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1 **Feline Injection Site Sarcoma: Current Paradigms and Future**

2 **Directions**

3 **ABSTRACT**

4 Feline injection site sarcoma (FISS) is an uncommon but important tumour in cats due
5 to its locally aggressive biologic behaviour, poor prognosis and that it is linked to
6 routinely administered vaccinations, which raises ethical questions regarding vaccine
7 practices. Post vaccinal granulomas are a common occurrence in cats therefore client
8 education is vital and careful monitoring should be adopted. Incisional biopsy is
9 recommended to confirm diagnosis of FISS and full staging is recommended prior to
10 determination of a treatment strategy. Tumour palpation has been shown to vastly
11 underestimate the extent of tumour infiltration and therefore prospective treatment
12 planning with advanced imaging is highly recommended. Although further studies are
13 required to determine the most effective combination of treatment modalities for
14 definitive treatment, a multi-modal approach is often required, based on expeditious
15 and aggressive surgery in combination with radiotherapy +/- chemotherapy.
16 Importantly early detection by careful post vaccination monitoring as well as a shift in
17 vaccination practices is key to improving the outcome of FISS.

18

19 **Key Words:** Neoplasms, Sarcoma, Cat Diseases: Pathology, Vaccinations, Tumour,
20 Radiation Therapy, Surgery

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INTRODUCTION

In 1991, a letter to the editor of the Journal of the American Veterinary Medical Association, written by Dr Hendrick and Dr Goldschmidt (Hendrick & Goldschmidt 1991), highlighted an increasing concern relating to a link between cat vaccination and the development of soft tissue sarcomas. Further studies supporting these claims were quick to follow; the debate within the veterinary community about this issue continues today and it remains a viable concern for both the veterinary industry and pet owners alike. While it is now suspected that feline injection site sarcoma (FISS), originally known as vaccine site-associated sarcomas, may be linked to other iatrogenic inflammatory insults such as insulin, antibiotics and steroid injections, (Kass et al 2003), feline leukaemia and rabies vaccinations have the strongest epidemiological link (Kass et al. 1993; Hendrick & Goldschmidt 1991; Coyne et al. 1997).

The true incidence and prevalence of this worldwide issue is likely an underestimate due to under-reporting, however research has demonstrated that the incidence of sarcoma development as a result of vaccination in the United States is between 0.63-10 in every 10,000 vaccinated cats, depending on the study consulted and most commonly occurs after administration of rabies virus and FeLV (feline leukaemia virus) vaccines (Gobar & Kass 2002; Hendrick et al. 1994; Coyne et al. 1997; Lester et al.). Interestingly, in the United Kingdom, where the frequency of rabies vaccination is lower than in North America, the incidence is similar and is estimated to be between 1 in 16,000 and 1 in 50,000 cats (Dean et al. 2013).

Veterinary surgeons have an ethical duty to protect our patients from disease. Our vaccine protocols have been developed to prevent easily acquirable, life limiting conditions, and as such, in the UK, the annual booster is often accepted as gold

1 standard practice. In human medicine, some might consider vaccine products that
2 have cancer causing potential at this level of risk unacceptable. In response to this
3 concern, the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) was created,
4 and various clinical recommendations were developed. Many of these
5 recommendations have been adopted in North America; yet, while guidance has been
6 published, these recommendations have not generally been adopted as standard
7 practice in the UK.

8 In this article, the pathogenesis, case management and prognosis of FISS,
9 including novel treatments and future directions, will be highlighted. Special
10 emphasis on clinical work up and surgical planning is imperative in improving
11 treatment outcome. Due to the considerable morbidity and expense involved in
12 treatment coupled with the challenges associated with achieving long-term tumour
13 control, prevention should focus on thoughtful vaccination protocols and adherence to
14 VAFSTF recommendations.

