3. STUDIES OF CANCER IN ANIMALS SEEN IN VETERINARY PRACTICE

3.1 Dogs

3.1.1 *Case reports*

Case reports in the veterinary literature describing malignant tumours at the site of metallic implants and miscellaneous non-metallic foreign bodies in dogs are summarized in Table 37. Sarcomas developed after metallic implants or deposition of other foreign bodies. The time lapse from implantation to sarcoma development was reported in 48 individual cases and ranged from one to fifteen years, with an average of approximately six years. The orthopaedic devices included pins, nails, plates and wires or combinations of these materials. Sarcomas developing adjacent to implants were most commonly found in the diaphyses of long bones (approximately 85%) in large breed dogs; about half occurred in the femur. The male:female ratio was 1.8:1. Non-metallic and miscellaneous foreign bodies included a surgical sponge, a pacemaker, glass and a total hip prosthesis. The sarcomas most commonly reported to develop at sites of implantation of foreign objects were osteosarcoma, chondrosarcoma, fibrosarcoma and undifferentiated sarcoma.

3.1.2 *Analytical studies*

Li *et al.* (1993) reported a case–control study that assessed the relationship between metallic implants used to stabilize fractures in dogs and the development of cancer in the canine population. The cases consisted of 222 dogs with tumours of any kind, preceded by fractures and fixation. The controls consisted of 1635 dogs who had a fracture and fixation for fracture without later development of tumours. The analysis considered the type of fixation, i.e., internal (implanted methods of fixation) versus external (casts). Information on the type of internal fixation was not available. In a multivariate analysis (controlling for sex, age, body weight and infection), the odds ratio for internal versus external fixation was 0.6 (95% CI, 0.4–0.8) for bone tumours and 2.2 (95% CI not reported) for soft-tissue tumours. No significant association was found between the type of fixation and the development of bone and soft-tissue tumours. [The Working Group noted that 400 potentially eligible cases and 1315 potentially eligible controls had been excluded from the analysis due to lack of information on the operative procedures.]

3.2 Cats

3.2.1 *Case reports*

Individual case reports of vaccination-site sarcomas in cats are summarized in Table 38.

Table 37. Case reports of sarcomas in dogs associated with metallic implants and miscellaneous foreign bodies

Reference	Device	Implantation age (years)	Site	Diagnostic interval (years)
Fracture-associated fixation				
Banks *et al.* (1975)	Plate	1	Radius	3.5
	Pin	2	Tibia	6
Harrison *et al.* (1976)	Pin	1	Humerus	11
	Plate	6	Tibia	5.5
Sinibaldi *et al.* (1976)	Pin	8	Radius	6
	Pin	4.5	Femur	2.5
	Pin	10	Humerus	1
	Pin	NR	Femur	4
	Pin	NR	Femur	NR
	NR	2	Femur	4
	Plate	0.7	Femur	4
Madewell *et al.* (1977)	Pin	7	Femur	11
Knecht & Priester (1978)	Splint	NR	Humerus	NR
	Pin	NR	Humerus	NR
	Pin	NR	Humerus	NR
	None	NR	Humerus	NR
	Splint	NR	Femur	NR
	Pin	NR	Femur	NR
	Pin	NR	Femur	NR
	Nail	NR	Femur	NR
	Pin	NR	Femur	NR
	NR	NR	Femur	NR
	Cast	NR	Tibia	NR
	Pin	NR	Tibia	NR
Bennett *et al.* (1979)	Plate	1	Tibia	12
Brunnberg *et al.* (1980)	Plate	4	Humerus	4
	Nail	0.7	Tibia	7
	Wire	2	Humerus	7
Van Bree *et al.* (1980)	Nail	0.7	Humerus	5
Stevenson *et al.* (1982)	Plate/screw	0.9	Femur	8.5
	Plate/screw	0.5	Femur	6
	Plate/screw	2.5	Tibia	3.5
	Plate/screw	0.8	Tibia	4
	Plate/screw	0.7	Femur	6
	Plate/screw	2.5	Femur	3.8
	Plate/screw	1.2	Radius and ulna	6.8

Table 37 (contd)

Reference	Device	Implantation age (years)	Site	Diagnostic interval (years)
Golubyeva & Mitin (1984)	Pin	6	Humerus	3
Stevenson (1991)	Pin/wire	1	Femur	7
	Plate/screw	4	Tibia	3
	Plate/screw	1	Femur	5
	Pin	< 1	Femur	7
	Plate/screw	< 1	Tibia	8.3
	Plate/screw	NR	Tibia	< 4
	Plate/screw	NR	Tibia	1
	Screw	1	Humerus	10
	Plate/screw	NR	Femur	NR
	Wire	1.5	Femur	6
	Plate/screw	4	Humerus	6
	Lag screw	0.7	Tibia	7
	+ plate	7	Radius and ulna	3
	Plate	1	Carpus	9
	Plate/pins	1.5	Femur	7
	Plate	0.5	Femur	6.5
	Pin/wire	2	Femur	7
	Plate	0.3	Femur	8.5
	NR	3	Humerus	4
	Plate/wire	1	Radius	10
	Plate/pin	1	Femur	15
	Plate/screw			
Non-metallic and miscellaneous foreign bodies				
Pardo *et al.* (1990)	Sponge	1	Jejunal	6
Rowland *et al.* (1991)	Pacemaker	15	Subcutaneous	0.7
McCarthy *et al.* (1996)	Glass	1	Subcutaneous	10
Murphy *et al.* (1997)	Total hip	2	Femur	7

