats in general practice and 85 in 10,000 cats in practices specialised in oncology (Kliczkowska et al., 2015). In the UK, the incidence of FISS seems to be relatively low (in 2007, the incidence risk of FISS per year was estimated to be 1 in 16,000–50,000 cats registered by practices, 1 in 10,000–20,000 cat consultations, and 1 in 5,000–12,500 vaccination visits) (Dean et al., 2013). One reason for the low rate might be that rabies vaccination is not a routine procedure for cats in UK. One study in Canada compared the annual prevalence of feline post-vaccinal sarcomas among 11,609 feline skin mass submissions from 1992 to 2010 and revealed no decrease in disease prevalence or increase in age of affected cats in response to change in vaccination formulations (introduction of recombinant non-adjuvanted rabies (and later FeLV) vaccines) or recommended changes in feline vaccination protocols (e.g., calling for more selective use of FeLV vaccination and less frequent rabies vaccination) (Wilcock et al., 2012). In contrast, studies in Switzerland demonstrated a marked drop in the relative frequency of fibrosarcoma diagnoses from 2005 to 2014 (Graf et al., 2018).

Pathogenesis

Despite extensive research on the pathogenesis of FISS, there is no definitive causal relationship that explains their occurrence nor a direct link with vaccination. The most widely accepted hypothesis suggests that chronic inflammatory reaction at the site of an injection provides a trigger for subsequent malignant transformation (Day et al., 2007). The mechanism by which the inflammatory reaction might cause tumour formation is not fully understood. Growth factors can promote proliferation, can induce malignant transformation, and also can be involved in the regulation of angiogenesis. Overexpression of growth factors and oncogene activation have been demonstrated in cats with FISS and are suspected to play a role in tumour development (Hendrick, 1998, 1999; Nieto et al., 2003). Fibroblasts can undergo neoplastic transformation through different mechanisms, such as activation of oncogenes and inactivation of tumour suppressor genes. Chronic inflammation can induce production of free radicals and metabolites that cause DNA damage and mutations, acting as an initiator of carcinogenesis. The environment provided by chronic inflammation, coupled with a genetic

predisposition, alters the susceptibility to carcinogenic injuries (O'Byrne and Dalgleish, 2001). One study showed that cyclooxygenase-2 (COX-2) is expressed within FISS and that there is a close relationship between COX-2 expression and the degree of inflammation (Santelices Iglesias et al., 2018). Generally, COX-2 participates in the synthesis of arachidonic acid derivatives, including prostaglandin E2, which is related to carcinogenic processes (Williams et al., 1999; O'Byrne and Dalgleish, 2001). Overexpression of COX-2 is associated with tumour proliferation and invasion, inhibition of apoptosis, suppression of immune surveillance, and angiogenesis (Williams et al., 1999). Activation of the nuclear factor-kappa B- (NF-κB-) signalling pathway can target genes associated with tumour progression and up-regulate expression of tumour-promoting cytokines and survival genes in tumours (Hsueh et al., 2019). Additionally, high expression rate of nuclear NF-κB p65 in FISS and dose-dependent inhibitory effects on the growth of FISS primary cells treated with NF-κB inhibitors suggested a role of NF-κB in FISS development (Hsueh et al., 2019). Activation of the Janus kinase signal transducer and activator of transcription 3 (STAT3) also might play an important role in the tumorigenesis of FISS (Shih et al., 2022). Interestingly, it was shown via immunohistochemistry that the expression of estrogen receptors in FISS, but not the expression of progesterone receptors, correlated with clinical and histopathological aspects (mitotic index and degree of pleomorphism) and thus, estrogen receptors expression could influence tumour growth (Zanuncio et al., 2021).

It has been suggested that especially adjuvanted vaccines would be linked to the development of FISS due to the more intense local inflammation associated with such products. However, in a prospective multi-center case-control study from 2003, no specific vaccine or vaccine brand could be incriminated in the formation of FISS (Kass et al., 2003). Adjuvants are mostly added to enhance a pro-inflammatory reaction at the site of injection, which is intended and a necessity when applying a killed agent in order to trigger the required immune response. Adjuvants, such as aluminium, have been identified in histological or ultrastructural studies of FISS biopsy samples (Hendrick et al., 1992; Madewell et al., 2001; Deim et al., 2008), and it was thought that these adjuvants originated from adjuvant-containing vaccines. Traces of adjuvants can be seen in the inflammatory reaction, specifically accumulated within macrophages or multinucleate giant cells, as well as in histological sections of FISS in the transformed fibroblasts (Hendrick et al., 1992). Intracellular crystalline particulate material was found in an ultrastructural study in five of 20 investigated FISS, and in one of the five cases was identified as aluminium-based material (Madewell et al., 2001). One study investigated the degree of inflammation after vaccination with adjuvant-containing vaccines versus vaccines without adjuvants. It showed that multi-component vaccines containing the recombinant canarypox-vector FeLV cause less inflammation at the injection site than multi-component vaccines with FeLV and an adjuvant. Three groups of 15 cats were injected with a single dose of one of the three the vaccines or saline as a negative control; cats in group A received a non-adjuvanted recombinant canarypox-vectored FeLV vaccine; cats in group B received an inactivated FeLV vaccine with a lipid-based adjuvant; cats in group C were vaccinated with an inactivated FeLV vaccine adjuvanted with an alum-Quil A mixture. On days 7, 21, and 62 post-vaccination, significantly less inflammation was associated with administration of the non-adjuvanted recombinant canarypox-vectored vaccine in group A compared to groups B and C. The inflammation was most severe in cats of group C receiving the aluminium-based adjuvant. Those cats receiving adjuvanted vaccines had evidence of residual adjuvant material accumulated within macrophages even at 62 days post-vaccination (Day et al., 2007). In 2020, a new 0.5 ml presentation of the non-adjuvanted recombinant canarypox-vectored FeLV vaccine was registered in Europe. One study (Haist et al., 2023) assessed the local reactions for three months after subcutaneous injection of this 0.5 ml vaccine in comparison to a vaccine adjuvanted with aluminium-hydroxide and *Quillaja saponaria* (AlOH/Quil A) by physical examination, histopathology, and by non-invasive computed tomography (CT). Swelling reactions were more frequent, more pronounced, and long-lasting in the adjuvanted vaccine group. Microscopically, moderate to severe inflammatory reactions were observed in the adjuvanted vaccine group on days 7 and 21 post-injection and reactions were still present on day 84, while mild inflammatory lesions were observed in the non-adjuvanted vaccine group only on days 7 and 21. With the adjuvanted vaccine, inflamed areas were measurable by CT in all cats on days 7 and 21, whereas they were detected only on day 7 and only in 20% of cats from the non-adjuvanted vaccine group. On day 7, the mean inflamed volume was nearly 300 times larger in adjuvanted vaccine group (Haist et al., 2023). Thus, an association between adjuvants and more pronounced tissue inflammation has been shown; however, the association between inflammation and tumour formation is more difficult to demonstrate. It has been suggested that inflammatory cells have an impact on cancer development by increasing the invasive capacity, angiogenesis, and motility of tumour cells (Coussens and Werb, 2002)One paper evaluating metallothionein expression in FISS, demonstrated an association between Ki67 index (a marker of cell proliferation) and tumour grade and inflammatory score in FISS, suggesting that inflammation plays an important role not only in pathogenesis but also in tumour progression (Mikiewicz et al., 2023).

At first, only rabies and FeLV vaccines were identified as risk factors (Kass et al., 1993; Hendrick et al., 1994; Coyne et al., 1997), but subsequently other vaccines, including vaccines against feline panleukopenia virus (FPV), feline herpesvirus (FHV), and feline calicivirus (FCV) also were found to be involved in the development of FISS in some cases (Hendrick et al., 1994; Lester et al., 1996; Burton and Mason, 1997; Coyne et al., 1997; DeMan and Ducatelle, 2007; Srivastav et al., 2012). In addition to vaccines, injections of long-acting drugs, e.g., glucocorticoids, penicillin, lufenuron (Esplin et al., 1999; Gagnon, 2000; Kass et al., 2003; Srivastav et al., 2012), cisplatin (Martano et al., 2012), and meloxicam (Munday et al., 2011), have been associated with sarcoma formation. In one study, the frequency of administration of long-acting corticosteroid injections (dexamethasone, methylprednisolone, and triamcinolone) was significantly higher in cats with FISS in the interscapular region than in control cats (Srivastav et al., 2012). Fibrosarcomas were also reported at the

site of a deep, non-absorbable suture in one cat (Buracco et al., 2002); at the site of a retained surgical sponge in the abdomen of one cat (Haddad et al., 2010); adjacent to the site of microchip implantation in two cases (Daly et al., 2008; Carminato et al., 2011); and associated with a subcutaneous fluid port device (McLeland et al., 2013). This suggests that any inflammatory reactions independent of the stimulus, theoretically, could have the potential to lead to the development of FISS through triggering uncontrolled proliferation of fibroblasts and myofibroblasts, which, in some cases, results in malignant transformation.

