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RESEARCH ARTICLE

Statistics of Canine Skin Tumors in Korea during 2005-2018

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ABSTRACT

The aim of this study was to investigate the incidence and anatomic location of canine cutaneous tumors and the sex, age, and breed distribution of dogs with skin tumor. A total of 2,172 tumor samples submitted for histopathological diagnosis from local animal hospitals during 2005-2018 were retrieved. Formalin-fixed paraffin embedded tissues were sectioned, stained, and examined. Clinical data provided by clinicians were also reviewed. Tumors with the highest incidence were sebaceous gland and modified sebaceous gland tumors (22%), follicular tumors (18%), lipoma and liposarcoma (15%), histiocytoma (10%), and mast cell tumors (9%). Gender wise distribution of patients were castrated male (31%), intact female (21%), spayed female (21%), and intact male (16%). The mean age of patients was 9.3 years. Location of lesions included limb (19%), dorsal skin (14%), perianal area (12%), foot (10%), head (7%), neck (6%), and abdominal skin (5%). The most affected breeds were shih-tzu (20%), Maltese (16%), cocker spaniel (9%), schnauzer (8%), Yorkshire terrier (7%), crossbreed (7%), and poodle (7%). In conclusion, this study provides additional information on the general incidence of canine skin tumors in Korea and the accompanying clinical signs.

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INTRODUCTION

Skin tumor is one of the most common type of tumor found in canine species, because there are variety of tumors which occur at this location (Dobson *et al*., 2002; Baioni *et al*., 2017). As skin tumors are relatively easily detected by owners and are comparatively simple to biopsy and excise surgically (Goldschmidt and Goldschmidt, 2017), skin samples account for the highest proportion of samples submitted to our small animal tumor diagnostic center.

Recent studies have reviewed 11,740 canine skin tumors in Switzerland (Graf *et al*., 2018); 2,553 cases in South Africa (Tompkins *et al*., 2019); and 546 cases in Brazil (Machado *et al*., 2018). In these reports, tumors with most incidence were mast cell tumor and lipoma in common, and it was in accord with a previous report from Korea (Pakhrin *et al*., 2007). These reports have provided much information on canine skin tumors, including their incidence, sex and breed of patients. However, a few features do not coincide with that in Asia, such as the breed of patients, as some breeds in the previous reports are not commonly raised in Asian countries. In addition, previous studies mainly described general data for the whole study population, not detailed data for common kinds of skin tumors. Furthermore, a previous study from Korea was brief and outdated (Pakhrin *et al*., 2007); thus, there is a need for an updated report on skin tumors in dogs from Korea.

The aims of this study were to investigate the incidence and anatomic location of canine skin tumors, report the sex, age, breed of dogs with different skin tumor types in Korea, and furthermore, to provide additional information on skin tumors in the canine population as a whole.

MATERIALS AND METHODS

Sample collection: Samples submitted from local animal hospitals for histopathological diagnosis during 2005–2018 were retrieved. Formalin-fixed-paraffin-embedded samples were sectioned and stained with hematoxylin and eosin (H&E). Clinical data, including sex, age, breed of the patients, and location of the tumor, provided by clinicians, were also recorded.

Histological evaluation: Tumors were evaluated and diagnosed based on the World Health Organization classification of skin tumors (Goldschmidt *et al*., 1998; Goldschmidt and Goldschmidt, 2017). A total of 2,172 samples were included in the present study. Immunohistochemistry was implemented if H&E staining could not yield a clear diagnosis. Immunohistochemistry was performed, following the protocols described in a previous study (Kim *et al*., 2018). Detailed information on primary antibodies used for immunohistochemistry are shown in Table 1. For mast cell tumors, 2-tier grading system and classification into cutaneous and subcutaneous mast cell tumors were applied (Kiupel *et al*., 2011; Thompson *et al*., 2011).

Statistical analysis: Statistical analysis including the frequency rate of each tumor, sex, age, breed, and site was performed with the statistical software package SPSS 22.0. For conciseness, frequency expressed as percentage was rounded to the nearest integer. Shapiro–Wilk tests were used to examine the normality of data distribution and one-way analysis of variance was used to analyze the relationship between histologic malignancy and mean age of occurrence in certain tumor types.

RESULTS

Overall statistics: Five of the most common tumors are presented in Fig. 1. Tumors with a relatively low incidence were apocrine gland and modified apocrine gland tumor (5%), hemangiopericytoma (4%), fibroma and fibrosarcoma (3%), melanocytoma (3%), hemangioma /hemangiosarcoma (2%), squamous cell carcinoma (2%), undifferentiated tumors (2%), bone or cartilage-derived tumors (1%), lymphoma (1%), and others (3%).