15

16 **PATHOGENESIS**

17 In some species such as canines and humans, inflammatory associated sarcomas occur
18 at very low rates; indeed the reported incidence of this disease in cats was also low
19 prior to the 1980's, at which time killed adjuvanted feline vaccines were marketed.
20 Shortly after this time the pathology department at the School of Veterinary Medicine
21 at Pennsylvania University identified an increase in inflammatory injection site
22 reactions in feline biopsy specimens (Hendrick & Dunagan 1991). FISS manifests
23 most commonly in cats as fibrosarcoma histologically, although, chondrosarcoma,
24 malignant fibrous histiocytoma and rhabdomyosarcoma have also been reported
25 (Hendrick & Brooks 1994). Tumours appear to originate from proliferating fibroblasts

1 and myofibroblasts (Hendricks and Brooks, 1994). This may be a reflection of the
2 differing feline fibroblastic response to injury relative to other species (Eggers Carroll
3 et al. 2002). Localised vaccine reactions are common in cats vaccinated with rabies
4 and feline leukemia virus vaccines, with one report suggesting that up to 80-100% of
5 cats will have a reaction to rabies vaccination (Macy & Hendrick 1996; McEntee &
6 Page 2001; Gobar & Kass 2002; Wilcock et al. 2012). In one study, it was found that
7 2.7% of these post vaccinal nodules will result in malignant transformation over
8 several months to years (Gobar & Kass 2002). It is not clear why some nodules
9 become malignant while many others resolve, but it has been suggested that some cats
10 may be genetically predisposed to neoplastic change (Hartmann et al. 2015). Ferrets
11 have been reported to develop injection site sarcomas spontaneously while rodents
12 can be experimentally induced to develop injection site sarcomas, suggesting this
13 phenomenon is not unique to cats (Munday et al. 2003; Huggins & Grand 1963;
14 Hendrick 2011).

15 One theory in FISS formation is that in a genetically ‘tumour-susceptible’ cat,
16 the chronic inflammatory stimuli provided by vaccine components leads to neoplastic
17 transformation of these fibroblastic cells (Jelínek 2003; Eggers Carroll et al. 2002).
18 Vaccine adjuvants such as aluminium have frequently been identified within these
19 sarcomas on histological sections and ultra-structural studies and strengthen the
20 suspicion of an injection-related tumour (Madewell et al. 2001; Hendrick et al. 1992).
21 Although non-adjuvanted vaccines have been associated with FISS, adjuvanted
22 vaccines, and particularly those containing aluminium products, are known to enhance
23 localized inflammatory reactions and therefore are frequently highlighted as a risk
24 factor for tumour development (Day et al. 2007). Further supporting the theory that
25 injections or vaccines are involved is the fact that tumours occur most frequently in

1 the sub-cutis of vaccine injection sites. Historically, tumours were more likely to
2 occur in the interscapular region, the most common site for injection, yet there has
3 been a statistically significant shift in tumour location to regions corresponding to
4 recommended vaccine sites in North America (Hendricks and Brooks, 1999, Shaw et
5 al 2009). To date, rabies and feline leukemia virus vaccines remain the injections
6 most clearly associated with the development of FISS; it is estimated that the number
7 of vaccines given simultaneously at the same location`n greatly increases the risk of
8 FISS development (Kass et al. 1993).

9 Precise mechanisms underlying tumour formation and progression in FISS are
10 not known although several studies have attempted to elucidate some information
11 regarding the molecular biology of these tumours. To date, researchers have
12 investigated receptor and non-receptor protein tyrosine kinases that are involved in
13 cell signalling, growth, differentiation and/or survival, p53 mutations that disrupt cell
14 death pathways, and chromosomal aberrations that may influence tumour
15 development and progression (Smith et al. 2009; Katayama et al. 2004; Lawrence et
16 al. 2012; Nambiar et al. 2000; Hershey et al. 2005; Banerji & Kanjilal 2006; Banerji
17 et al. 2007; Mayr et al. 1995; Petterino et al. 2006; Thomas et al. 2009).
18 Understanding changes and alterations in tumour cells is important as it provides
19 possible avenues for novel treatment approaches,

20 **PRESENTATION AND DIAGNOSTIC WORK UP**

21 FISS is most commonly identified at the site of previous vaccination and although
22 there is a rapid rate of growth of this aggressive, locally invasive tumour, the lag time
23 from vaccination to tumour formation can be variable. Compared to other non-
24 injection site related sarcomas, cats with FISS tend to be younger. Epidemiological

1 evidence points to two peak presentations; 6-7 years and 10-11 years (Kass et al.
2 1993). Recognising that many cats will develop post vaccinal nodules at the site of
3 injection, the VAFSTF established a protocol in 1999 leading to the creation of the **3-**
4 **2-1 rule** (box 1). These guidelines recommend that any mass persisting for more than
5 **3** months after injection (vaccination), measuring more than **2** cm in diameter and
6 increasing in size **1** month after injection should be biopsied (Morrison & Starr 2001).