Many causes of inflammation could be associated with FISS development, and FISS can occur in animals following vaccination with inactivated, recombinant or modified live vaccines as well as with non-vaccine injections; e.g., in the UK, the Veterinary Medicines Directorate (VMD) received notifications of FISS in cats associated with different vaccine types. However, these reports did not take the number of injected vaccines into account (Davis et al., 2013, 2015, 2016; Dyer et al., 2007, 2008, 2009, 2010, 2011, 2012). In a prospective case-control study conducted at the University of California, Davis, USA, it was demonstrated that, among injections, vaccines were more frequently associated with FISS development compared to other compounds; amongst vaccines, the risk was significantly higher when adjuvanted vaccines were used (Srivastav et al., 2012). One study in Switzerland showed a marked decrease in the number of FISS from 2005 to 2014, when compared to older studies in the same region (Graf et al., 2015, 2016), and the authors of the paper concluded that the introduction of a non-adjuvanted FeLV vaccine in 2007 might have accounted for the decrease (Graf et al., 2018). However, the decrease in FISS incidence was in no relation to the non-adjuvanted vaccines sold at the time, and the timespan that is necessary for FISS development was not considered. Other factors were not addressed in the study, such as increased awareness of good vaccination practice, not injecting cold vaccines, and vaccinating only if necessary (e.g., Switzerland became rabies-free in 1999).

One study (Srivastav et al., 2012) compared associations between vaccine types and other injectable drugs with the development of FISS in a case-control study of 181 cats with soft tissue sarcomas (cases), 96 cats with tumours at non-vaccine regions (control group I), and 159 cats with basal cell tumours (control group II). There was an association between the administration of various types of vaccines and other injectable products (e.g., long-acting corticosteroids) and FISS development. Of 192 sarcomas, 101 had received vaccinations at the site of tumour development during the preceding three years, and 23 had received other injections at that site (Srivastav et al., 2012). This study also showed that adjuvanted-inactivated rabies vaccines were significantly more commonly associated with FISS development than recombinant rabies vaccines in the broad hindlimb region; of 35 vaccinated cats with sarcoma on the hindlimb, 25 had received inactivated vaccines (predominantly rabies), seven cats had received modified live virus (MLV) vaccines (FPV, FHV and FCV), and only one cat had received a recombinant rabies vaccine. However, these findings also indicate that no vaccines were risk-free and that other factors also can be associated with the development of FISS (Srivastav et al., 2012). The latter finding is also supported by the data from the UK VMD receiving notifications of FISS in cats vaccinated with MLV, inactivated, and recombinant vaccines (Davis et al., 2013, 2015, 2016; Dyer et al., 2007, 2008, 2009, 2010, 2011, 2012).

A possible role of FeLV and its mutant feline sarcoma virus (FeSV) in the development of FISS was not demonstrated by presence of either FeLV or FeSV in tumours (Ellis et al., 1996). One study from Brazil reported positive immunohistochemistry staining for FeLV p27 antigen in nine of 21 FISS (Carneiro et al., 2019); however, the method used (polyclonal antibodies for histology) had, most likely, a low specificity and thus, the significance of the results is doubtful. Furthermore, no other viruses, including feline immunodeficiency virus, feline foamy virus, polyomaviruses or papillomaviruses, were detected in tumour tissues (Kidney et al., 2000, 2001a, 2001b, 2002). Additionally, no evidence was found for the replication or the expression of endogenous retroviruses being involved in FISS development (Kidney et al., 2001a, 2001b).

The observation that only few cats develop FISS after vaccination suggests that there might be a genetic predisposition. It has been proposed that there is a higher incidence of FISS in siblings of affected cats, and that some cats tend to develop more than one FISS. Alterations with unknown relevance, such as hyperploidy (Kalat et al., 1991), translocations (Mayr et al., 1996), and triploidy (Mayr et al., 1991) of oncogene and tumour suppressor loci have been found on extra chromosomes and monosomic chromosomes in affected cats. Mutations have been identified in the tumour suppressor gene p53, which is implicated in cancer initiation and progression in sarcoma tissue of cats with FISS (Mayr et al., 1995, 1998; Nambiar et al., 2000, 2001; Banerji and Kanjilal, 2006). A case-control study (50 domestic shorthair cats with a confirmed diagnosis of FISS and 100 disease-free matched controls) investigating a possible association between polymorphisms in the genomic sequence of the feline p53 gene and a predisposition to FISS, found a strong association between FISS and the presence of specific nucleotides at two of the polymorphic sites (Banerji et al., 2007). However, another study, conducted in Germany could not reproduce these findings and observed no association with the polymorphisms described (Mucha et al., 2014). Thus, the significance of these polymorphisms in FISS development is unknown.

Clinical signs

FISS are tumours characterized by invasive local growth in the subcutis (rarely within the muscle), often with spread along fascial planes (Hirschberger and Kessler, 2001). Most FISS are fibrosarcomas (Doddy et al., 1996), but other malignancies, such as osteosarcomas (Esplin et al., 1993), chondrosarcomas (Hendrick and Brooks, 1994), rhabdomyosarcomas (Hendrick and Brooks, 1994), malignant

fibrous histiocytomas (Esplin et al., 1993; Hendrick and Brooks, 1994), and myofibroblastic sarcomas (Dubielzig et al., 1993) have also been rarely described. FISS are usually firm, indolent, seemingly well-circumscribed, subcutaneous masses that are often not freely moveable.

FISS behave more aggressively than sarcomas at other sites (Hendrick et al., 1994). The rate of metastasis ranges from 10% to 28% (Couto and Macy, 1998; Hershey et al., 2000). The lung is the most common site of metastasis, followed by regional lymph nodes and abdominal organs, such as kidney, spleen, intestines, and liver (Sandler et al., 1997; Kobayashi et al., 2002).

Diagnosis

In contrast to fibrosarcomas in other areas, FISS have different histological characteristics with typical perivascular infiltration of lymphocytes and macrophages at the tumour periphery, a central area of necrosis, inflammation and local infiltration of tumour cells (Fig. 4) (Doddy et al., 1996; Madewell et al., 2001).

In CT, common features of FISS are a marked local invasiveness into the musculature and heterogeneity of the tissue in the periphery of the neoplasia (Travetti et al., 2013).

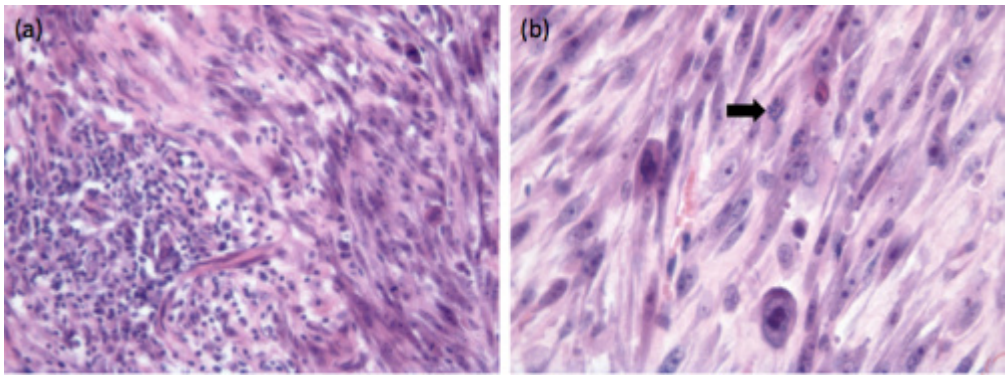

Fig. 4. Histological sections of a 2 cm diameter mass removed from the lateral thorax of a 13-year-old domestic shorthair cat. A similar interscapular mass had been removed from this cat 2 months previously. (a) A focus of lymphoplasmacytic inflammation is contained within the surrounding sarcoma. (b) Higher magnification of the neoplastic tissue reveals a pleomorphic population of neoplastic spindle cells with occasional giant nuclei and irregular mitotic activity (arrow). Haematoxylin and eosin stain. Courtesy of Michael Day, School of Veterinary Sciences, University of Bristol, United Kingdom

Treatment

Multimodal therapy, incorporating combinations of surgery, radiation therapy, and sometimes chemotherapy or immunotherapy, is recommended (Saba, 2017). Appropriate treatment should most importantly first include staging and careful planning of the surgery (Ladlow, 2013), because aggressive, radical excision is crucial to avoid tumour recurrence. The prognosis improves if, in addition to radical surgery, additional treatments such as radiotherapy, chemotherapy, or immunotherapy are used. Preoperatively, (contrast-enhanced) CT or magnetic resonance imaging (MRI) should be obtained for staging and to determine the extent of the tumour and the size of the radiation field required to maximize the chance of a successful outcome (Rousset et al., 2013). CT or ultrasound can also assess peritumoural inflammation (Zardo et al., 2016), and CT angiogram and MRI can aid to target peritumoural lesions (Nemanic et al., 2016; Löhr et al., 2021), but neither CT angiography nor MRI imaging features can predict the tumour type and grade of FISS (Fleming et al., 2019). Using CT, a dynamic approach has been suggested for tumour volume measurement to optimally evaluate invasiveness of FISS (Longo et al., 2018). It was shown that the actual size of tumours determined by CT can be up to twice the size estimated at physical examination (McEntee, 2000; Martano et al., 2011; Ferrari et al., 2017), and the size of the tumour is considered one of the most important prognostic markers (Porcellato et al., 2017).

