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Retrospective study of canine cutaneous tumors in Japan, 2008–2017

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ABSTRACT. Cutaneous tumors are commonly found in dogs. To date, few studies have investigated the epidemiology of canine cutaneous tumors in Asian countries. The present study aims to report the prevalence of canine cutaneous tumors in Japan, and assess the association of breed, age, sex, and anatomical locations with the development of common tumor types. A total of 1,435 cases of cutaneous tumors were examined, of which 813 (56.66%) cases were malignant, and 622 (43.34%) were benign. Soft tissue sarcomas (18.40%), mast cell tumor (16.24%), lipoma (9.69%), hair follicle tumors (9.34%), and benign sebaceous tumors (8.50%) outnumbered the other tumor types. Tumors were commonly found on the head (13.87%), hindlimb (10.52%), forelimb (8.01%), chest (5.78%), and neck (5.57%). The risk of developing cutaneous tumors increased significantly in dogs aged 11-year and above ($P<0.001$). Mixed-breed dogs (14.63%), Miniature Dachshund (9.90%), and Labrador Retriever (8.01%) were the three most presented breeds; while Boxer, Bernese Mountain Dog, and Golden Retriever had an increased risk of cutaneous tumor development in comparison to mixed-breed dogs ($P<0.05$). Epidemiological information from the present study will serve as a useful reference for regional veterinarians to establish a preliminary diagnosis of canine cutaneous tumors.

KEY WORDS: anatomic location, breed, cutaneous, dog, skin tumor

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Cutaneous tumors, comprising a heterogeneous group of benign and malignant neoplasms, are commonly found in dogs [6, 11, 16, 17, 25]. Several retrospective studies have been conducted to investigate the epidemiology of canine cutaneous tumors [6, 9, 16, 28, 37]. These studies varied in terms of data collection, study population, sample size, inclusion criteria, geographical region, and results analysis. Some studies calculated the tumor incidence based on population data from the national canine cancer registries and veterinary authorities [6, 16]. Others utilized information from diagnostic laboratories and reported the relative frequency of skin tumors [9, 28, 37]. Despite the differences in data collection methods and study population, these studies shared a common aim to elucidate cutaneous tumors' frequency, along with their distribution in relation to breed, age, sex, and anatomical location, in a specific geographical region. Interestingly, several cutaneous tumor types, namely mast cell tumor, lipoma, histiocytoma, and soft tissue sarcomas (*i.e.*, perivascular wall tumor), were consistently overrepresented in dogs, regardless of the differences between studies [6, 9, 16, 28, 37].

Epidemiological information on canine cutaneous tumors is limited in Asia [28, 33]. Studies conducted in Europe and the United States may not entirely reflect the incidence or prevalence of cutaneous tumors in Asian countries, where climates, breed preferences, breeding practices, and living conditions of pets vary significantly. The aims of this retrospective study were to (1) report the prevalence of canine cutaneous tumors in Japan; (2) characterize the breed, age, sex, and anatomical distributions of commonly diagnosed tumor types; and (3) assess the prevalence of cutaneous tumors in Japanese native dog breeds. A multinomial logistic regression model was also used to elucidate the influence of sex, breed, and age on the development of skin tumors. Epidemiological information generated from this study will serve as a useful reference for regional veterinarians to establish a preliminary diagnosis of canine cutaneous tumors.

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MATERIALS AND METHODS

Study population

From January 2008 to December 2017, tissue biopsies from 8,425 dogs were submitted to the Laboratory of Veterinary Pathology, The University of Tokyo for histopathological examination. Clinical details including breed, age, and sex were recorded. Crossbreed dogs were regarded as mixed breed. Surgical biopsies of canine cutaneous tumors diagnosed during the aforementioned time interval were identified from the laboratory database. Exclusion criteria include cases with more than one missing clinical information (*e.g.*, sex, age, breed or anatomical locations) and cases with a diagnosis of epithelial cyst, ceruminous gland tumor, mammary gland tumor, anal sac gland tumor, hepatoid gland tumor, and meibomian gland tumor. Modified sebaceous and apocrine gland tumors were excluded to focus on cutaneous tumors that may arise from any of the haired skin regions. Core biopsies were included when definitive diagnosis can be made. Hamartomas were included in the study. A tumor with multicentric development was regarded as a single tumor event. Simultaneous occurrence of different tumor types and tumor recurrence in one patient were considered multiple separate events [16]. Based on these criteria, 1,435 cases of canine cutaneous tumors and tumor-like lesions were included in the present retrospective analysis. The relative frequency (% of all cutaneous tumor types), prevalence rate (% of the total canine population in the database during the study period), and breed-specific prevalence of cutaneous tumors were calculated. An attempt was made to analyze the occurrence of cutaneous tumors in Japanese native dog breeds registered by the Nihon-ken Hozon-kai (http://www.nihonken-hozonkai.or.jp/), *i.e.*, Shiba Inu, Kishu Ken, Shikoku, Hokkaido, Kai Ken, and Akita. Anatomical locations were categorized as head, ear, neck, shoulder, axilla, chest, ventral abdomen, flank, back, groin, trunk, buttock, tail, forelimb, forefoot, hindlimb, hindfoot, perigenital area (female), perigenital area (male), multicentric, and skin not otherwise specified (NOS). Forelimb/hindlimb and forefoot/hindfoot were separately deemed with the latter indicating the extremity of the former. Anatomical location was recorded as multicentric when a particular tumor type developed in multiple cutaneous regions. The term "skin (NOS)" was used when the exact site of tumor development was not known.

Tumor diagnosis and classification

Cases were classified by 2 Japanese College of Veterinary Pathologists (JCVP) board-certified pathologists (J.K.C. and K.U.), according to the World Health Organization (WHO) International Histological Classification of Tumors of Domestic Animals and its recent updates [13, 14, 18, 19, 36]. Mast cell tumors, perivascular wall tumors, peripheral nerve sheath tumors, and anaplastic plasmacytomas were regarded as malignant tumors. Mast cell tumors were classified as cutaneous and subcutaneous types. Cutaneous mast cell tumors were graded according to the Kiupel's 2-tier grading system [21]. For cases exhibiting multicentric growth, the higher histologic grade was recorded. Special stainings (*e.g.*, toluidine blue for suspected mast cell tumor cases) and immunohistochemistry were performed as deemed necessary to confirm the histopathological diagnosis. Anaplastic plasmacytoma was distinguished from the indolent variant as the former tend to exhibit a higher degree of cellular and nuclear atypia, occasional multinucleated cells, and frequent mitoses. Multiple myeloma with cutaneous involvement was diagnosed in a dog, as supported by findings from complete blood count, serum biochemistry, bone marrow biopsy, and immunohistochemistry. Cases of lymphoma were classified into specific subtype when immunohistochemical information was available. Immunohistochemical markers used in tumor diagnosis and subtyping are detailed in Table 1. Metastatic carcinoma was diagnosed based on clinical history, diagnostic imaging (*i.e.*, radiography, ultrasonography, and/or computed tomography), and histological findings of both primary tumor and skin metastases.