7 For any mass that occurs at an injection site associated with a vaccination,
8 incisional biopsy is recommended for confirmation of diagnosis. As with other soft
9 tissue sarcomas, a wedge, punch or needle biopsy should not extend into healthy
10 tissue in order to avoid compromising future surgical or irradiated margins. Although
11 fine needle aspiration cytology can be performed to rule out other causes of soft tissue
12 masses such as mast cell tumour or abscess, biopsy is recommended where sarcoma is
13 suspected due to the frequency of false negative results with fine needle aspirates
14 (Morrison & Starr 2001; Wilcock et al. 2012).

15 **STAGING**

16 Once a histological diagnosis has been made from biopsy, thorough staging should be
17 performed in order to identify the extent of disease and aid in determining treatment
18 options. Staging should include urinalysis, FIV and FeLV testing, haematology and
19 biochemistry profiles to rule out concurrent diseases that may affect treatment
20 decisions. Three view inflated thoracic radiographs and/or computed tomography
21 (CT) should be performed to identify potential metastatic disease. The pulmonary
22 parenchyma is the most common metastatic site although other sites such as lymph
23 node and abdominal viscera have been reported. The overall rate of metastasis in FISS
24 is reported to be between 10 and 28% (Couto & Macy 1998; Hendrick et al. 1994;

Hershey et al. 2000; Romanelli et al. 2008), which is higher than in other feline soft tissue sarcomas. An early paper investigating positive prognostic factors for FISS indicated that the first surgical attempt was the most effective in terms of achieving long term control (Hershey et al. 2000). While this has not been well established in more recent studies, prospective treatment planning remains vital prior to determining a definitive approach to treatment. Advanced imaging with both pre and post contrast studies (CT or magnetic resonance imaging (MRI)) is strongly recommended prior to determining optimal treatment as it has been shown that palpation vastly underestimates the true extent of the tumour (Ferrari et al. 2015). CT in particular can be used for surgical or radiation therapy planning and can provide a reasonable estimate as to whether or not surgery alone is likely to be successful or if multimodality therapy is more appropriate (Figure 1). It is also important to recognize that microchips may be associated with imaging artefact, particularly on MRI thus knowledge about the presence and location of a microchip is beneficial (SAITO et al. 2010).

TREATMENT AND PROGNOSIS

Prior to commencing treatment, as per the VASFSTF guidelines, it would be advisable to consult a veterinary oncologist for advice on the most up to date treatment recommendations based on the current literature (Box 2). Additionally, it has been demonstrated that there is a significant improvement in disease-free interval (DFI) when a complete first excision is performed at a referral institution compared to excision with a referring veterinary surgeon (274 days versus 66 days) (Hershey et al. 2000).

FISS should be treated both promptly and aggressively for the best long-term

1 outcome. Wide, en-bloc surgical excision, with a margin of 5cm of macroscopically
2 healthy tissue and two fascial planes deep which therefore may include partial
3 scapulectomy, hemipelvectomy or osteotomy of spinous processes, is the surgical
4 treatment of choice (Phelps et al. 2011). Histopathologic assessment is important to
5 confirm the diagnosis of FISS and to assess the margins; clean surgical margins do
6 not guarantee long-term survival and approximately 20-30% of tumours that are
7 cleanly excised will have recurrence (Romanelli et al. 2008; Cronin et al. 1998;
8 McEntee & Page 2001; Phelps et al. 2011; Kobayashi et al. 2002). However, it is
9 likely that surgical success rate is improved if complete radical surgical excision is
10 achieved at the first surgery whereas recurrence is higher if clean margins are not
11 achieved (Giudice et al. 2010). Notably, following wide en bloc excision, a recurrence
12 rate of 14% was documented in a series of cats (Phelps et al. 2011), although this may
13 reflect a number of temporal changes, such as surgical dose, surgeon experience,
14 initial size of the tumour at diagnosis, and histopathology evaluation. Current
15 vaccination guidelines stress the importance of vaccinating as distally as possible on a
16 limb (below the elbow or stifle) or tail so that if a tumour develops, high amputation,
17 potentially involving scapular or femoral disarticulation may have a higher likelihood
18 of achieving complete margins (Hartmann et al. 2015; Shaw et al. 2009). While
19 radical surgery is currently pursued by many veterinary oncologic surgeons, smaller,
20 more conservative surgeries are frequently performed. The optimal surgical approach
21 will vary with each patient and concise guidelines for all cats are not currently
22 available. Less is known about more conservative approaches, as there has been a
23 strong desire to achieve complete margins on histopathology. Additional knowledge
24 of outcome and surgical dose and approach is still being garnered and may contribute
25 to future recommendations regarding treatment.