Surgeons should attempt to achieve complete, *en bloc*, surgical tumour resection with at least 3 cm (preferably 5 cm) margins (Phelps et al., 2011) and the removal of one fascial plane underlying the tumour, because incomplete resection can result in recurrence as early as two weeks after surgery (Lester et al., 1996; Scherk et al., 2013). Tumour-free margins are very important to achieve a longer disease-free interval, which was 700 days when complete tumour excision was accomplished in addition to adjuvant radiation therapy, but only 112 days for incomplete resection in addition to adjuvant radiation therapy (Cronin et al., 1998). However, even with clean surgical margins, the recurrence rate can be as high as 50% (McEntee and Page, 2001; Giudice et al., 2010). A retrospective analysis of

cats with FISS located on the chest or abdominal wall or the interscapular region using a standardized radical resection technique with 3 cm lateral margins found that cats operated on for recurrent tumours were significantly more likely to die from tumour-related reasons compared with patients with *de novo* tumours, and that cats operated on for tumour recurrences had a significantly higher chance of another recurrence. In addition, tumour bed biopsies that did not contain tumour cells were associated with a significantly lower recurrence rate compared with those with tumour cells (Müller and Kessler, 2018). It has to be considered that significant decreases in surgical margin length occur following excision and subgross evaluation of tumour-free margins overestimates the actual (histologic) tumour-free margins (Terry et al., 2017), while shrinkage of FISS volume following excision and formalin fixation seems to be negligible (Terry et al., 2016). New techniques, such as optical coherence tomography (OCT), an imaging technology that uses light waves to generate real-time views of tissue architecture, can help to assess surgical margins correctly by allowing fast, high-resolution scanning of margins, even for less experienced people (Coleman et al., 2021).

Treatment using surgical excision alone has a recurrence rate of up to 70%, with tumour regrowth usually occurring within the first six months after surgery (Hendrick et al., 1994), but preoperative or postoperative radiation therapy significantly decreases recurrence rates and prolongs remission times (Cronin et al., 1998; Kobayashi et al., 2002; Steger-Lieb et al., 2002; Eckstein et al., 2009; Mayer et al., 2009). One study evaluating 22 cats retrospectively suggested that iridium-192 brachytherapy might also be useful as adjuvant treatment (Bloch et al., 2020), but larger prospective studies are necessary. In one case series including three cats, histotripsy, a non-invasive focused ultrasound therapy using controlled acoustic cavitation to mechanically disintegrate tissue, was used three to six days before surgery and was well tolerated (Ruger et al., 2023); this might be an interesting additional treatment option in the future.

On the other hand, chemotherapy in addition to surgery is less effective than radiation therapy in addition to surgery. However, two studies showed some benefits of chemotherapy. In one study, some efficacy of three epirubicin doses before and after surgery was demonstrated, compared to the outcomes of historical controls (Bray and Polton, 2016). Doxorubicin has also been suggested as adjuvant treatment (Petznek et al., 2014). In a randomized multicentre study, liposome-encapsulated doxorubicin (LED) and doxorubicin (DOX) treatment in addition to surgery (but without radiation) led to a prolonged median disease-free interval when compared to surgery alone, with no difference in efficacy between LED and DOX (Poirier et al., 2002). Newer approaches, such as combining DOX-loaded phosphatidyldiglycerol-based thermosensitive liposomes with local hyperthermia, also hold some promise (Zimmermann et al., 2016). One study using both bleomycin and cisplatin as an adjuvant electrochemotherapy (ECT) protocol demonstrated superior rates of tumour-free survival and disease-free interval (Spugnini et al., 2020). In contrast to these approaches, the tyrosine kinase inhibitor toceranib, which is licensed for the treatment of canine mast cell tumours, did not lead to a positive clinical response in cats with FISS (Holtermann et al., 2017). Some *in vitro* studies looked into the efficacy of other chemotherapeutic drugs to inhibit growth of FISS cell lines, such as the proteasome inhibitor bortezomib (Laver et al., 2022), but *in vivo* studies are missing. Chemosensitivity can be determined by FISS tissue γH2AX immunohistochemistry that can indicate DNA damage, as γH2AX expression might be useful to determine chemosensitivity (Kang et al., 2017), but further studies are needed. Thus, in general, chemotherapy mainly remains an option for palliative treatment in cats with non-resectable FISS, when radiation therapy is not available (Zabielska-Koczywąs et al., 2017).

Additional immunotherapy appears to be a promising option (Jahnke et al., 2007; Huttinger et al., 2008; Jas et al., 2015). Results of prospective randomized controlled studies on cytokine gene transfer techniques for adjuvant-immunological treatment of FISS showed reduced recurrence rates. In cats receiving gene immunotherapy by the peritumoural administration of histo-incompatible Vero cells expressing human interleukin-2, in addition to surgery and radiation therapy, only five of 16 FISS cats (31%) had FISS recurrence, while eleven of 16 control cats (69%) that only had surgery and radiation therapy, but no immunotherapy, had FISS recurrence within 16 months (Quintin-Colonna et al., 1996). Use of neo-adjuvant gene therapy using a non-viral vector that expresses feline granulocyte-macrophage colony-stimulating factor (GM-CSF) or a combination of the feline genes GM-CSF, IL-2, and interferon-γ (IFN-γ) was well tolerated by cats (Jahnke et al., 2007; Huttinger et al., 2008) and showed promising results. Recombinant feline IL-2 is now commercially available in Europe for the treatment of FISS in combination with excision and radiation therapy. In a randomised controlled clinical trial, administration of a recombinant canarypox virus expressing feline IL-2 was well tolerated and resulted in a significantly longer median time to relapse and a significant reduction in the risk of relapse at one year and two years (Jas et al., 2015).

ABCD recommends that cats that have, or have had, a FISS should no longer receive any injectable vaccine (and instead focus on limiting the risk of infections) or any other avoidable injections.

Prognosis

The prognosis of FISS is most importantly influenced by the size of the tumour (Porcellato et al., 2017), and radical excision is crucial for a favourable outcome, and thus, prognosis is primarily influenced by the tumour site and its accessibility to surgery and the possibility of obtaining tumour-free margins (Lester et al., 1996; Cronin et al., 1998; Phelps et al., 2011; Scherk et al., 2013). Therefore, pre-operative diagnostic imaging (contrast-enhanced CT and/or MRI) is extremely important to determine the true extent of the tumour (Rousset et al., 2013). Prognosis is better if, in addition to radical surgery, further therapeutic options such as radiotherapy (Cronin et

al., 1998; Kobayashi et al., 2002; Steger-Lieb et al., 2002; Eckstein et al., 2009; Mayer et al., 2009) or immunotherapy (Jahnke et al., 2007; Huttinger et al., 2008; Jas et al., 2015) are applied. In addition, neutrophil-to-lymphocyte ratio, white blood cell count and neutrophil count were determined as prognostic parameters for local recurrence of FISS (Chiti et al., 2020). Infrared thermography can be used to differentiate between malignant and benign skin and soft tissue tumours in cats, but the temperatures detected in FISS did not differ significantly according to histologic subtype or tumour grade, or between primary and recurring tumours (Nitrini et al., 2021); thus, the technique is of limited prognostic value when a FISS has already been diagnosed.

Prevention

Prevention consists of three general considerations (Table 1). First, injections in cats should always be given at sites at which surgery (such as amputation of a limb or excision of lateral abdominal skin) would likely lead to a complete cure with the least complicated surgical procedure. Second, general recommendations to reduce the inflammatory reaction at injection sites should be followed, such as avoiding the administration of irritating substances. And third, it is advised to vaccinate as often as necessary, but as infrequently as possible (e.g., according to the principles of current vaccination guidelines, such as triennial vaccination for FHV and FCV in cats with low risk of exposure, avoiding FeLV vaccination in already FeLV-infected cats and avoiding FPV vaccination in cats with pre-existing antibodies against FPV).