Statistical analysis

To assess the influence of sex, age, and breed on the development of cutaneous tumors, multinomial logistic regression analysis, integrated with likelihood ratio test and Pearson's χ^2 test, was performed according to previous study [16], using IBM® SPSS® Statistics version 23 (IBM SPSS, Armonk, NY, U.S.A.). Dependent variable was defined as cutaneous tumor development (yes/no).

Table 1. Immunohistochemical markers used in the diagnosis and subclassification of specific tumor types

Tumor type	Immunohistochemical markers[a)]
Merkel cell carcinoma	Chromogranin A, CK20, and synaptophysin
Melanoma	S100
Plasmacytic tumors	IgG and lambda light chains
B-cell lymphoma	CD20
T-cell lymphoma	CD3
Langerhans cell histiocytosis	E-cadherin and Iba1
Histiocytosis and histiocytic sarcoma	HLA-DR and Iba1

CK, cytokeratin; Iba1, ionized calcium-binding adapter molecule 1; IgG, dog immunoglobulin G-heavy and light chain; pAb, polyclonal antibody. a) CD3 (pAb; Dako, Tokyo, Japan), CD20 (pAb; Biocare Medical, Concord, CA, U.S.A.), chromogranin A (pAb; Yanaihara Institute, Shizuoka, Japan), CK20 (clone Ks20.8; Dako), E-cadherin (clone 36/E-Cadherin; BD Biosciences, San Jose, CA, U.S.A.), HLA-DR (clone TAL 1B5; Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.), Iba1 (pAb; Wako, Osaka, Japan), IgG (pAb; Bethyl Laboratories, Montgomery, TX, U.S.A.), lambda light chains (pAb; Dako), synaptophysin (clone DAK-SYNAP; Dako), and S100 (pAb; Dako).

Factors were defined as sex (female, spayed female, male, and castrated male; reference=female), breed (reference=mixed breed), and age (reference=dogs aged 6 years). Six-year-old dogs were used as reference, as they belonged to the youngest age group with a sufficient number of cases to compare with others. Results were reported as odds ratios (OR) with its associated confidence interval (CI), and a *P*-value of less than 0.05 was considered to be significant. Dogs older than 16 years were not analyzed due to their low number (n=20) in the database.

RESULTS

Canine population in the database, 2008–2017

From 2008 to 2017, a total of 8,425 dogs, with a median age of 10 (range=0–19), were recorded in the archive. Female to male ratio was 1:1.01 (intact female 20.87%, spayed female 28.88%, intact male 26.14%, and castrated male 24.11%). The 10 most common breeds in the database were Miniature Dachshund (15.09%), mixed-breed dogs (9.10%), Toy Poodle (6.14%), Chihuahua (5.04%), Shih Tzu (5.03%), Labrador Retriever (4.27%), Golden Retriever (3.96%), Pembroke Welsh Corgi (3.88%), Beagle (3.77%), and Yorkshire Terrier (3.70%). The proportion of small and medium/large purebred dogs in the database was 74.38% and 25.62%, respectively.

Study population

During the 10-year study period, 1,435 cases from 1,214 dogs were diagnosed as cutaneous tumors. Two or more tumor types were diagnosed in 104 dogs. Median age of the affected dogs, at the time of diagnosis, was 10 (range=0–19, median=10). Four hundred and nine cases were collected from spayed female (28.50%), 397 cases (27.67%) from intact male, 352 cases (24.53%) from castrated male, and 277 cases (19.30%) from intact female, with a female to male ratio of 1:1.09. Among the 73 dog breeds presented with skin tumors, cases were commonly from the mixed-breed dogs (n=210; 14.63%), Miniature Dachshunds (n=142; 9.90%), Labrador Retrievers (n=115; 8.01%), Golden Retrievers (n=103; 7.18%), Shih Tzus (n=67; 4.67%), Toy Poodles (n=64; 4.46%), Shetland Sheepdogs (n=58; 4.04%), and American Cocker Spaniels (n=55; 3.83%), which accounts for 56.72% of the total cases. Small and medium/large breed dogs accounted for 61.22% and 38.78% of purebred dogs with cutaneous tumors, respectively.

Anatomical distributions of skin tumors

The 10 anatomical sites where cutaneous tumors frequently developed, and the corresponding five or six most commonly diagnosed tumor types were shown in Fig. 1. Skin tumors were mostly found on the head (n=199; 13.87%), hindlimb (n=151; 10.52%), forelimb (n=115; 8.01%), chest (n=83; 5.78%), and neck (n=80; 5.57%), with 80 or more cases being recorded in each body region. One hundred and seventy-six (12.26%) cutaneous tumor cases showed multicentric development.

Tumor types

The relative frequency and prevalence rate (calculated based on total canine population in the database, 2008–2017) of cutaneous tumors were shown in Table 2. Of the 1,435 cases, 813 (56.66%) cases were diagnosed as malignant, while 622 (43.34%) were benign. Soft tissue sarcomas (n=264; 18.40%) were most frequently diagnosed, followed by mast cell tumors (n=233; 16.24%), lipomas (n=139; 9.69%), benign hair follicle tumors (n=134; 9.34%), and benign sebaceous tumors (n=122; 8.50%). These tumors comprised 62.17% of total cutaneous tumor cases. The breed, age, and sex distributions of the 10 most commonly diagnosed tumor types are summarized in Table 3.

In the present study, soft tissue sarcomas consisted of fibrosarcomas, perivascular wall tumors, peripheral nerve sheath tumors, liposarcomas, and sarcomas NOS. This tumor group was often diagnosed in mixed-breed dogs (n=52; 19.70% of all affected breeds), Labrador Retrievers (n=28; 10.61%), and Golden Retrievers (n=22; 8.33%). A relatively high breed-specific prevalence (6.78%, 7.78%, and 6.59% in mixed-breed dogs, Labrador Retriever, and Golden Retriever, respectively) of soft tissue sarcomas was recorded in these breeds. Male dogs were more commonly presented (female to male ratio=1:1.47). Soft tissue sarcomas were mostly found on the forelimb (n=49; 18.56%) and hindlimb (n=46; 17.42%). Among the soft tissue sarcomas, perivascular wall tumors (n=120; 45.45% of all soft tissue sarcomas) were most common. The tumors were often found on the appendages (forelimb, n=30; hindlimb, n=29).

Mast cell tumor was the second most common tumor type. The tumors were categorized into cutaneous (n=197, 84.55% of all mast cell tumor cases) and subcutaneous types (15.45%). One hundred and thirty-two (67%) cutaneous mast cell tumor cases were diagnosed as low-grade, and 65 cases (33%) were high-grade. Mast cell tumors were often found on the hindlimb (n=36; 15.45%), and 37 (15.88%) cases were multicentric. Labrador Retrievers (n=30; 12.88% of all affected breeds; breed-specific prevalence=8.33%), mixed-breed dogs (n=29; 12.45%), and Pugs (n=22; 9.44%) were most commonly affected. In particular, Pugs were overrepresented, with a breed-specific prevalence of 15.07% (1.81- and 3.99-fold higher than that of Labrador Retriever and mixed-breed dogs, respectively). Most cutaneous mast cell tumors in Pugs were low-grade (n=11; 84.62%) and almost half of them (45.45%) were multicentric.