1 Whilst surgery alone for some tumours may provide long term control, the
2 majority of FISS occurring in the interscapular region are difficult to control with
3 surgery alone and many require a combination of radiation therapy and surgery to
4 decrease the incidence and time to recurrence (Kobayashi et al. 2002; Cronin et al.
5 1998; Eckstein et al. 2009). Prospective treatment planning is vital and typically
6 involves an oncologist, radiation oncologist and surgeon. Radiation therapy can be
7 prescribed preoperatively or postoperatively, depending on the clinical scenario and
8 planned approach. Preoperative radiation therapy attempts to sterilise the margins of
9 bulky disease in order to decrease the likelihood of tumour recurrence. The benefit of
10 preoperative approaches is that a smaller treatment field is typically treated and a
11 lower overall dose can be utilised, thus may be more tolerable for the cat (Figure 2).
12 Alternatively, postoperative radiation therapy attempts to kill residual tumour cells
13 following surgery but typically requires that a larger volume of normal tissue is
14 included in the irradiated field to a higher overall dose. Both preoperative and
15 postoperative radiation therapy are associated with similar outcomes and delay the
16 time to tumour recurrence (Eckstein et al. 2009; Cronin et al. 1998; Romanelli et al.
17 2008; Bregazzi et al. 2001; Kobayashi et al. 2002). Currently there is insufficient
18 evidence in the literature to assess the role of adjunctive chemotherapy in definitive
19 treatment, however chemotherapy (often anthracycline-based) is currently considered
20 to be potentially useful when postoperative radiation therapy is not available (Poirier
21 et al. 2002; Bray & Polton 2014). More advanced radiation therapy equipment and
22 planning software that allow for intensity modulated radiation therapy (IMRT) or
23 stereotactic radiation therapy (SRT) may improve the ability of radiation to target
24 tumour volumes while sparing normal tissue, thus placing more importance on the
25 role of radiation in cats with tumours not amenable to surgery alone (Nolan et al.

1 2013).

2 A number of palliative options exist for cats with advanced injection site
3 sarcomas where definitive treatment is not possible. Chemotherapy or palliative
4 radiation therapy can be used as single modalities or as part of a multimodality
5 approach. Chemotherapy drugs (Barber et al. 2014; Poirier et al. 2002; Saba et al.
6 2012; Kobayashi et al. 2002) such as doxorubicin alone or in combination with
7 cyclophosphamide and CCNU have shown responses in the gross disease setting
8 although other drugs may be tried as well given the undefined role of chemotherapy.
9 Palliative intent radiation therapy, in which large doses of radiation are used
10 infrequently, may improve quality of life and offer temporary tumour control in many
11 cases (Nolan et al. 2013; Eckstein et al. 2009). Medical management with analgesia is
12 also important as tumours can cause significant pain as they grow and invade normal
13 structures.

14 **NOVEL THERAPIES**

15 As many injection site sarcomas recur in cats despite multimodality approaches, it is
16 clear that novel treatment options are needed. FISS has been shown to express a
17 number of dysregulated growth factor receptors, including the tyrosine kinase
18 receptor platelet derived growth factor receptor (PDGFR), making this an attractive
19 target. Initial in-vivo preclinical work investigating imatinib and masitinib
20 demonstrate inhibition of PDGFR signalling, have shown some beneficial effects but
21 require additional investigation to validate their clinical benefit and to determine their
22 role in definitive management (Katayama et al. 2004; Lawrence et al. 2012; Turek et
23 al. 2014; Holtermann et al. 2016).