In general, injecting distally in the limb aids in the treatment of subsequent FISS (by amputation of the leg) because these tumours are very difficult to excise completely and often recur after resection (Macy, 1995). Administration of vaccines (or other injections) between the scapulae is generally contraindicated because tumour resection is almost impossible in this location. To assess the acceptance of the Vaccine-Associated Feline Sarcoma Task Force of the American Association of Feline Practitioners (AAFP) recommendations that include not injecting vaccines interscapularly (published in 1999) by veterinarians, a study including 392 cats with FISS compared the anatomical locations of tumours between cases with FISS diagnosed before and after the publication of these recommendations (Vaccine-Associated Feline Sarcoma Task Force, 1999). Comparing the prevalence of cases arising before and after the publication of the vaccination recommendations, the proportions of FISS significantly decreased in the interscapular (53% to 40%) and right and left thoracic (10% to 4% and 9% to 1%, respectively) regions, whereas the proportions of FISS significantly increased in the right thoracic limb (1% to 10%), in the combined regions of the right pelvic limb with the right lateral aspect of the abdomen (13% to 25%) and the left pelvic limb with the left lateral aspect of the abdomen (11% to 14%). Thus, despite publication of the vaccination recommendations, a high proportion of tumours still developed in the interscapular region. There was also an increase in lateral abdominal FISS, which could be attributable to aberrant placement of injections intended for the hindlimbs. Thus, veterinarians are complying with vaccination recommendations to some extent, but only the administration of vaccines as distally as possible on a limb would allow for complete surgical margins if limb amputation is required (Shaw et al., 2009). Data in Europe show a similar situation. In a study examining the location of FISS in cats presented to the oncology service of the LMU Small Animal Clinic in Munich, Germany, most FISS still occurred between the scapulae (40%), followed by the right (19%) and left thoracic walls (13%) (Haas, 2009). A study from Brazil, investigating anatomical location of biopsy samples compatible with FISS submitted between 2007 and 2017, found that 35% of the tumours were located on the thoracic wall, 29% in the flank, 21% in the interscapular region, and 15% in the limbs (Cecco et al., 2019).

A cross-sectional study in the UK evaluated cat owners' attitudes towards surgical treatments of different anatomical region: less than half of the owners (39%) would pursue surgery regardless of tumour site; 1% would not pursue surgery; of the remainder, respondents would not allow amputation of the forelimb (20%), hindlimb (15%), or tail (15%). On the other hand, the majority of respondents were willing to travel up to 100 miles for radiotherapy or chemotherapy (66% and 69%, respectively) (Carwardine et al., 2014). Thus, owner education by the veterinarian explaining optimum treatment options is important.

Unfortunately, there is still a lack of information to provide evidence-based vaccine site recommendations. The majority of safety and efficacy data comes from licensing studies in which vaccines are administered subcutaneously in the interscapular region, which should not be used for any injection in field cats. Radical surgical resection of injection-site sarcomas including margins of at least 3 cm, but preferably 5 cm (Phelps et al., 2011), is associated with the highest response rate and long-term survival (Hershey et al., 2000). With this in mind, the AAFP panel on vaccination guidelines conducted an informal survey of veterinarians whose practices focused on radiation (12), surgical (36), and medical (44) oncology for opinions on what the preferred vaccination sites should be (Scherk et al., 2013). These experts agreed that distal to the stifle followed by distal to the elbow were their preferred sites. Nearly as popular was the tail. Respondents frequently commented that vaccines should be administered as low on the leg as possible. They added that vaccination of cats resting in a crouched position often results in inadvertent injection of the skin fold of the flank, resulting in tumours that are difficult to resect (Scherk et al., 2013). This is reflected in a study that found an increase in lateral abdominal injection-site sarcomas since the publication of the Vaccine Associated Feline Sarcoma Task Force vaccination recommendations in 1999 (Phelps et al., 2011). Based on this, the AAFP recommends distal limb injection to facilitate amputation with 5 cm margins in two fascial planes in FISS cases (Stone et al., 2020). Ventral abdominal subcutaneous injections also have been used because of the perceived relative ease of tumour removal without the need for amputation. However, the need to remove two fascial planes and 5 cm margins would still necessitate aggressive tissue removal from the abdomen and abdominal cavity (Stone et al., 2020). Tail vaccination has also been

reported as being well tolerated and elicited acceptable antibody responses when compared to vaccination in the distal limbs (Hendricks et al., 2014). However, to facilitate 5 cm margins in case of FISS removal, vaccinations must be administered in the distal tail, something that might not be practical for most clinicians (Stone et al., 2020). Further studies should be performed to confirm that this would be an alternative option leading to similar vaccine-induced protection rates.

In addition to considering appropriate injection sites, post vaccination monitoring plays an important role. Vaccination sites should be noted in clinical records (Day et al., 2016; Stone et al., 2020), and veterinarians should instruct their clients to monitor vaccination (or injection) sites for swelling or lumps so that potential FISS can be detected early, and thus can be removed successfully.

Veterinarians should be aware that any skin or subcutaneous mass in a cat requires further diagnostic and interventional approaches. At the very least, owners should follow the "**3-2-1**"-rule: incisional wedge biopsies or total removal and histological examination of any mass is warranted if the mass is still present **three** months after vaccination or if the mass becomes larger than **2** cm in diameter or if the mass is increasing in size **one** month after vaccination. Fine-needle aspirates might not provide diagnostic cellular tissue, whereas excisional biopsies rarely meet the appropriate margins (5 cm in two fascial planes) as required in the case of FISS, thus increasing the morbidity and mortality risks associated with sarcoma invasion (Stone et al., 2020). In general, diagnostic investigation is warranted when any cutaneous mass is noted in a cat.

Concerning general recommendations to prevent inflammatory reactions at injection sites, there are a few rules to follow. Generally, cats should receive as few subcutaneous injections as possible. Intramuscular injections in cats should be avoided because intramuscular tumours develop with a similar frequency but are more difficult to detect early. Whenever feasible, cats should receive drugs orally or intravenously. The subcutaneous injection of long-acting irritating substances (such as long-acting glucocorticoids) should be avoided.

One study examined potential risk factors when administering vaccines (Kass et al., 2003), and few factors were associated with the development of FISS. It was observed that the size of the needle and the syringe, the velocity of injection, and whether manual pressure was applied after injection or not, played no role. In contrast, the temperature of the vaccine made a significant difference, with cold vaccines being associated with a higher risk of FISS development than vaccines at room temperature (Kass et al., 2003). Thus, vaccines should be taken out of the refrigerator and be brought to room temperature before injection, e.g., by keeping the vial in the palm of the hand for a short time but should be kept only briefly out of the refrigerator to avoid reduction in vaccinal efficacy. For lyophilized vaccines, the diluent can be kept out of the refrigerator for a longer period. In addition, multi-dose vaccine vials, i.e. ten doses of the same vaccine within one vial, that are only rarely used in cats nowadays, were associated with a higher risk of FISS development (Kass et al., 2003).

Regarding the risk of FISS development, intranasal vaccines are to be preferred over injectable vaccines in cats if similar efficacy has been demonstrated. However, in most countries, only injectable vaccines are available. Therefore, the vaccines that are preferred are those that cause the least subcutaneous inflammatory reaction. Considering injectable vaccines, there has been much discussion of whether non-adjuvanted vaccines should be generally preferred over those containing adjuvant, if available and with proven similar efficacy. However, currently, there is insufficient information to make definitive recommendations on the vaccine type (Kass, 2018).

> *The current knowledge is as follows:*
>
> - It is a fact that every injectable vaccine can cause FISS (Kass et al., 2003; Srivastav et al., 2012).
> - It is a fact that vaccines containing adjuvant cause more inflammation than vaccines without adjuvants (Day et al., 2007).
> - It has been reported that inflammation might contribute to FISS development (Mikiewicz et al., 2023).
> - There are conflicting data whether vaccine adjuvants truly are associated with increased risk of FISS development (Kass et al., 2003; Srivastav et al., 2012).
> - It is currently difficult to truly compare vaccine efficacy studies because of differences in study designs.

Therefore, there is insufficient information to make definitive recommendations on the vaccine type and it is important to consider efficacy data. Where efficacy studies have shown higher protection rates in cats vaccinated with adjuvanted vaccines versus non-adjuvanted vaccines, the former are preferable in cats at high risk of infection. Otherwise, given the current state of knowledge, if vaccines without adjuvants have been proven to be equally effective as adjuvant-containing ones, it is reasonable to suggest that vaccines without adjuvants should be preferred, at least until the pathogenesis of FISS is better understood.

Finally, to prevent the development of FISS, cats should only be vaccinated as frequently as necessary, and long vaccination intervals

should be applied in adult animals where possible. Although all vaccines are licensed with specific vaccination intervals, ABCD guidelines (Hosie et al., 2015) sometimes suggest longer intervals depending on the cats' lifestyle. No non-core vaccines, such as FeLV, should be administered to cats without an exposure risk. In addition, immune cats should not be vaccinated (e.g., with a FPV vaccine if the presence of FPV antibodies is demonstrated as FPV antibodies are correlated with protection) (Bergmann et al., 2018; Egberink et al., 2022). This clearly demonstrates the necessity of individual vaccination schedules (Hosie et al., 2013; Stone et al., 2020).