Lipoma and benign hair follicle tumors were the third and fourth most common tumor types, respectively. Lipomas were frequently presented on the chest (n=20; 14.39%) and had a relatively high tendency for multicentric growth (n=33; 23.74%). Benign hair follicle tumors consisted mainly of trichoblastomas (n=44; 32.84% of all benign hair follicle tumor cases), trichoepitheliomas (n=41; 30.60%), and infundibular keratinizing acanthomas (n=30; 22.39%). The tumors were commonly

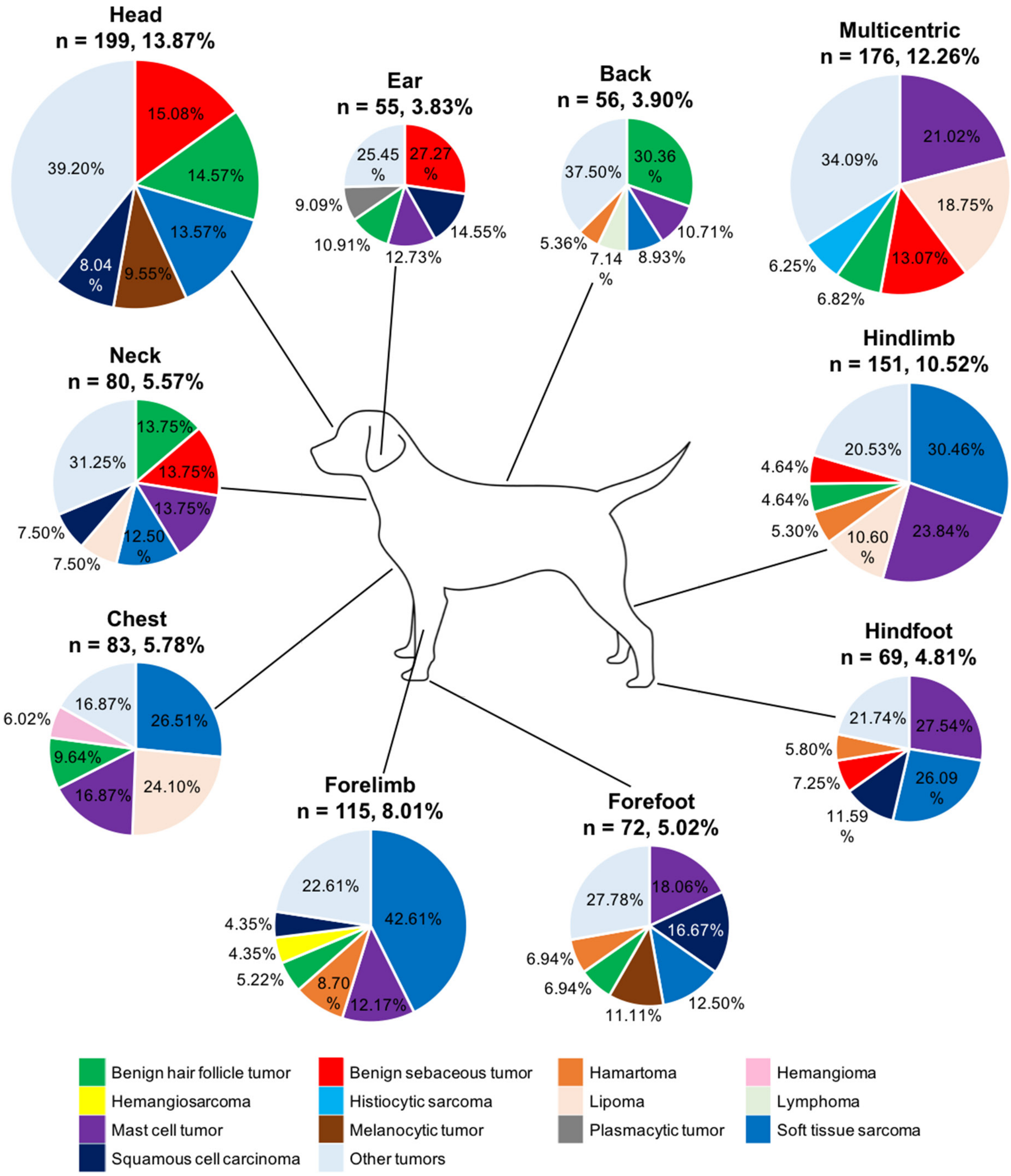

Fig. 1. Ten most common anatomical locations of canine cutaneous tumors (n=numbers of tumors) and the relative frequency (%) of the five or six most frequently encountered tumor types in each site.

presented in mixed-breed dogs (n=19; 14.18% of all affected breeds), Toy Poodles (n=16; 11.94%), and Shih Tzus (n=14; 10.45%). Benign hair follicle tumors were often found on the head (n=29; 21.64%), back of the body (n=17; 12.67%), and neck (n=11; 8.21%). In particular, trichoblastomas (n=23) were overrepresented on the head, comprising 79.31% of benign hair follicle tumors diagnosed in that region. Twelve cases of benign hair follicle tumor showed multicentric growth, of which 9 cases were diagnosed as trichoepithelioma. A higher proportion of multicentric trichoepithelioma cases (7 out of 9 cases) was found in Golden Retrievers. Malignant trichoepithelioma (n=7) was the only type of malignant hair follicle tumor in the present study.

Benign sebaceous tumors were often reported as sebaceous adenomas (n=63; 51.64% of all benign sebaceous tumors) and sebaceous epitheliomas (n=59; 48.36%). This tumor group was most often found in mixed-breed dogs (n=23; 18.85% of all affected breeds), American Cocker Spaniels (n=19; 15.57%), Miniature Dachshunds (n=16; 13.11%), and Shih Tzus (n=16; 13.11%). In particular, American Cocker Spaniel recorded a high breed-specific prevalence (9.41%). Tumors commonly occurred

Table 2. Histopathological diagnosis, relative frequency, and prevalence rate (total population=8,425 dogs) of the 1,435 canine skin tumors recorded in the database of the Laboratory of Veterinary Pathology, the University of Tokyo, 2008–2017