NR, not reported

Table 38. Case reports of vaccination-site sarcomas in cats

Reference	Tumour site	Lag time (years)	Vaccine	Histological type
Dubielzig *et al.* (1993)	Thigh	0.3	Rabies	Fibrosarcoma
Esplin & Campbell (1995)	Interscapular	2	FeLV	Fibrosarcoma
Esplin *et al.* (1996)	Interscapular	0.5	FeLV	Liposarcoma
Rudmann *et al.* (1996)	Interscapular	1.1	Rabies FeLV	Fibrosarcoma
Sandler *et al.* (1997)	Flank	Not reported	Rabies	Fibrosarcoma
Briscoe *et al*. (1998)	Interscapular	1	Rabies	Fibrosarcoma

3.2.2 *Case series*

A temporal relationship between previous vaccination and subsequent development of sarcomas at vaccination sites in cats has been reported. A 61% increase was noted in the number of fibrosarcomas in feline biopsy accessions from 1987 to 1991 at the University of Pennsylvania School of Veterinary Medicine and corresponded to the introduction of two vaccines for feline leukaemia and rabies containing adjuvant in the late 1980s in the United States. These fibrosarcomas occured primarily at sites of previous vaccination. A 25% increase in fibrosarcomas in cats was reported in a large veterinary diagnostic laboratory in the western United States during the same five-year period. Vaccination-site tumours were sarcomas of various subtypes, fibrosarcoma being the most commonly reported. Vaccination-site sarcomas were differentiated from non-vaccination-site sarcomas by their higher mitotic rate, pleomorphism, presence of inflammation, subcutaneous location and the presence of macrophages that contained foreign material identical to that previously described in post-vaccinial inflammatory site reactions. The substance in the macrophages is thought to be vaccine adjuvant and one study has identified it as containing aluminium in some clinical cases (Hendrick *et al.*, 1992, 1994).

Although most studies have implicated feline leukaemia virus (FeLV) vaccines and rabies vaccines (Hendrick *et al.*, 1992; Kass *et al.*, 1993; Coyne *et al.*, 1997), no single vaccine has been singled out or excluded from suspicion. All FeLV and rabies vaccines used are killed viral products, and most, but not all, contain adjuvants. FeLV and rabies vaccines with both aluminium or non-aluminium adjuvants have been associated with vaccination-site sarcomas (Kass *et al.*, 1993; Hendrick *et al.*, 1994).

Only one study has reported a vaccine other than FeLV or rabies to be associated with vaccination-site sarcoma (Lester *et al.*, 1996). In this study, 18 cases of vaccination site sarcomas were reported in association with the use of a killed panleukopenia vaccine containing adjuvant.

Adjuvants are rarely used with vaccines other than FeLV and rabies. Tumorigenesis is thought to result from a profound inflammatory response to a localized high concentration of adjuvant and vaccine antigen. This hypothesis is supported by the observation

that, in some clinical cases, 'transitional' microscopic foci of sarcoma have been found in areas of granulomatous inflammation similar to those observed in sarcomas that develop in the eyes of cats following persistent or previous trauma (Hendrick *et al.*, 1992).

In a series of cases reported by Kass *et al.* (1993), the median time from previous vaccination to sarcoma development in cats was 340 days, with a range of three months to 3.5 years. The risk for sarcoma development increased with the number of vaccines given at an individual site. The prevalence of vaccine-associated sarcomas has been reported to be between one and 3.6 cases per 10 000 cats for FeLV and rabies vaccine (Coyne *et al.*, 1997) and 13 per 10 000 for a killed panleukopenia vaccine containing adjuvant (Lester *et al.*, 1996).

A summary of the 652 cases reported in five case series is presented in Table 39.

Table 39. Case series of vaccination-site sarcomas in cats

Reference	No. of cases	Site
Hendrick *et al.* (1992)	222	Interscapular/thigh
Lester *et al.* (1996)	18	Interscapular
Kass *et al.* (1993)	185	Interscapular/thigh
Coyne *et al.* (1997)	158	Interscapular/thigh
Hendrick *et al.* (1994)	69	Interscapular/thigh

3.2.3 *Analytical studies*

Kass *et al.* (1993) performed a retrospective study involving 345 cats with fibrosarcoma diagnosed between January 1991 and May 1992. Cats with fibrosarcomas developing at body locations where vaccines are typically administered (n = 185) were compared with controls (n = 160) having fibrosarcomas at locations not typically used for vaccination. In cats receiving FeLV vaccination within two years before tumorigenesis, the time between vaccination and tumour development was significantly shorter for tumours developing at sites where vaccines are typically administered than for tumours at other sites. Univariate analysis, adjusting for age, revealed associations between FeLV vaccination (odds ratio, 2.8; 95% CI, 1.5–5.2), rabies vaccination at the interscapular space (odds ratio, 2.1; 95% CI, 1.0–4.3) and rabies vaccination at the femoral region (odds ratio, 1.8; 95% CI, 0.7–5.1) with fibrosarcoma development at the vaccination site within one year of vaccination. The risk of cats developing fibrosarcoma from a single vaccination in the interscapular region was almost 50% higher than in cats not receiving vaccines at that site; the risk in cats with two vaccinations was 127% higher and the risk with three or four vaccinations was approximately 175% higher.