Table 1: Important considerations to avoid feline injection-site sarcoma (FISS) development

Vaccination of cats provides essential protection and should not be stopped because of the risk of FISS. It is important to realize that vaccines are not the only injectable medical products associated with FISS.
An individually tailored vaccination schedule is important for each cat. Cats should be vaccinated only as often as necessary in accordance with current guidelines.
Appropriate sites for injections should be selected. The interscapular region as well as the lateral thoracic wall should generally be avoided for any injection. Vaccines should be injected at a site where a mass can be easily surgically removed, preferably distally in a limb.
Vaccines should be brought to room temperature prior to administration but should not be kept unrefrigerated for hours.
Multi-dose vaccine vials should not be used in cats.
Mucosal intranasal vaccines are preferred over injectable vaccines, if available.
Subcutaneous injection is preferred to intramuscular injection.
Among injectable vaccines, there is insufficient information to make definitive recommendations on the preferred vaccine type.
Vaccines with a long duration of immunity are preferred over those with a short duration of immunity.
Generally, any skin or subcutaneous mass in a cat requires further diagnostics. Specifically thorough post-vaccination monitoring should be performed (the "**3-2-1**"-rule): Any lump at the site of injection that is still present **three** months after vaccination, or that is larger than **2** cm in diameter, or that is increasing in size **one** month after vaccination, should be surgically removed and investigated through histopathology.
ABCD recommends that veterinarians carry out a risk-benefit analysis for each vaccine in order to avoid unnecessary vaccination of cats, monitor the injection site, and report all VAAEs to the manufacturer and/or to their competent authority.

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References

Banerji N, Kanjilal S (2006): Somatic alterations of the p53 tumor suppressor gene in vaccine-associated feline sarcoma. Am J Vet Res 67, 1766-1772.

Banerji N, Kapur V, Kanjilal S (2007): Association of germ-line polymorphisms in the feline p53 gene with genetic predisposition to vaccine-associated feline sarcoma. J Hered 98, 421-427.

Bergmann M, Schwertler S, Reese S, Speck S, Truyen U, Hartmann K (2018): Antibody response to feline panleukopenia virus vaccination in healthy adult cats. J Feline Med Surg 20, 1087–1093.

Bloch J, Rogers K, Walker M, Dawson J, Wilson-Robles H (2020): Treatment of feline injection-site sarcoma with surgery and iridium-192 brachytherapy: retrospective evaluation of 22 cats. J Feline Med Surg 22(4), 313-321. doi: 10.1177/1098612X19844345. Epub 2019 Apr 15.

Bray J, Polton G (2016): Neoadjuvant and adjuvant chemotherapy combined with anatomical resection of feline injection-site sarcoma: results in 21 cats. Vet Comp Oncol 14, 147-160.

Buracco P, Martano M, Morello E, Ratto A (2002): Vaccine-associated-like fibrosarcoma at the site of a deep nonabsorbable suture in a

cat. Vet J 163, 105-107.

Burton G, Mason KV (1997): Do postvaccinal sarcomas occur in Australian cats? Aust Vet J 75, 102-106.

Carminato A, Vascellari M, Marchioro W, Melchiotti E, Mutinelli F (2011): Microchip-associated fibrosarcoma in a cat. Vet Dermatol 22, 565-569.

Carneiro CS, de Queiroz GF, Pinto AC, Dagli ML, Matera JM (2019): Feline injection site sarcoma: immunohistochemical characteristics. Feline Med Surg 21(4), 314-321. doi: 10.1177/1098612X18774709. Epub 2018 May 23.

Carroll EE, Dubielzig RR, Schultz RD (2002): Cats differ from mink and ferrets in their response to commercial vaccines: a histologic comparison of early vaccine reactions. Vet Pathol 39, 216-227.

Carwardine D, Friend E, Toscano M, Bowlt K (2014): UK owner preferences for treatment of feline injection site sarcomas. J Small Anim Pract 55, 84-88.

Cecco BS, Henker LC, De Lorenzo C, Schwertz CI, Bianchi RM, da Costa FVA, Driemeier D, Pavarini SP, Sonne L (2019): Epidemiological and Pathological Characterization of Feline Injection Site Sarcomas in Southern Brazil. J Comp Pathol 172, 31-36. doi: 10.1016/j.jcpa.2019.08.009. Epub 2019 Sep 30.

Chiti LE, Martano M, Ferrari R, Boracchi P, Giordano A, Grieco V, Buracco P, Iussich S, Giudice C, Miniscalco B, Zani DD, Proverbio D, Morello E, Stefanello D (2020): Evaluation of leukocyte counts and neutrophil-to-lymphocyte ratio as predictors of local recurrence of feline injection site sarcoma after curative intent surgery. Vet Comp Oncol 18(1), 105-116. doi: 10.1111/vco.12534. Epub 2019 Sep 10.

Coleman MJ, Selmic LE, Samuelson JP, Jennings R, Huang PC, McLaughlin EM, Wavreille VA, Dornbusch JA, Lapsley J, Howard J, et al (2021): Diagnostic accuracy of optical coherence tomography for surgical margin assessment of feline injection-site sarcoma. Vet Comp Oncol 19(4), 632-640.

Coussens LM, Werb Z (2002): Inflammation and cancer. Nature 420, 860–867.

Couto CG, Macy DW (1998): Review of treatment options for vaccine-associated feline sarcoma. J Am Vet Med Assoc 213, 1426-1427.

Coyne MJ, Reeves NC, Rosen DK (1997): Estimated prevalence of injection-site sarcomas in cats during 1992. J Am Vet Med Assoc 210, 249-251.

Cronin K, Page RL, Spodnick G, Dodge R, Hardie EN, Price GS, et al (1998): Radiation therapy and surgery for fibrosarcoma in 33 cats. Vet Radiol Ultrasound 39, 51-56.

Daly MK, Saba CF, Crochik SS, Howerth EW, Kosarek CE, Cornell KK, et al (2008): Fibrosarcoma adjacent to the site of microchip implantation in a cat. J Feline Med Surg 10, 202-205.

Davis G, Cooles S, Diesel G, Blenkinsop J (2016): Summary of suspected adverse events, 2014. Vet Rec 178, 187–189.

Davis G, Cooles S, Vasan N (2015): Suspected adverse events, 2013. Vet Rec 176, 11–14.

Davis G, Rooney A, Cooles S, Evans G (2013): Suspected adverse events, 2012. Vet Rec 173, 573–576.

Day MJ, Horzinek MC, Schultz RD, Squires RA (2016): Vaccination Guidelines Group (VGG) of the World Small Animal Veterinary Association (WSAVA). WSAVA Guidelines for the vaccination of dogs and cats. J Small Anim Pract 57, 4-8.

Day MJ, Schoon HA, Magnol JP, Saik J, Devauchelle P, Truyen U, et al (2007): A kinetic study of histopathological changes in the subcutis of cats injected with non-adjuvanted and adjuvanted multi-component vaccines. Vaccine 25, 4073-4084.

Dean R, Adams V, Whitbread T, Scase T, Dunham S, Mellor D, et al (2006): Study of feline injection site sarcomas. Vet Rec 159, 641-642.

Dean RS, Pfeiffer DU, Adams VJ (2013): The incidence of feline injection site sarcomas in the United Kingdom. BMC veterinary research 9, 17.

Deim Z, Palmai N, Cserni G (2008): Feline vaccine-associated fibrosarcoma induced by aluminium compound in two cats: short communication. Acta Vet Hung 56, 111-116.

De Man MM, Ducatelle RV (2007): Bilateral subcutaneous fibrosarcomas in a cat following feline parvo-, herpes- and calicivirus vaccination. J Feline Med Surg 9, 432-434.

Doddy FD, Glickman LT, Glickman NW, Janovitz EB (1996): Feline fibrosarcomas at vaccination sites and non-vaccination sites. J Comp Pathol 114, 165-174.

Dubielzig RR, Hawkins KL, Miller PE (1993): Myofibroblastic sarcoma originating at the site of rabies vaccination in a cat. J Vet Diagn Invest 5, 637-638.

Dyer F, Brown E, Cooles S, Tait A (2009): Suspected adverse reactions (2008). Vet Rec 165, 162–164.

Dyer F, Diesel G, Cooles S, Tait A (2010): Suspected adverse reactions, 2009. Vet Rec 167, 118–121.

Dyer F, Diesel G, Cooles S, Tait A (2011): Suspected adverse reaction surveillance scheme, 2010. Suspected adverse events. Vet Rec 168, 610–613.

Dyer F, Diesel G, Cooles S, Tait A (2012): Suspected adverse events, 2011. Vet Rec 170, 640–643.

Dyer F, Spagnuolo-Weaver M, Coolees S, Tait A (2007): Suspected adverse reactions, 2006. Vet Rec 160, 748–750.

Dyer F, Spagnuolo-Weaver M, Coolees S, Tait A (2008): Suspected adverse reactions, 2007. Vet Rec 163, 69–72.