Diagnosis	No. of cases	Relative frequency (% of all skin tumors)	Prevalence rate (%)
Epithelial tumors	413	28.78	4.90
Epidermal tumors	89	6.20	1.06
Basal cell carcinoma	3	0.21	0.04
Papilloma	16	1.11	0.19
Pigmented viral plaque	3	0.21	0.04
Squamous cell carcinoma	67	4.67	0.80
Hair follicle tumors	141	9.83	1.67
Infundibular keratinizing acanthoma	30	2.09	0.36
Tricholemmoma	4	0.28	0.05
Trichoblastoma	44	3.07	0.52
Trichoepithelioma	41	2.86	0.49
Malignant trichoepithelioma	7	0.49	0.08
Pilomatricoma	15	1.05	0.18
Sebaceous gland tumors	128	8.92	1.52
Sebaceous adenoma	63	4.39	0.75
Sebaceous epithelioma	59	4.11	0.70
Sebaceous carcinoma	6	0.42	0.07
Apocrine gland tumors	42	2.93	0.50
Apocrine adenoma	18	1.25	0.21
Apocrine carcinoma	21	1.46	0.25
Cutaneous clear cell adnexal carcinoma	3	0.21	0.04
Epithelial tumors NOS	13	0.91	0.15
Adenocarcinoma (NOS)	3	0.21	0.04
Metastatic carcinoma	10	0.70	0.12
Neuroendocrine tumor	1	0.07	0.01
Merkel cell carcinoma	1	0.07	0.01
Melanocytic tumors	45	3.14	0.53
Melanocytoma	10	0.70	0.12
Melanoma	35	2.44	0.42
Mesenchymal tumors	513	35.75	6.09
Benign soft tissue tumors	142	9.90	1.69
Fibroma	3	0.21	0.04
Lipoma	139	9.69	1.65
Soft tissue sarcomas	264	18.40	3.13
Fibrosarcoma	33	2.30	0.39
Perivascular wall tumor	120	8.36	1.42
Peripheral nerve sheath tumor	33	2.30	0.39
Liposarcoma	22	1.53	0.26
Sarcoma NOS	56	3.90	0.66
Vascular tumors	96	6.69	1.14
Hemangioma	53	3.69	0.63
Lymphangioma	3	0.21	0.04
Hemangiosarcoma	32	2.23	0.38
Lymphangiosarcoma	8	0.56	0.09
Musculoskeletal tumors	11	0.77	0.13
Leiomyoma	5	0.35	0.06
Rhabdomyosarcoma	1	0.07	0.01
Osteosarcoma	5	0.35	0.06

on the head (n=30; 24.59%) and ear regions (n=15; 12.30%), and a higher proportion showed multicentric development (n=33; 27.05%). Sebaceous carcinomas were rarely encountered (n=6; 0.42% of all cutaneous tumors).

Squamous cell carcinoma (n=67; 4.67% of all cutaneous tumors), lymphoma (n=55; 3.83%), and plasmacytic tumor (n=41; 2.86%) were the sixth, eighth, and tenth most frequently encountered tumor types, respectively. Squamous cell carcinomas developed in mature to geriatric dogs (age range 6–16), with a higher tumor frequency being recorded in male dogs (female to male ratio=1:1.91). Lymphomas were subclassified into epitheliotropic T-cell lymphomas (n=17; 30.91% of all lymphoma cases),

Table 2. contitnued

Diagnosis	No. of cases	Relative frequency (% of all skin tumors)	Prevalence rate (%)
Hemolymphatic tumors	388	27.04	4.61
Mast cell tumors	233	16.24	2.77
Low grade	132	9.20	1.57
High grade	65	4.53	0.77
Subcutaneous	36	2.51	0.43
Plasmacytic tumors	41	2.86	0.49
Indolent plasmacytoma	18	1.25	0.21
Anaplastic plasmacytoma	22	1.53	0.26
Multiple myeloma	1	0.07	0.01
Lymphomas	55	3.83	0.65
Diffuse large B-cell lymphoma	1	0.07	0.01
Epitheliotropic T-cell lymphoma	17	1.18	0.20
Nonepitheliotropic T-cell lymphoma	14	0.98	0.17
Peripheral T-cell lymphoma NOS	6	0.42	0.07
Lymphoma NOS	17	1.18	0.20
Histioproliferative disorders	59	4.11	0.70
Histiocytoma	23	1.60	0.27
Langerhans cell histiocytosis	3	0.21	0.04
Histiocytosis	4	0.28	0.05
Histiocytic sarcoma	29	2.02	0.34
Hamartomas	75	5.23	0.89
Hamartoma	62	4.32	0.74
Acrochordon	13	0.91	0.15
Total	1,435	100.00	17.03

NOS, not otherwise specified.

nonepitheliotropic T-cell lymphomas (n=14; 25.45%), peripheral T-cell lymphomas NOS (n=6; 10.91%), and diffuse large B-cell lymphoma (n=1; 1.82%), based on their immunophenotype, epidermal involvement (epitheliotropic versus nonepitheliotropic), and inflammatory cell infiltration. Seventeen lymphoma cases (30.91% of all lymphomas) were not classified into specific subtype. Lymphomas commonly developed on the head (n=13; 23.64%) or presented as multicentric lesions (n=14; 25.45%). Epitheliotropic T-cell lymphomas contributed to half of the cases with multicentric lesions. Plasmacytic tumors (n=41; 2.86%) included indolent plasmacytomas (n=18; 43.90% of all plasmacytic tumors), anaplastic plasmacytomas (n=22; 53.66%), and multiple myeloma (n=1; 2.44%). Plasmacytic tumors were most frequently found in American Cocker Spaniels (n=6; 14.63% of all affected breeds; breed specific prevalence=2.97%). Male dogs were more commonly affected than females (female to male ratio=1:1.73), and the anaplastic type had a tendency for multicentric development (n=6; 75% of all plasmacytic tumors with multicentric growth).

Other less common tumor types included melanoma (n=35; 2.44% of all cutaneous tumors), hemangiosarcoma (n=32; 2.23%), histiocytic sarcoma (n=29; 2.02%), and metastatic carcinoma (n=10; 0.70%). Multicentric development was detected in 11 cases of histiocytic sarcoma and 3 cases of metastatic carcinoma. Histiocytic sarcomas were overrepresented in large breed dogs (n=22; 75.86% of all histiocytic sarcoma cases), *i.e.*, Flat-coated Retrievers (n=6; 27.27%; breed-specific prevalence=13.33%), Bernese Mountain Dogs (n=6; 27.27% of histiocytic sarcoma cases in large breed dogs; breed-specific prevalence=7.41%), Golden Retrievers (n=6, 27.27%; breed-specific prevalence=1.80%), and Labrador Retrievers (n=4; 18.18%; breed-specific prevalence=1.11%). In Flat-Coated Retrievers, 83.33% (n=5) of the histiocytic sarcoma cases showed multicentric development. The primary site of 6 metastatic carcinoma cases was confirmed namely the lung (n=3; 30% of all cutaneous metastases), mammary gland (n=2; 20%), and kidney (n=1; 10%). A case of Merkel cell carcinoma and three cases of Langerhans cell histiocytosis were diagnosed with the aid of immunohistochemistry. Merkel cell carcinoma was presented in a 6-year-old female Boxer which developed multicentric growth on the skin. On the other hand, Langerhans cell histiocytosis was found in French Bulldogs (n=2; multicentric tumor growth) and Italian Greyhound (n=1; back of the body), and all three cases were diagnosed at 5 years of age.