24 There is interest in the use of immunotherapy following approval of a

1 recombinant feline IL-2 vaccine in Europe (conditional licensure in the USA) for the
2 treatment of FISS in conjunction with surgery and radiation therapy (Jas et al. 2015;
3 Jahnke et al. 2007; Quintin-Colonna et al. 1996). IL-2 is a cytokine known to
4 stimulate an anti-tumour immune response and it is thought that it may upregulate
5 cytotoxic T lymphocyte and natural killer (NK) cell activity. Preliminary work with
6 the vaccine suggested that cats treated with recombinant feline IL-2 in conjunction
7 with surgery and brachytherapy had longer median time to recurrence compared to
8 cats treated with local therapy alone, however additional work should evaluate its
9 utility when conventional external beam radiation therapy is utilised (Jas et al. 2015).
10 As the recombinant feline IL-2 vaccine is administered intra-tumourally or via
11 subcutaneous injection at the surgery site, there is theoretical concern regarding the
12 use of an injection that induces inflammation in an 'FISS disposed' cat; further
13 studies will hopefully alleviate these concerns.

14 **PREVENTION**

15 While novel treatments are needed to improve long-term control of FISS, the most
16 important factor to decrease the impact FISS has on cats is prevention. In response to
17 the concern over the link between vaccination and FISS, several strong
18 recommendations have been published regarding frequency and site of vaccination in
19 cats (box 3). The World Small Animal Veterinary Association (WSAVA) and the
20 American Association of Feline Practitioners (AAFP) recommend vaccination of
21 feline herpes virus (FHV), feline calicivirus (FCV) and feline panleukopenia virus
22 (FPV) at an interval of 3 years and vaccination against feline leukaemia virus (FeLV)
23 at a yearly interval only if that particular cat is at risk on contracting FeLV (Day et al.
24 2010; Richards et al. 2006). Therefore an indoor cat with a very low chance of

1 exposure to FeLV does not require or benefit from this vaccine. The European
2 Advisory Board on Cat Diseases (ABCD) advises FeLV vaccination every 2-3 years
3 in cats over 3-4 years old. Guidelines published by the ABCD and the AAFP
4 recommend rabies vaccination in the right hindlimb and FeLV in the left hindlimb
5 while all other vaccinations should be given in the right foreleg; vaccinations should
6 be administered distal to the elbows and stifles (Hartmann et al. 2015; Richards et al.
7 2006) (Figure 3). Of particular importance, all guidelines recommend avoidance of
8 the interscapular region of any injections. To date, vaccinations are still recommended
9 while considering the risk of disease in each cat although one may muse that
10 discontinuing vaccinations may be the most effective means of prevention.

11 To assess the effectiveness of this guidance, a study within the USA
12 comparing vaccine location and incidence of FISS, before and after the VAFSTF
13 guidance was published in 1996. Results were encouraging despite the fact that the
14 highest incidence of FISS remained in the interscapular region, as there was a
15 significant decrease in the incidence of interscapular FISS from 53% to 40% and a
16 significant increase in the incidence of FISS in the right thoracic limb from 1% to
17 10% (Shaw et al. 2009), indicating a shift in vaccine practices. A study by Dean et al
18 (2012) evaluated vaccine protocols used by UK veterinarians and found that despite
19 published guidelines, most UK practices vaccinate for FHV, FPV, FCV and FeLV
20 annually, most commonly in the interscapular region. Although distal limb can be a
21 difficult site to vaccinate, a recent study suggested that cats not only tolerate
22 vaccination in both locations, but also that the tail may represent an alternative site to
23 the distal limb (Hendricks et al. 2014).

24 In addition to adherence to vaccine locations, efforts should be made to

1 facilitate early detection and reduce inflammation at the injection site. All clients
2 should be educated at the time of vaccination on post vaccinal nodules and how to
3 monitor the injection site. Intramuscular vaccination should be avoided if possible, as
4 tumours that develop within muscle are more difficult to detect. Administration of a
5 cold vaccine has been associated with higher risk of FISS (Kass et al. 2003),
6 therefore, while vaccines need to be kept refrigerated to maintain efficacy,
7 consideration should be given to taking feline vaccines out of the fridge 15 minutes
8 before administration. (Hartmann et al. 2015). Finally, although any vaccine can
9 induce inflammation that may led to malignant transformation, non-adjuvanted
10 vaccines, modified-live or recombinant vaccines, and/or those vaccines that provide
11 prolonged immunity should be preferred over adjuvanted, killed, or short-acting
12 vaccines. In an effort to reduce the number of vaccinations each cat receives in its
13 lifetime, there is an argument to consider antibody titre measurement in order to
14 assess the immune status of each individual cat prior to vaccination but this is not
15 currently considered standard practice.