Eckstein C, Guscetti F, Roos M, Martín de las Mulas J, Kaser-Hotz B, Rohrer Bley C (2009): A retrospective analysis of radiation therapy for the treatment of feline vaccine-associated sarcoma. Vet Comp Oncol 7(1), 54-68.

Egberink H, Frymus T, Hartmann K, Möstl K, Addie DD, Belák S, Boucraut-Baralon C, Hofmann-Lehmann R, Lloret A, Marsilio F, et al. (2022): Vaccination and antibody testing in cats. Viruses 14, 1602.

Ellis JA, Jackson ML, Bartsch RC, McGill LG, Martin KM, Trask BR, et al (1996): Use of immunohistochemistry and polymerase chain reaction for detection of oncornaviruses in formalin-fixed, paraffin-embedded fibrosarcomas from cats. J Am Vet Med Assoc 209, 767-771.

Esplin DG, Bigelow M, McGill LD, Wilson SR (1999): Fibrosarcoma at the site of a Lufenuron injection in a cat. Vet Cancer Soc Newsletter 23, 8-9.

Esplin DG, McGill LD, Meininger AC, Wilson SR (1993): Postvaccination sarcomas in cats. J Am Vet Med Assoc 202, 1245-1247.

Ferrari R, Di Giancamillo M, Stefanello D, Giudice C, Grieco V, Longo M, Ravasio G, Boracchi P (2017): Clinical and computed tomography tumour dimension assessments for planning wide excision of injection site sarcomas in cats: how strong is the agreement? Vet Comp Oncol 15, 374-382.

Fleming K, Nemanic S, Löhr CV, Terry J, Milovancev M (2019): CT angiography and MRI imaging features do not predict the tumor type and grade of feline injection site sarcoma**.** Vet Radiol Ultrasound 60(6), 668-679. doi: 10.1111/vru.12807. Epub 2019 Sep 12.

Gagnon A (2000): Drug injection-associated fibrosarcoma in a cat. Feline Practice 28, 18-21.

Giudice C, Stefanello D, Sala M, Cantatore M, Russo F, Romussi S, Travetti O, Di Giancamillo M, Grieco V (2010): Feline injection-site sarcoma: recurrence, tumour grading and surgical margin status evaluated using the three-dimensional histological technique**.** Vet J 186(1), 84-88. doi: 10.1016/j.tvjl.2009.07.019. Epub 2009 Sep 6.

Gobar GM, Kass PH (2002): World Wide Web-based survey of vaccination practices, postvaccinal reactions, and vaccine site-associated sarcomas in cats. J Am Vet Med Assoc 220, 1477-1482.

Graf R, Grüntzig K, Boo G, Hässig M, Axhausen KW, et al (2016): Swiss Feline Cancer Registry 1965-2008: the influence of sex, breed and age on tumour types and tumour locations. J Comp Pathol 154, 195-210.

Graf R, Grüntzig K, Hässig M, Axhausen KW, Fabrikant S, Welle M, Meier D, Guscetti F, Folkers G, Otto V, Pospischil A (2015): Swiss Feline Cancer Registry: A retrospective study of the occurrence of tumours in cats in Switzerland from 1965 to 2008. J Comp Pathol 153(4), 266-277. doi: 10.1016/j.jcpa.2015.08.007. Epub 2015 Sept 28.

Graf R, Guscetti F, Welle M, Meier D, Pospischil A (2018): Feline Injection Site Sarcomas: Data from Switzerland 2009-2014. J Comp Pathol 163, 1-5.

Haas J (2009): Klinik, Labordiagnostik und verwendete Impfstoffe bei Katzen mit einem Fibrosarkom: eine Übersicht über die Patienten der Medizinischen Kleintierklinik 1999-2007. Munich, Germany, Ludwig Maximilian University.

Haddad JL, Goldschmidt MH, Patel RT (2010): Fibrosarcoma arising at the site of a retained surgical sponge in a cat. Vet Clin Pathol 39, 241-246.

Haist V, Bellebeau-Barbier F, Montange C, Lemaitre L, Diawara A, Guiot A-L, Nicolier A, Latronico E, Chereul E, Brunet S, Tronel J-P (2023): Comparison of the local safety of two multi-component feline vaccines, adjuvanted (1 mL) versus non-adjuvanted at reduced volume (0.5 mL), using computed tomography imaging. Vaccine 41, 4752–4761.

Hartmann K, Day MJ, Thiry E, Lloret A, Frymus T, Addie D, Boucraut-Baralon C, Egberink H, Gruffydd-Jones T, Horzinek MC, Hosie MJ, Lutz H, Marsilio F, Pennisi MG, Radford AD, Truyen U, Möstl K (2015): Feline injection-site sarcoma: ABCD guidelines on prevention and management. J Feline Med Surg 17(7), 606-613.

Hartmann K, Egberink H, Möstl K, Addie DD, Boucraut-Baralon C, Frymus T, Belák S, Lloret A, Hofmann-Lehmann R, Marsilio F, Pennisi MG, Tasker S, Thiry E, Truyen U, Hosie MJ (2023): Feline Injection-Site Sarcoma and Other Adverse Reactions to Vaccination in Cats. Viruses 15,1708.

Hendrick MJ (1998): Feline vaccine-associated sarcomas: current studies on pathogenesis. J Am Vet Med Assoc 213, 1425-1426.

Hendrick MJ (1999): Feline vaccine-associated sarcomas. Cancer Invest 17, 273-277.

Hendrick MJ, Brooks JJ (1994): Postvaccinal sarcomas in the cat: histology and immunohistochemistry. Vet Pathol 31, 126-129.

Hendrick MJ, Dunagan CA (1991): Focal necrotizing granulomatous panniculitis associated with subcutaneous injection of rabies vaccine in cats and dogs: 10 cases (1988-1989). J Am Vet Med Assoc 198, 304-305.

Hendrick MJ, Goldschmidt MH (1991): Do injection site reactions induce fibrosarcomas in cats? J Am Vet Med Assoc 199, 968.

Hendrick MJ, Goldschmidt MH, Shofer FS, Wang YY, Somlyo AP (1992): Postvaccinal sarcomas in the cat: epidemiology and electron probe microanalytical identification of aluminum. Cancer Res 52, 5391-5394.

Hendrick MJ, Shofer FS, Goldschmidt MH, Haviland JC, Schelling SH, Engler SJ, et al (1994): Comparison of fibrosarcomas that developed at vaccination sites and at nonvaccination sites in cats: 239 cases (1991-1992). J Am Vet Med Assoc 205, 1425-1429.

Hendricks CG, Levy JK, Tucker SJ, Olmstead SM, Crawford PC, Dubovi EJ, et al (2014): Tail vaccination in cats: a pilot study. J Feline Med Surg 16, 275-280.

Hershey AE, Sorenmo KU, Hendrick MJ, Shofer FS, Vail DM (2000): Prognosis for presumed feline vaccine-associated sarcoma after excision: 61 cases (1986-1996). J Am Vet Med Assoc 216, 58-61.

Hirschberger J, Kessler M (2001): Das feline Fibrosarkom. Tierärztliche Praxis 29, 66-71.

Holtermann N, Kiupel M, Hirschberger J (2017): The tyrosine kinase inhibitor toceranib in feline injection site sarcoma: efficacy and side effects. Vet Comp Oncol 15, 632-640. doi: 10.1111/vco.12207. Epub 2016 Jan 14.

Hosie MJ, Addie D, Belák S, Boucraut-Baralon C, Egberink H, Frymus T, Gruffydd-Jones T, Hartmann K, Lloret A, Lutz H, et al. (2013): Matrix vaccination guidelines: ABCD recommendations for indoor/outdoor cats, rescue shelter cats and breeding catteries. J Feline Med Surg 15, 540–544.

Hosie MJ, Addie D, Boucraut-Baralon C, Egberink H, Frymus T, Gruffydd-Jones T, Hartmann K, Horzinek MC, Lloret A, Lutz H et al. (2015): Matrix vaccination guidelines: 2015 ABCD recommendations for indoor/outdoor cats, rescue shelter cats and breeding catteries. J Feline Med Surg 17, 583–587.

Hsueh C-S, Wu C-H, Shih C-H, Yeh JL-S, Jeng C-R, Fei Pang V, Chiou H-Y, Chang H-W (2019): Role of nuclear factor-kappa B in feline injection site sarcoma. BMC Vet Res 25 15(1), 365.

Huttinger C, Hirschberger J, Jahnke A, Kostlin R, Brill T, Plank C, et al (2008): Neoadjuvant gene delivery of feline granulocyte-macrophage colony-stimulating factor using magnetofection for the treatment of feline fibrosarcomas: a phase I trial. J Gene Med 10, 655-667.

Jahnke A, Hirschberger J, Fischer C, Brill T, Kostlin R, Plank C, et al (2007): Intra-tumoral gene delivery of feIL-2, feIFN-gamma and feGM-CSF using magnetofection as a neoadjuvant treatment option for feline fibrosarcomas: a phase-I study. J Vet Med A Physiol Pathol Clin Med 54, 599-606.