Prevalence of cutaneous tumors in dog breeds native to Japan

Five Japanese native dog breeds were recorded in the database, including Shiba Inu (n=311), Kishu Ken, Shikoku, Kai Ken, and Akita. With exception to Shiba Inu, the number of each native breed in the database were less than 25. The breeds presented with cutaneous tumors included Shiba Inu (n=53; 96.36% of all affected native dog breeds), Shikoku (n=1; 1.82%), and Kai Ken (n=1; 1.82%). Owing to the low number of cutaneous tumor cases in most native breeds, the study was focused on Shiba Inu. In this breed, cutaneous tumors were detected in animals aged between 4 and 19 years old (median age=12). The most commonly encountered tumor types were mast cell tumor (n=11; breed-specific prevalence=3.54%), soft tissue sarcomas (n=9, 2.89%), lipoma

Table 3. Breed, age, and female to male ratio of the 10 most common skin tumor types

Tumor type (n=number of cases)	3 most commonly affected breeds				Age	Female to male ratio
	Breed	n	% of all affected breeds	Prevalence within breed, %		
Soft tissue sarcoma (n=264)	Mix	52	19.70	6.78	Range=0–17	1:1.47
	Labrador Retriever	28	10.61	7.78	Median=11	
	Golden Retriever	22	8.33	6.59	Mode=11	
Mast cell tumor (n=233)	Labrador Retriever	30	12.88	8.33	Range=2–15	1:0.70
	Mix	29	12.45	3.78	Median=10	
	Pug	22	9.44	15.07	Mode=9	
Lipoma (n=139)	Mix	25	17.99	3.26	Range=1–15	1:0.99
	Miniature Dachshund	22	15.83	1.73	Median=10	
	Labrador Retriever	16	11.51	4.44	Mode=9	
Benign hair follicle tumor (n=134)	Mix	19	14.18	2.48	Range=1–16	1:0.91
	Toy Poodle	16	11.94	3.09	Median=9	
	Shih Tzu	14	10.45	3.30	Mode=9	
Benign sebaceous tumor (n=122)	Mix	23	18.85	3.00	Range=2–19	1:1.14
	American Cocker Spaniel	19	15.57	9.41	Median=12	
	Miniature Dachshund	16	13.11	1.26	Mode=14	
	Shih Tzu	16	13.11	3.77		
Squamous cell carcinoma (n=67)	Mix	12	17.91	1.56	Range=6–16	1:1.91
	Labrador Retriever	8	11.94	2.22	Median=11	
	Golden Retriever	7	10.45	2.10	Mode=13	
Hamartoma (n=62)	Mix	9	14.52	1.17	Range=1–19	1:1.21
	Labrador Retriever	8	12.90	2.22	Median=11	
	Miniature Dachshund	6	9.68	0.47	Mode=11	
Lymphoma (n=55)	Miniature Dachshund	11	20.00	0.87	Range=3–16	1:1.20
	Golden Retriever	7	12.73	2.10	Median=11	
	Mix	5	9.09	0.65	Mode=12	
Hemangioma (n=52)	Miniature Dachshund	10	19.23	0.79	Range=3–16	1:1.17
	Mix	7	13.46	0.91	Median=11	
	Golden Retriever	5	9.62	1.50	Mode=12	
Plasmacytic tumor (n=41)	American Cocker Spaniel	6	14.63	2.97	Range=2–15	1:1.73
	Mix	5	12.20	0.65	Median=11	
	French Bulldog	4	9.76	1.53	Mode=11	
	Jack Russell Terrier	4	9.76	2.60		

(n=8; 2.57%), and benign hair follicle tumors (n=5; 1.61%). These four tumor types accounted for 62.26% of the total cutaneous tumor cases in Shiba Inus.

Multinomial logistic regression analysis: The influence of sex, age, and breed on the development of cutaneous tumors

Results of the analysis were presented in Table 4. There was no association between sex and cutaneous tumor development. In general, the risk of developing skin tumors increased in dogs aged 9-year-old and above (9-year-old, $P<0.05$; 11- to 16-year-old, $P<0.001$; reference age=6 years). Leonberger, Miniature Poodle, Polish Lowland Sheepdog, Boxer, Bernese Mountain Dog, and Golden Retriever had significantly increased risk of tumor development in comparison to mixed-breed dogs ($P<0.05$). A wide range of confidence interval was recorded in Leonberger, Miniature Poodle, and Polish Lowland Sheepdog.

DISCUSSION

The skin is a resilient organ, housing diverse populations of epithelial, mesenchymal, and resident immune cells, which play important roles in homeostasis and protection against external insults. Due to its structural complexity and constant exposure to carcinogenic agents (*e.g.*, ultraviolet radiation from sunlight), the skin is one of the most common sites of tumor development, where heterogeneous tumor types are diagnosed in companion animals [6, 11, 15–17, 25]. The present study described the epidemiological trends of canine cutaneous tumors in Japan, based on the analysis of 1,435 biopsy cases submitted to the laboratory over the past 10 years (2008–2017). Despite the relatively small sample size as compared with investigations conducted in European regions and the United States [16, 37], this study is adequate in elucidating commonly diagnosed tumor types, dog breeds at risk (common breeds), and anatomical predilection of canine cutaneous tumors in Japan. Contrary to previous investigations [16, 28], the present study recorded a higher proportion of malignant tumors. The number of benign tumors may be underestimated, as cases were mainly received from referral veterinary hospitals. It is also plausible that benign tumors (*e.g.*, histiocytomas and hair follicle tumors) were not surgically resected or not routinely submitted for histological examination. A comparison of present and past epidemiological studies on canine cutaneous tumors is summarized in Table 5. A careful interpretation is required as the discrepancy in findings may also be attributed to methodological variations (*e.g.*, data source and inclusion/exclusion criteria) between studies [16, 28, 37].

Soft tissue sarcomas and mast cell tumors were the most commonly encountered malignant neoplasms, in agreement with previous studies [6, 11, 16]. The present study showed that Labrador Retriever and Golden Retriever were predisposed to soft tissue sarcomas. This finding is supported by a previous study (study population=236 dogs) which observed similar overrepresentation of soft tissue sarcomas in these breeds [24]. Perivascular wall tumor was the most frequently diagnosed soft tissue sarcoma, in agreement with previous reports [9, 16].

The high incidence and variable biological behaviors of mast cell tumors in dogs are well-documented, and various histologic grading systems were proposed for prognostication of cutaneous mast cell tumors [5, 11, 16, 21, 28, 29]. In the present study, approximately two-thirds of cutaneous mast cell tumor cases were classified as low-grade and one-third as high-grade according to Kiupel's grading system, which was similar to the results of previous studies [21, 34, 35]. Subcutaneous mast cell tumor was less prevalent than the cutaneous variant. These two entities were examined separately as the existing histologic grading scheme was not developed for subcutaneous mast cell tumor, which generally exhibits indolent behavior [21, 34]. A relatively high breed-specific prevalence for mast cell tumors was recorded in Labrador Retrievers and Pugs. Several studies also showed the predisposition of Labrador Retriever to mast cell tumors [37, 38]. Although Pugs were predisposed to the development of multicentric mast cell tumor, most lesions were of low grade. This result supports findings from the previous study by McNiel *et al.* [23].

Table 4. Multinomial logistic regression analysis showing the association of cutaneous tumor development with sex, age, and breed

Factor	Odds ratio	95% CI
Sex		
Female	1.00	NA
Spayed female	0.88	0.74–1.05
Male	1.13	0.94–1.35
Castrated male	1.04	0.86–1.24
Age (years)		
<1	0.09[a)]	0.02–0.38
1	0.47[a)]	0.24–0.95
2	0.94	0.53–1.66
3	0.41[a)]	0.20–0.86
4	0.55[a)]	0.31–0.97
5	1.02	0.66–1.58
6	1.00	NA
7	1.27	0.87–1.83
8	1.24	0.87–1.78
9	1.73[a)]	1.23–2.43
10	1.36	0.96–1.91
11	1.93[b)]	1.38–2.70
12	1.94[b)]	1.38–2.73
13	2.27[b)]	1.59–3.22
14	2.49[b)]	1.67–3.70
15	3.98[b)]	2.51–6.31
16	5.10[b)]	2.49–10.42
Breed		
Mixed-breed	1.00	NA
Leonberger	24.93[a)]	2.77–224.31
Miniature Poodle	13.90[a)]	2.74–70.50
Polish Lowland Sheepdog	6.05[a)]	1.05–35.00
Boxer	3.36[a)]	1.28–8.80
Bernese Mountain Dog	1.69[a)]	1.01–2.81
Golden Retriever	1.36[a)]	1.02–1.82

CI confidence interval; NA, not applicable. a) $P<0.05$, b) $P<0.001$.