16 **CONCLUSIONS**

17 It is now known that vaccination of cats, once thought to be associated with little or
18 no risk, is not without significant risk. Development of invasive injection-site
19 sarcomas is arguably the most serious of the reported adverse reactions in cats, despite
20 its relatively low incidence. While we as veterinarians and veterinary nurses must
21 continue to protect cats against life limiting, preventable conditions with vaccination,
22 the vaccination protocol for each individual patient should be carefully thought
23 through from a holistic viewpoint, rather than a routine procedure. Administration of
24 any irritant injection such as a vaccination or other injectable substance should be
25 performed only if deemed necessary and as infrequently as possible, seeking oral

1 alternatives where available. When vaccines or other injections are administered, the
2 interscapular area should be avoided. It appears that there may be resistance to
3 published vaccine guidelines in the UK but it is unclear if this observation is uniform
4 across the UK, if it is due to lack of awareness of these guidelines or if the guidelines
5 are viewed as impractical.

6 There is an array of vaccination recommendations available to practitioners,
7 not limited to the originally published VAFSTS guidelines. These include those by
8 the World Small Animal Veterinary Association (WSAVA), the American
9 Association of Feline Practitioners (AAFP), the European Advisory Board on Cat
10 Diseases (ABCD), in addition to the vaccine manufacturer's datasheets published in
11 the National Office of Animal Health compendium (NOAH, 2016). These guidelines
12 all differ slightly from each other and as yet there is no cohesive conclusions or
13 standardized approach regarding frequency, type and location of vaccination. For
14 example, the AAFP recommend that FeLV vaccination should be repeated at intervals
15 depending on an individual cat's risk (Richards et al. 2006). The WSAVA
16 recommend this vaccination should be repeated not more than every three years but
17 only if there is a sustained risk of exposure (Day et al. 2010), whilst the ABCD
18 recommends that cats over the age 3-4 years, should be re-vaccinated at a 2-3 year
19 interval (Dean et al. 2012; Hartmann et al. 2015). On the other hand, data sheet
20 recommendations produced by vaccination manufacturers for the majority of FeLV
21 vaccinations available in the UK (NOAH, 2016) advise yearly re-vaccination. A
22 survey analysing vaccine practices by UK veterinarians (Dean et al. 2012) showed
23 that 84% of practices routinely gave FeLV vaccination annually, 1% every 2 years
24 and no practices reported that their standard policy was to repeat FeLV vaccination
25 every three years. The remainder of the practices surveyed decided on vaccination

1 frequency on an individual cat basis. Arguably, practitioners may be more inclined to
2 follow manufacturer data sheet recommendations rather than other guidelines,
3 particularly as these guidelines do not have unified conclusions and therefore perhaps
4 come across as confusing. Gentle reminders to carry out thoughtful vaccination
5 practices that include routine monitoring of post vaccinal nodules, as well as to
6 intervene and consider referral early may help reduce the impact that injection site
7 sarcomas have on cats in the UK.

8

9 **KEY POINTS**

- 10 1. Vaccine practices with specific attention to the location and frequency of
11 vaccines should be carefully considered and protocols determined based on the
12 cat's individual risk.
- 13 2. Careful monitoring of vaccination sites and client education should be
14 routinely performed in practice.
- 15 3. Early intervention and adequate local control of the disease is important to
16 treatment outcome.

17

18

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1 **FIGURE LEGENDS**

2 Figure 1: CT images illustrating the infiltrative nature of injection site sarcoma.
3 (A) represents a rapidly growing, deeply invasive sarcoma that developed in the
4 interscapular region. Note the proximity to critical structures such as the heart
5 and lung. (B) represents a tumour located on the proximal hindlimb but due to
6 its size and proximal location, amputation without hemipelvectomy would not
7 achieve good control.

8

9 Figure 2: Sagittal (A) and axial (B) CT images used for radiation treatment
10 planning with dose colour wash displayed. Radiation dose is represented by
11 various colours with red indicating the prescribed dose of radiation, with a
12 transition to yellow, green and blue as radiation dose diminishes. Note the
13 excessively large size of the infiltrative tumour and the normal structures (spinal
14 cord, lungs) that are irradiated due to their proximity to the tumour volume. Cats
15 with extensive disease such as this may benefit from preoperative radiation
16 therapy in order to reduce the overall radiation dose to normal tissues.

17

18 Figure 3: Recommended vaccination locations for common feline vaccines based
19 on AAFP and ABCD guidelines.

Figure 1 A

Figure 1 B

Figure 2 A

Figure 2 B

Figure 3