Jas D, Soyer C, DeFornel-Thibaud P, et al (2015): Adjuvant immunotherapy of feline injection-site sarcomas with the recombinant canarypox virus expressing feline interleukine-2 evaluated in a controlled monocentric clinical trial when used in association with surgery and brachytherapy. Trials Vaccinol 4, 1-8.

Kalat M, Mayr B, Schleger W, Wagner B, Reifinger M (1991): Chromosomal hyperdiploidy in a feline sarcoma. Res Vet Sci 51, 227-228.

Kang S, Southard T, Hume KR (2017): DNA damage is a feature of feline injection-site sarcoma. Vet Comp Oncol 15(2), 518-524. doi: 10.1111/vco.12195. Epub 2016 Jan 19. PMID: 26781433

Kass PH (2018): Prevention of Feline Injection-Site Sarcomas: Is There a Scientific Foundation for Vaccine Recommendations at This

Time? Vet Clin North Am Small Anim Pract 48, 301-306.

Kass PH, Barnes WG Jr, Spangler WL, Chomel BB, Culbertson MR (1993): Epidemiologic evidence for a causal relation between vaccination and fibrosarcoma tumorigenesis in cats. J Am Vet Med Assoc 203, 396-405.

Kass PH, Spangler WL, Hendrick MJ, McGill LD, Esplin DG, Lester S, et al (2003): Multicenter case-control study of risk factors associated with development of vaccine-associated sarcomas in cats. J Am Vet Med Assoc 223, 1283-1292.

Kidney BA, Ellis JA, Haines DM, Jackson ML (2000): Evaluation of formalin-fixed paraffin-embedded tissues obtained from vaccine site-associated sarcomas of cats for DNA of feline immunodeficiency virus. Am J Vet Res 61, 1037-1041.

Kidney BA, Haines DM, Ellis JA, Burnham M, Jackson ML (2001a): Evaluation of formalin-fixed paraffin-embedded tissues from vaccine site-associated sarcomas of cats for polyomavirus DNA and antigen. Am J Vet Res 62, 828-832.

Kidney BA, Haines DM, Ellis JA, Burnham ML, Jackson ML (2002): Evaluation of formalin-fixed paraffin-embedded tissues from feline vaccine site-associated sarcomas for feline foamy virus DNA. Am J Vet Res 63, 60-63.

Kidney BA, Haines DM, Ellis JA, Burnham ML, Teifke JP, Czerwinski G, et al (2001b): Evaluation of formalin-fixed paraffin-embedded tissues from vaccine site-associated sarcomas of cats for papillomavirus DNA and antigen. Am J Vet Res 62, 833-839.

Kliczkowska K, Jankowska U, Jagielski D, Czopowicz M, Sapierzyński R (2015): Epidemiological and morphological analysis of feline injection site sarcomas. Pol J Vet Sci 18, 313-322.

Kobayashi T, Hauck ML, Dodge R, Page RL, Price GS, Williams LE, et al (2002): Preoperative radiotherapy for vaccine associated sarcoma in 92 cats. Vet Radiol Ultrasound 43, 473-479.

Ladlow J (2013): Injection site-associated sarcoma in the cat: treatment recommendations and results to date. J Feline Med Surg 15, 409-418.

Laver T, Lee BM, Gogal RM (2022): Bortezomib inhibits the proteasome, leading to cell death via apoptosis in feline injection site sarcoma cells in vitro. Am J Vet Res 8, 83(6):ajvr.21.09.0152.

Lester S, Clemett T, Burt A (1996): Vaccine site-associated sarcomas in cats: clinical experience and a laboratory review (1982-1993). J Am Anim Hosp Assoc 32, 91-95.

Löhr CV, Stieger-Vanegas SM, Terry JL, Milovancev M, Medlock J (2021): Targeting Peritumoral Lesions Identified by Computed Tomography and Magnetic Resonance Imaging in Feline Injection-Site Sarcomas for Microscopic Examination. Vet Pathol 58(5), 923-934. doi: 10.1177/03009858211012949. Epub 2021 May 10.

Longo M, Zani DD, Ferrari R, Bassi J, Andreis ME, Stefanello D, Giudice C, Grieco V, Liuti T, Handel I, Di Giancamillo M (2018): Dynamic tomographic studies of interscapular feline injection-site sarcoma: essential or useless practice? J Feline Med Surg 20(6), 502-508. doi: 10.1177/1098612X17717176. Epub 2017 Jun 30.

Macy DW (1995): The potential role and mechanisms of FeLV vaccine-induced neoplasms. Semin Vet Med Surg (Small Anim) 10, 234-237.

Madewell BR, Griffey SM, McEntee MC, Leppert VJ, Munn RJ (2001): Feline vaccine-associated fibrosarcoma: an ultrastructural study of 20 tumors (1996-1999). Vet Pathol 38, 196-202.

Martano M, Morello E, Buracco P (2011): Feline injection-site sarcoma: past, present and future perspectives. Vet J 188, 136-141.

Martano M, Morello E, Iussich S, Buracco P (2012): A case of feline injection-site sarcoma at the site of cisplatin injections. J Feline Med Surg 14, 751-754.

Mayer MN, Treuil PL, LaRue SM (2009): Radiotherapy and surgery for feline soft tissue sarcoma. Vet Radiol Ultrasound 50, 669-672.

Mayr B, Bockstahler B, Loupal G, Reifinger M, Schleger W (1996): Cytogenetic variation between four cases of feline fibrosarcoma. Res Vet Sci 61, 268-270.

Mayr B, Eschborn U, Kalat M (1991): Near triploidy in a feline fibrosarcoma. Zentralbl Veterinarmed A 38, 617-620.

Mayr B, Reifinger M, Alton K, Schaffner G (1998): Novel p53 tumour suppressor mutations in cases of spindle cell sarcoma, pleomorphic sarcoma and fibrosarcoma in cats. Vet Res Commun 22, 249-255.

Mayr B, Schaffner G, Kurzbauer R, Schneider A, Reifinger M, Loupal G (1995): Mutations in tumour suppressor gene p53 in two feline fibrosarcomas. Br Vet J 151, 707-713.

McEntee MC (2000): The utility of contrast enhanced computed tomography in feline vaccine associated sarcomas: 35 cases. Vet Radiol Ultrasound 41, 575.

McEntee MC, Page RL (2001): Feline vaccine-associated sarcomas. J Vet Intern Med 15, 176-182.

McLeland SM, Imhoff DJ, Thomas M, Powers BE, Quimby JM (2013): Subcutaneous fluid port-associated soft tissue sarcoma in a cat. J Feline Med Surg 15, 917-920.

Mikiewicz M, Pa´zdzior-Czapula K, Fiedorowicz J, Gesek M, Otrocka-Domagała I (2023): Metallothionein expression in feline injection site fibrosarcomas. BMC Vet Res 19, 42.

Moore GE, HogenEsch H (2010): Adverse vaccinal events in dogs and cats. Vet Clin North Am Small Anim Pract 40(3), 393-407. doi: 10.1016/j.cvsm.2010.02.002.

Morrison WB, Starr RM (2001): Vaccine-Associated Feline Sarcoma Task Force. J Am Vet Med Assoc 218, 697-702.

Mucha D, Laberke S, Meyer S, Hirschberger J (2014): Lack of association between p53 SNP and FISS in a cat population from Germany. Vet Comp Oncol 12, 130-137.

Müller N, Kessler M (2018): Curative-intent radical en bloc resection using a minimum of a 3 cm margin in feline injection-site sarcomas: a retrospective analysis of 131 cases. J Feline Med Surg 20(6), 509-519. doi: 10.1177/1098612X17717882. Epub 2017 Jul 11.

Munday JS, Banyay K, Aberdein D, French AF (2011): Development of an injection site sarcoma shortly after meloxicam injection in an unvaccinated cat. J Feline Med Surg 13, 988-991.

Munday JS, Stedman NL, Richey LJ (2003): Histology and immunohistochemistry of seven ferret vaccination-site fibrosarcomas. Vet Pathol 40, 288-293.

Nambiar PR, Haines DM, Ellis JA, Kidney BA, Jackson ML (2000): Mutational analysis of tumor suppressor gene p53 in feline vaccine site-associated sarcomas. Am J Vet Res 61, 1277-1281.

Nambiar PR, Jackson ML, Ellis JA, Chelack BJ, Kidney BA, Haines DM (2001): Immunohistochemical detection of tumor suppressor gene p53 protein in feline injection site-associated sarcomas. Vet Pathol 38, 236-238.

Nemanic S, Milonvancev M, Terry JL, Stieger-Vanegas SM, Löhr CV (2016): Microscopic Evaluation of Peritumoral Lesions of Feline Injection Site Sarcomas Identified by Magnetic Resonance Imaging and Computed Tomography**.** Vet Surg 45(3), 392-401. doi: 10.1111/vsu.12448. Epub 2016 Feb 24.