In benign hair follicle tumors, trichoblastomas and trichoepitheliomas were often diagnosed, while tricholemmomas were rarely seen. Trichoblastomas were often found on the head, as observed in a previous study [1]. Trichoepitheliomas had a predilection for multicentric growth, which were often found in Golden Retrievers. Basset Hound is another breed known for its predisposition to multicentric trichoepithelioma [13]. Being the fifth most common cutaneous neoplasm, benign sebaceous tumors were often found on the head and ear regions, with a tendency for multicentric growth, and there was a marked predisposition in American Cocker Spaniels. These findings are in agreement with the literature [13]. Most cutaneous tumors had a wide age-range for tumor development. Contrary to other cutaneous tumors, squamous cell carcinomas specifically developed in mature and senior dogs. Squamous cell carcinomas occurred primarily on the head, limb extremities, and ear. Similarly, previous study has reported a high occurrence of squamous cell carcinoma on the digit [16]. Digital squamous cell carcinoma is known to have a distinct prognosis as compared to those on other skin regions [3]. Belluco *et al.* demonstrated that canine digital squamous cell carcinoma rarely metastasized, but had a tendency for multicentric growth [3]. In the present study, all of the squamous cell carcinomas on limb extremities were solitary. The discrepancy in the findings may reflect different etiologies and biological behavior of digital squamous cell carcinomas across geographical regions.

Despite its rarity, cutaneous lymphoma represents an important entity of canine cutaneous tumors and has received increasing attention over the past decade [12, 22, 27]. Four cutaneous lymphoma subtypes were identified in the present study, namely epitheliotropic T-cell lymphoma, nonepitheliotropic T-cell lymphoma, peripheral T-cell lymphoma, and diffuse large B-cell lymphoma. No breed, age, sex or anatomical predisposition was observed, although it has been reported that English Cocker Spaniel, Boxer, Bulldog, Scottish Terrier, and Golden Retriever are at risk of developing cutaneous lymphoma [18]; and in epitheliotropic T-cell lymphoma, the feet and mucocutaneous junctions are most often affected [26]. In the present study, epitheliotropic T-cell lymphoma was the most presented subtype, and a significant proportion (43.75%) of the tumor showed multiple growths on the skin.

Our findings, together with previous studies, suggest a higher predisposition for plasmacytic tumors in male dogs compared to female dogs, and American Cocker Spaniel is the most commonly affected breed [2, 7, 31]. Although most plasmacytic tumors are

Table 5. Comparison of present and past epidemiological studies on canine cutaneous tumors

	3 most common tumor types				Breed predispositions for cutaneous tumor in purebred dogs
	Benign tumor	(% of all cases)	Malignant tumor	(% of all cases)	
Japan (present study) n=1,435	Lipoma	9.69	Soft tissue sarcoma	18.40	Soft tissue sarcoma−Labrador Retriever, Golden Retriever
	Benign hair follicle tumors	9.34	Mast cell tumor	16.24	Mast cell tumor−Pug, Labrador Retriever
	Benign sebaceous tumors	8.50	Squamous cell carcinoma	4.67	Benign sebaceous tumor−American Cocker Spaniel
					Histiocytic sarcoma−Flat-Coated Retriever, Bernese Mountain Dog
Korea [28] n=748	Lipoma	11.36	Mast cell tumor	8.82	NR
	Histiocytoma	7.49	Apocrine carcinoma	3.07	
	Basal cell tumor	6.82	Melanoma	2.41	
Switzerland [16] n=11,740	Lipoma	12.47	Mast cell tumor	16.35	Mast cell tumor−Boxer, Nova Scotia Duck Tolling Retriever, Rhodesian Ridgeback
	Hair follicle tumor	12.34	Soft tissue sarcoma	10.86	Histiocytoma−Flat-Coated Retriever
	Histiocytoma	12.10	Melanocytic tumor	8.63	Melanocytic tumors−Magyar Vizsla, Airedale Terrier
					Epidermal tumors−Standard Schnauzer, Giant Schnauzer
North America [37] n=25,996	Lipoma	27.44	Mast cell tumor	10.98	Mast cell tumor−Boxer, Rhodesian Ridgeback, Vizsla, Boston Terrier
	Adenoma	14.08	Hemangiopericytoma	2.93	Soft tissue sarcoma−Rhodesian Ridgeback
	Papilloma	7.02	Other sarcomas[a)]	2.84	Melanoma−Vizsla, Miniature Schnauzer, Chesapeake Bay Retriever, Boxer
					Lymphoma−Scottish Terrier
					Hemangiosarcoma−Boxer
					Squamous cell carcinoma−Dalmatian

NR, no record. a) Other sarcomas consisted of myxosarcoma, osteosarcoma, leiomyosarcoma, chondrosarcoma, lymphangiosarcoma, rhabdomyosarcoma, and unspecified sarcomas.

solitary [2, 7], the present study recorded a relatively high number of plasmacytomas with multicentric development, most of which were diagnosed as anaplastic type. Multicentric plasmacytoma had been diagnosed after ruling out the systemic involvement [4].

Metastatic lesions in the skin were rarely described in dogs. Few studies reported cutaneous dissemination of carcinomas arising from the mammary gland, stomach, duodenum, kidney, and urinary bladder [8, 10, 20, 30, 32]. In the present study, metastatic lesions of pulmonary adenocarcinoma were most often seen, followed by mammary adenocarcinoma and renal cell carcinoma. Our findings, together with those in previous studies, suggest that cutaneous metastases in dogs are likely to be originated from carcinoma of the lung, mammary gland, and gastrointestinal and urinary systems.

Several cutaneous tumors had a tendency for multicentric development, and they comprised approximately 12% of all cases. Benign lesions with occasional multicentric development included lipomas, benign sebaceous tumors, and trichoepitheliomas. Our study also showed an increased risk of multicentric trichoepithelioma in Golden Retriever, which require further studies with a larger sample size to confirm the hereditary factor in tumor development. Multicentric malignant lesions observed in the present study included mast cell tumors, epitheliotropic T-cell lymphomas, anaplastic plasmacytomas, histiocytic sarcomas, histiocytosis, Langerhans cell histiocytosis, and Merkel cell carcinoma. Histiocytic sarcomas were predominantly found in large breed dogs, and there was a marked predisposition in Bernese Mountain Dogs and Flat-Coated Retrievers, as described in previous literature [16, 18].