The mean age of patients was 9.3 years. The sex distribution of the dogs is shown in Table 2. The major breeds of affected dogs are presented in Table 3.

The most affected lesion site is presented in Fig. 2. The rest lesions were flank (5%), thoracic skin (5%), axillary (3%), tail (3%), ear (including auricle and ear canal; 2%), inguinal (2%), lip (1%), eyelid (1%), and perivulvar (1%). The location of 3% of lesions was unknown. The incidence of the five most common tumors were presented in Table 4.

Sebaceous gland and modified sebaceous gland tumors

Sebaceous gland neoplasm: The mean age of occurrence was 9.97, 11.85 and 14.11 years in cases of adenoma, epithelioma, and carcinoma, respectively. There was a statistically significant association between this histologic malignancy and the mean age of occurrence (P<0.001). The sex distribution of this tumor type was castrated males (32%), intact females (22%), spayed females (20%), intact males (10%), and unknown (16%). The five breeds most affected were shih-tzu (28%), cocker spaniel (19%), Maltese (11%), Yorkshire terrier (9%) and poodle (8%).

Tumor sites were dorsal skin (18%), foot (15%), limb (14%), neck and ear (9% each), eyelid (6%), flank (5%), perianal skin (4%), head - except the lip and ear, abdomen (3%, respectively), thoracic skin, tail, lip, axillary skin, inguinal skin (2% each) and unknown (5%). The mean size of tumors was 1.98 cm in diameter, ranging from 0.1 to 20 cm in diameter, in 62 cases in which size was reported.

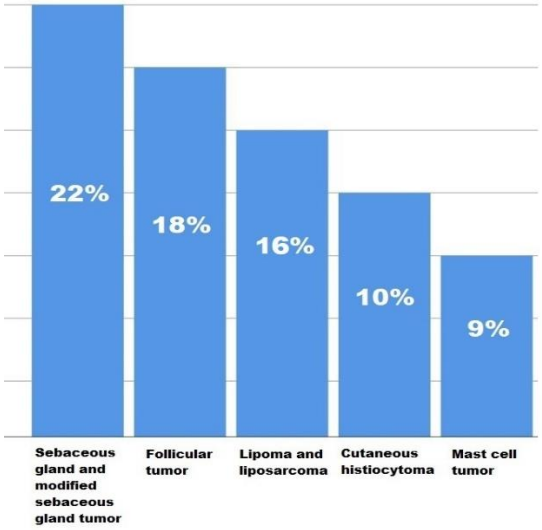

Fig. 1: Frequency of the five most common tumors. The bar chart shows the five most common tumors.

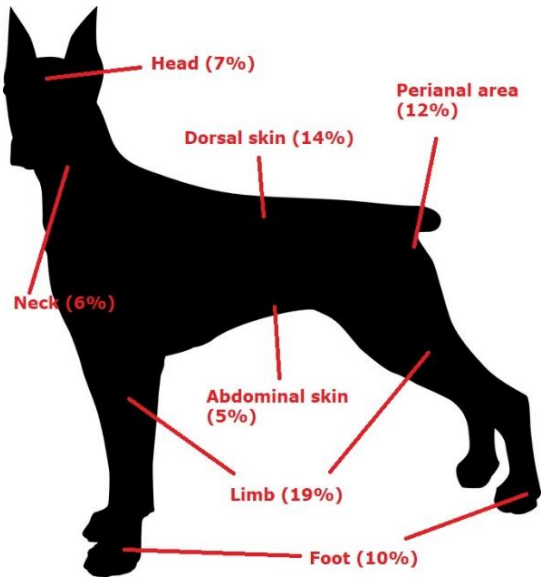

Fig. 2: Location of tumors. Tumors were most commonly found on the limbs, dorsal skin, perianal area, foot, head (except ear and lip), neck, and abdominal skin.

The reported clinical signs in 78 cases included inflammation (36%), multiple masses (>3 masses; 19%), progressive increase in size (>1 month; 13%), sudden increase in size (≤1 month; 12%), hemorrhage (8%), pruritus and bacterial infection (4% each), hypercalcemia, no change in size, repeated enlargement and regression, and recurrence (1% each).