Nieto A, Sanchez MA, Martinez E, Rollan E (2003): Immunohistochemical expression of p53, fibroblast growth factor-b, and transforming growth factor-alpha in feline vaccine-associated sarcomas. Vet Pathol 40, 651-658.

Nitrini AGC, Cogliati B, Matera JM (2021): Thermographic assessment of skin and soft tissue tumors in cats. J Feline Med Surg 23(6), 513-518.

O'Byrne KJ, Dalgleish AG (2001): Chronic immune activation and inflammation as the cause of malignancy. Review. Br J Cancer 85(4), 473-483.

Petznek H, Kleiter M, Tichy A, Fuchs-Baumgartinger A, Hohenadl C (2014): Murine xenograft model demonstrates significant radio-sensitising effect of liposomal doxorubicin in a combination therapy for Feline Injection Site Sarcoma. Res Vet Sci 97(2), 386-390. doi: 10.1016/j.rvsc.2014.07.008. Epub 2014 Jul 21.

Phelps HA, Kuntz CA, Milner RJ, Powers BE, Bacon NJ (2011): Radical excision with five-centimeter margins for treatment of feline injection-site sarcomas: 91 cases (1998-2002). J Am Vet Med Assoc 239, 97-106.

Poirier VJ, Thamm DH, Kurzman ID, Jeglum KA, Chun R, Obradovich JE, O'Brien M, Fred RM 3rd, Phillips BS, Vail DM (2002): Liposome-encapsulated doxorubicin (Doxil) and doxorubicin in the treatment of vaccine-associated sarcoma in cats. Vet Intern Med 16, 726-731.

Porcellato I, Menchetti L, Brachelente C, Sforna M, Reginato A, Lepri E, Mechelli L (2017): Feline Injection-Site Sarcoma. Vet Pathol 54, 204-211. doi: 10.1177/0300985816677148. Epub 2016 Dec 22.

Quintin-Colonna F, Devauchelle P, Fradelizi D, Mourot B, Faure T, Kourilsky P, et al (1996): Gene therapy of spontaneous canine melanoma and feline fibrosarcoma by intratumoral administration of histoincompatible cells expressing human interleukin-2. Gene Ther 3, 1104-1112.

Rousset N, Holmes MA, Caine A, Dobson J, Herrtage ME (2013): Clinical and low-field MRI characteristics of injection site sarcoma in 19

cats. Vet Radiol Ultrasound 54, 623-629.

Ruger L, Yang E, Coutermarsh-Ott S, Vickers E, Gannon J, Nightengale M, Hsueh A, Ciepluch B, Dervisis N, Vlaisavljevich E, et al (2023): Histotripsy ablation for the treatment of feline injection site sarcomas: a first-in-cat in vivo feasibility study. Int J Hyperthermia 40(1), 2210272.

Saba CF (2017): Vaccine-associated feline sarcoma: current perspectives**.** Vet Med (Auckl) 12;8, 13-20. doi: 10.2147/VMRR.S116556.eCollection 2017.

Sandler I, Teeger M, Best S (1997): Metastatic vaccine associated fibrosarcoma in a 10-year-old cat. Can Vet J 38, 374.

Santelices Iglesias OA, Wright C, Duchene AG, Risso MA, Risso P, Zanuzzi CN, Nishida F, Lavid A, Confente F, Díaz M, Portiansky EL, Gimeno EJ, Barbeito CG (2018): Association between Degree of Anaplasia and Degree of Inflammation with the Expression of COX-2 in Feline Injection Site Sarcomas. J Comp Pathol 165, 45-51. doi: 10.1016/j.jcpa.2018.09.002. Epub 2018 Oct 24.

Scherk MA, Ford RB, Gaskell RM, Hartmann K, Hurley KF, Lappin MR, et al (2013): 2013 AAFP Feline Vaccination Advisory Panel Report. J Feline Med Surg 15, 785-808.

Shaw SC, Kent MS, Gordon IK, Collins CJ, Greasby TA, Beckett LA, et al (2009): Temporal changes in characteristics of injection-site sarcomas in cats: 392 cases (1990-2006). J Am Vet Med Assoc 234, 376-380.

Shih CH, Chang YC, Lai YC, Chiou HY (2022): Investigating the role of signal transducer and activator of transcription 3 in feline injection site sarcoma. BMC Vet Res 18, 276.

Spugnini EP, Vincenzi B, Carocci F, Bonichi C, Menicagli F, Baldi F (2020): Combination of bleomycin and cisplatin as adjuvant electrochemotherapy protocol for the treatment of incompletely excised feline injection-site sarcomas: A retrospective study. Open Vet J 10(3), 267-271. doi: 10.4314/ovj.v10i3.4. Epub 2020 Jul 31.

Srivastav A, Kass PH, McGill LD, Farver TB, Kent MS (2012): Comparative vaccine-specific and other injectable-specific risks of injection-site sarcomas in cats. J Am Vet Med Assoc 241, 595-602.

Steger-Lieb A, Kostorz A, Hauser B, Sumova A, Kaser-Hotz B (2002): Einsatz der Strahlentherapie beim vakzineassoziierten Sarkom der Katze, Erfahrungen aus 18 Fällen. Tierärztliche Praxis 30, 35-40.

Stone AE, Brummet GO, Carozza EM, Kass PH, Petersen EP, Sykes J, Westman ME (2020): 2020 AAHA/AAFP Feline Vaccination Guidelines. J Feline Med Surg 22, 813–830.

Terry JL, Milovancev M, Löhr CV, Nemanic S (2016): Changes in the dimension and volume of feline injection-site sarcomas following formalin fixation as determined by use of the ellipsoid volume formula and three-dimensional computed tomography software. J Vet Res 77(6), 620-626. doi: 10.2460/ajvr.77.6.620.

Terry JL, Milovancev M, Nemanic S, Löhr CV (2017): Quantification of surgical margin length changes after excision of feline injection site sarcomas-A pilot study. Vet Surg 46(2), 189-196. doi: 10.1111/vsu.12602. Epub 2016 Dec 19.

Travetti O, di Giancamillo M, Stefanello D, Ferrari R, Giudice C, Grieco V, Saunders JH (2013): Computed tomography characteristics of fibrosarcoma — a histological subtype of feline injection-site sarcoma**. J** Feline Med Surg 15(6), 488-493. doi: 10.1177/1098612X12472174. Epub 2013 Jan 7.

Vaccine-Associated Feline Sarcoma Task Force (1999): Vaccine-Associated Feline Sarcoma Task Force guidelines. Diagnosis and treatment of suspected sarcomas. J Am Vet Med Assoc 214, 1745.

Vaccine-Associated Feline Sarcoma Task Force (2005): The current understanding and management of vaccine-associated sarcomas in cats. J Am Vet Med Assoc 226, 1821-1842.

Vascellari M, Melchiotti E, Bozza MA, Mutinelli F (2003): Fibrosarcomas at presumed sites of injection in dogs: characteristics and comparison with non-vaccination site fibrosarcomas and feline post-vaccinal fibrosarcomas. J Vet Med A Physiol Pathol Clin Med 50, 286-291.

Wei Q, Ramsey SA, Larson MK, Berlow NE, Ochola D, Shiprack C, Kashyap A, Séguin B, Keller C, Löhr CV (2019): Elucidating the transcriptional program of feline injection-site sarcoma using a cross-species mRNA-sequencing approach**.** BMC Cancer 19(1), 311. doi: 10.1186/s12885-019-5501-z.

Wilcock B, Wilcock A, Bottoms K (2012): Feline postvaccinal sarcoma: 20 years later. Can Vet J 53, 430-434.

Williams CS, Mann M, DuBois RN (1999): The role of cyclooxygenases in inflammation, cancer, and development. Review. Oncogene

18(55), 7908-7916.

Zabielska-Koczywąs K, Wojtalewicz A, Lechowski R (2017): Current knowledge on feline injection-site sarcoma treatment. Acta Vet Scand 59, 47.

Zanuncio VV, Conceição LG, Loures FH, Cassali GD, Rocha K, Lima BM (2021): Hormone receptor expression, clinical and histopathological analysis in feline injection site sarcomas. Vet Comp Oncol 19, 473–481.

Zardo KM, Damiani LP, Matera JM, Fonseca-Pinto AC (2016): Recurrent and non-recurrent feline injection-site sarcoma: computed tomographic and ultrasonographic findings. J Feline Med Surg 18, 773-782.

Zimmermann K, Hossann M, Hirschberger J, Troedson K, Peller M, Schneider M, Brühschwein A, Meyer-Lindenberg A, Wess G, Wergin M, Dörfelt R, Knösel T, Schwaiger M, Baumgartner C, Brandl J, Schwamberger S, Lindner LH (2016): A pilot trial of doxorubicin containing phosphatidyldiglycerol based thermosensitive liposomes in spontaneous feline soft tissue sarcoma. Int J Hyperthermia 25, 1-13.