The present study calculated the relative risk for cutaneous tumor development in purebred dogs by using the mixed-breed as reference. Breeds at risk included Leonberger, Miniature Poodle, Polish Lowland Sheepdog, Boxer, Bernese Mountain Dog, and Golden Retriever. However, it should be noted that the odds ratio for Leonberger, Miniature Poodle, and Polish Lowland Sheepdog had a wide 95% confidence interval, which was likely attributed to their low sample size, and thereby limiting our conclusions. Besides that, some predisposed breeds were not shown in the regression analysis, as their risk for tumor development was relatively lower than that of mixed-breed dogs. These breeds included Labrador Retriever, Shetland Sheepdog, American Cocker Spaniel, and Pug, all of which had a high breed-specific prevalence (>25%) of cutaneous tumor development (data not shown). Due to the low number of cases, the study on native Japanese breeds was limited to Shiba Inu. Mast cell tumor, soft tissue sarcomas, lipoma, and benign hair follicle tumors were the most commonly seen tumor types in this breed. It is worth to note that Shiba Inu had a lower breed-specific prevalence (17.04%; result not shown) for cutaneous tumors as compared to the aforementioned breeds. Despite using different reference age group, our results are consistent with the study by Graf *et al.* [16] showing that older dogs, particularly those between 11 and 15 years of age, are at increased risk for cutaneous tumors.

In summary, the present paper describes the epidemiology of canine cutaneous tumors in Japan. Soft tissue sarcomas, mast cell tumor, lipoma, hair follicle tumors, and benign sebaceous tumors were the most presented tumor types. Boxer, Bernese Mountain Dog, Golden Retriever, Labrador Retriever, Shetland Sheepdog, American Cocker Spaniel, and Pug were predisposed to developing cutaneous tumors. Several types of cutaneous tumors with a tendency for multicentric development were identified, including mast cell tumor, trichoepithelioma, and histiocytic sarcoma, which were often encountered in Pugs, Golden Retrievers, and Flat-Coated Retrievers, respectively, prompting future studies to investigate possible genetic factors related to these findings.

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REFERENCES

1. Abramo, F., Pratesi, F., Cantile, C., Sozzi, S. and Poli, A. 1999. Survey of canine and feline follicular tumours and tumour-like lesions in central Italy. *J. Small Anim. Pract.* **40**: 479–481. [Medline] [CrossRef]
2. Baer, K. E., Patnaik, A. K., Gilbertson, S. R. and Hurvitz, A. I. 1989. Cutaneous plasmacytomas in dogs: a morphologic and immunohistochemical study. *Vet. Pathol.* **26**: 216–221. [Medline] [CrossRef]
3. Belluco, S., Brisebard, E., Watrelot, D., Pillet, E., Marchal, T. and Ponce, F. 2013. Digital squamous cell carcinoma in dogs: epidemiological, histological, and immunohistochemical study. *Vet. Pathol.* **50**: 1078–1082. [Medline] [CrossRef]
4. Boostrom, B. O., Moore, A. S., DeRegis, C. J., Robat, C., Freeman, K. and Thamm, D. H. 2017. Canine cutaneous plasmacytosis: 21 cases (2005–2015). *J. Vet. Intern. Med.* **31**: 1074–1080. [Medline] [CrossRef]
5. Bostock, D. E. 1973. The prognosis following surgical removal of mastocytomas in dogs. *J. Small Anim. Pract.* **14**: 27–41. [Medline] [CrossRef]
6. Brønden, L. B., Eriksen, T. and Kristensen, A. T. 2010. Mast cell tumours and other skin neoplasia in Danish dogs-data from the Danish Veterinary Cancer Registry. *Acta Vet. Scand.* **52**: 6. [Medline] [CrossRef]
7. Cangul, I. T., Wijnen, M., Van Garderen, E. and van den Ingh, T. S. 2002. Clinico-pathological aspects of canine cutaneous and mucocutaneous plasmacytomas. *J. Vet. Med. A Physiol. Pathol. Clin. Med.* **49**: 307–312. [Medline] [CrossRef]
8. Carvalho, P. H., Conceição, L. G., Duarte, T. S., Ferrarini, M. C., Hage, N. S., Barros, M. S., Moreira, J. C., Amorim, R. L. and Pinczowski, P. 2011. Renal cell carcinoma with cutaneous metastasis in a dog. *Braz. J. Vet. Pathol.* **4**: 132–137.
9. Chikweto, A., McNeil, P., Bhaiyat, M. I., Stone, D. and Sharma, R. N. 2011. Neoplastic and nonneoplastic cutaneous tumors of dogs in grenada, west indies. *ISRN Vet. Sci.* **2011**: 416435. [Medline] [CrossRef]
10. Dell'Orco, M., Bertazzolo, W., Vergine, M., Ferla, M., Pozzo, S., Rondena, M. and Roccabianca, P. 2005. Gastric mucinous adenocarcinoma with cutaneous metastases in a dog: diagnosis by fine-needle aspiration cytology. *J. Small Anim. Pract.* **46**: 449–453. [Medline] [CrossRef]
11. Dobson, J. M., Samuel, S., Milstein, H., Rogers, K. and Wood, J. L. N. 2002. Canine neoplasia in the U.K.: estimates of incidence rates from a population of insured dogs. *J. Small Anim. Pract.* **43**: 240–246. [Medline] [CrossRef]
12. Fontaine, J., Bovens, C., Bettenay, S. and Mueller, R. S. 2009. Canine cutaneous epitheliotropic T-cell lymphoma: a review. *Vet. Comp. Oncol.* **7**: 1–14. [Medline] [CrossRef]
13. Goldschmidt, M. H. and Goldschmidt, K. H. 2017. Epithelial and melanocytic tumors of the skin. pp. 88–141, 976–978. *In*: Tumors in Domestic Animals, 5th ed. (Meuten, D. J. ed.), John Wiley & Sons, Ames.
14. Goldschmidt, M. H., Dunstan, R. W., Stannard, A. A., von Tscharner, C., Walder, E. J. and Yager, J. A. 1998. Histological classification of epithelial and melanocytic tumors of the skin of domestic animals. *In*: WHO Histological Classification of Tumors of Domestic Species, 2nd ed. (Schulman, F. Y. ed.), Armed Forces Institute of Pathology, Washington, D.C.
15. Graf, R., Grüntzig, K., Hässig, M., Axhausen, K. W., Fabrikant, S., Welle, M., Meier, D., Guscetti, F., Folkers, G., Otto, V. and 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**: 266–277. [Medline] [CrossRef]
16. Graf, R., Pospischil, A., Guscetti, F., Meier, D., Welle, M. and Dettwiler, M. 2018. Cutaneous tumors in Swiss dogs: retrospective data from the Swiss Canine Cancer Registry, 2008–2013. *Vet. Pathol.* **55**: 809–820. [Medline] [CrossRef]
17. Grüntzig, K., Graf, R., Hässig, M., Welle, M., Meier, D., Lott, G., Erni, D., Schenker, N. S., Guscetti, F., Boo, G., Axhausen, K., Fabrikant, S., Folkers, G. and Pospischil, A. 2015. The Swiss canine cancer registry: a retrospective study on the occurrence of tumours in dogs in Switzerland from 1955 to 2008. *J. Comp. Pathol.* **152**: 161–171. [Medline] [CrossRef]
18. Hendrick, M. J. 2017. Mesenchymal tumors of the skin and soft tissues. pp. 142–175. *In*: Tumors in Domestic Animals, 5th ed. (Meuten, D. J. ed.), John Wiley & Sons, Ames.
19. Hendrick, M. J., Mahaffey, E. A., Moore, F. M., Vos, J. H. and Walder, E. J. 1998. Histological classification of mesenchymal tumors of skin and soft tissues of domestic animals. *In*: WHO Histological Classification of Tumors of Domestic Species, 2nd ed. (Schulman, F. Y. ed.), Armed Forces Institute of Pathology, Washington, D.C.
20. Juopperi, T. A., Cesta, M., Tomlinson, L. and Grindem, C. B. 2003. Extensive cutaneous metastases in a dog with duodenal adenocarcinoma. *Vet. Clin. Pathol.* **32**: 88–91. [Medline] [CrossRef]
21. Kiupel, M., Webster, J. D., Bailey, K. L., Best, S., DeLay, J., Detrisac, C. J., Fitzgerald, S. D., Gamble, D., Ginn, P. E., Goldschmidt, M. H., Hendrick, M. J., Howerth, E. W., Janovitz, E. B., Langohr, I., Lenz, S. D., Lipscomb, T. P., Miller, M. A., Misdorp, W., Moroff, S., Mullaney, T. P., Neyens, I., O'Toole, D., Ramos-Vara, J., Scase, T. J., Schulman, F. Y., Sledge, D., Smedley, R. C., Smith, K., W Snyder, P., Southorn, E., Stedman, N. L., Steficek, B. A., Stromberg, P. C., Valli, V. E., Weisbrode, S. E., Yager, J., Heller, J. and Miller, R. 2011. Proposal of a 2-tier histologic grading system for canine cutaneous mast cell tumors to more accurately predict biological behavior. *Vet. Pathol.* **48**: 147–155. [Medline] [CrossRef]
22. Mauldin, E. A. and Peters-Kennedy, J. 2015. Integumentary system. pp. 733–735. *In*: Jubb, Kennedy & Palmer's Pathology of Domestic Animals: Vol. 1, 6th ed. (Maxie, M. G. ed.), Elsevier, St. Louis.
23. McNiel, E. A., Prink, A. L. and O'Brien, T. D. 2006. Evaluation of risk and clinical outcome of mast cell tumours in pug dogs. *Vet. Comp. Oncol.* **4**: 2–8. [Medline] [CrossRef]
24. McSporran, K. D. 2009. Histologic grade predicts recurrence for marginally excised canine subcutaneous soft tissue sarcomas. *Vet. Pathol.* **46**: 928–933. [Medline] [CrossRef]
25. Merlo, D. F., Rossi, L., Pellegrino, C., Ceppi, M., Cardellino, U., Capurro, C., Ratto, A., Sambucco, P. L., Sestito, V., Tanara, G. and Bocchini, V. 2008. Cancer incidence in pet dogs: findings of the animal tumor registry of Genoa, Italy. *J. Vet. Intern. Med.* **22**: 976–984. [Medline] [CrossRef]

26. Moore, P. F., Affolter, V. K., Graham, P. S. and Hirt, B. 2009. Canine epitheliotropic cutaneous T-cell lymphoma: an investigation of T-cell receptor immunophenotype, lesion topography and molecular clonality. *Vet. Dermatol.* **20**: 569–576. [Medline] [CrossRef]
27. Moore, P. F., Affolter, V. K. and Keller, S. M. 2013. Canine inflamed nonepitheliotropic cutaneous T-cell lymphoma: a diagnostic conundrum. *Vet. Dermatol.* **24**: 204–211. [Medline] [CrossRef]
28. Pakhrin, B., Kang, M. S., Bae, I. H., Park, M. S., Jee, H., You, M. H., Kim, J. H., Yoon, B. I., Choi, Y. K. and Kim, D. Y. 2007. Retrospective study of canine cutaneous tumors in Korea. *J. Vet. Sci.* **8**: 229–236. [Medline] [CrossRef]
29. Patnaik, A. K., Ehler, W. J. and MacEwen, E. G. 1984. Canine cutaneous mast cell tumor: morphologic grading and survival time in 83 dogs. *Vet. Pathol.* **21**: 469–474. [Medline] [CrossRef]
30. Pérez Alenza, M. D., Tabanera, E. and Peña, L. 2001. Inflammatory mammary carcinoma in dogs: 33 cases (1995–1999). *J. Am. Vet. Med. Assoc.* **219**: 1110–1114. [Medline] [CrossRef]
31. Platz, S. J., Breuer, W., Pfleghaar, S., Minkus, G. and Hermanns, W. 1999. Prognostic value of histopathological grading in canine extramedullary plasmacytomas. *Vet. Pathol.* **36**: 23–27. [Medline] [CrossRef]
32. Reed, L. T., Knapp, D. W. and Miller, M. A. 2013. Cutaneous metastasis of transitional cell carcinoma in 12 dogs. *Vet. Pathol.* **50**: 676–681. [Medline] [CrossRef]
33. Rungsipipat, A., Sunyasootcharee, B., Ousawaphlangchai, L., Sailasuta, A., Thanawongnuwech, R. and Teankum, K. 2003. Neoplasms of dogs in Bangkok. *Wetchasan Sattawaphaet* **33**: 59–66.
34. Sabattini, S., Scarpa, F., Berlato, D. and Bettini, G. 2015. Histologic grading of canine mast cell tumor: is 2 better than 3? *Vet. Pathol.* **52**: 70–73. [Medline] [CrossRef]
35. Stefanello, D., Buracco, P., Sabattini, S., Finotello, R., Giudice, C., Grieco, V., Iussich, S., Tursi, M., Scase, T., Di Palma, S., Bettini, G., Ferrari, R., Martano, M., Gattino, F., Marrington, M., Mazzola, M., Elisabetta Vasconi, M., Annoni, M. and Marconato, L. 2015. Comparison of 2- and 3-category histologic grading systems for predicting the presence of metastasis at the time of initial evaluation in dogs with cutaneous mast cell tumors: 386 cases (2009–2014). *J. Am. Vet. Med. Assoc.* **246**: 765–769. [Medline] [CrossRef]
36. Valli, V. E., Jacobs, R. M., Parodi, A. L., Vernau, W. and Moore, P. F. 2002. Histological classification of hematopoietic tumors of domestic animals. *In*: WHO Histological Classification of Tumors of Domestic Species, 2nd ed. (Schulman, F. Y. ed.), Armed Forces Institute of Pathology, Washington, D.C.
37. Villamil, J. A., Henry, C. J., Bryan, J. N., Ellersieck, M., Schultz, L., Tyler, J. W. and Hahn, A. W. 2011. Identification of the most common cutaneous neoplasms in dogs and evaluation of breed and age distributions for selected neoplasms. *J. Am. Vet. Med. Assoc.* **239**: 960–965. [Medline] [CrossRef]
38. Warland, J. and Dobson, J. 2013. Breed predispositions in canine mast cell tumour: a single centre experience in the United Kingdom. *Vet. J.* **197**: 496–498. [Medline] [CrossRef]