Hepatoid Gland Tumor: The mean age of patients was 11.47 years overall, and 10.92, 11.97, and 12.12 years for patients with adenoma, epithelioma, and carcinoma, respectively. There was a statistically significant relationship between this type of malignancy and the mean age of occurrence (P=0.005). The sex distribution of patients was: intact males (47%), castrated males (24%), spayed females (13%), intact females (6%), and unknown (10%). The five breeds with most frequency was: shih-tzu (28%), crossbreed (11%), Maltese (11%), cocker spaniel (10%), and Yorkshire terrier (9%).

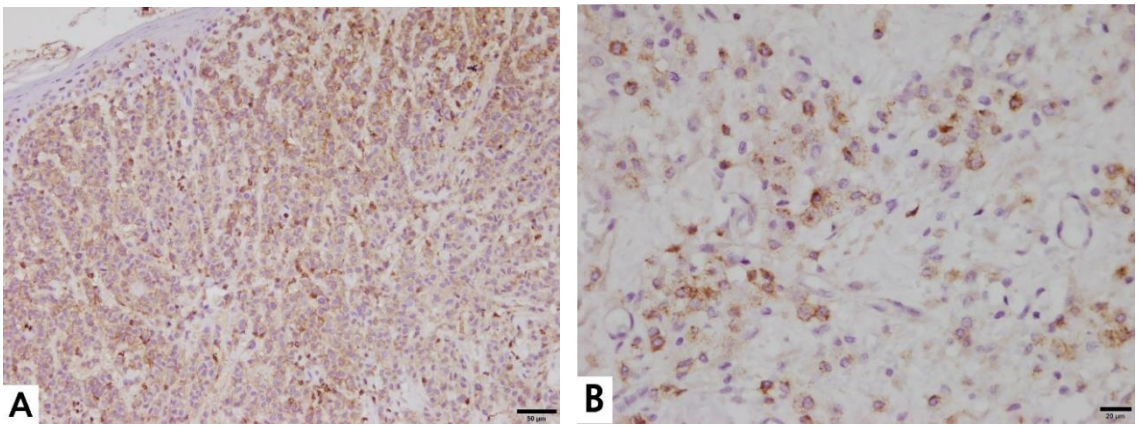

Fig. 3: Immunohistochemistry for cutaneous histiocytoma and mast cell tumor. Neoplastic histiocytes and mast cells shows positivity to CD18 (A) and CD117 (B), respectively. Counterstained with Mayers' hematoxylin, Bar=50 μm (A); Bar=20 μm (B).

Table 1: Primary antibodies for immunohistochemistry and protocols

Primary antibody	Clone	Supplier	Antigen retrieval	Dilution	Incubation
Pan-Cytokeratin	AE1/AE3	Agilent	Citric acid, 8 min	1:100	4°C, overnight
Vimentin	V9	Agilent	Tris-EDTA, 10 min	1:800	Room temperature, 2 hours
CD18	Polyclonal	Not applicable (Custom-made)	Tris-EDTA, 20 min	1:50	4°C, overnight
c-kit (CD117)	Polyclonal	Agilent	Tris-EDTA, 15 min	1:300	4°C, overnight
Alpha smooth muscle actin	1A4	Agilent	Not applicable	1:200	4°C, overnight
MelanA	A103	Novocastra	Tris-EDTA, 15 min	1:100	4°C, overnight
CD3	Polyclonal	Agilent	Citric acid, 10 min	1:200	4°C, overnight
PAX-5	24/Pax-5 (RUO)	BD bioscience	Citirc acid, 16 min	1:25	4°C, overnight
MUM-1	MUM1p	Agilent	Tris-EDTA, 15 min	1:200	Room temperature, 3 hours

Table 2: Sex distribution of the patients

Sex of patient	Number	Percentage %
Castrated male	671	31
Intact female	462	21
Spayed female	457	21
Intact male	353	16
Not Applicable	229	11
	2172	100

The location of these tumors mostly involved the perianal region (96%), but they also occurred in the tail (2%), preputial skin (1%) and abdominal skin (1%). The mean size of the neoplasm was 2.74 cm in diameter, varying from 0.2 to 10 cm in diameter.

Clinical signs reported in 67 cases included a sudden increase in size (≤1 month; 25%), inflammation (18%), hemorrhage (16%), prostate gland hyperplasia (10%), progressive increase in size (7%), constipation (6%), rupture (4%), recurrence (3%), perineal hernia, no change in size, lameness of a hindlimb, invasion into the muscle, enlargement of a sublumbar lymph node, and bacterial infection (1% each).

Meibomian Gland Tumor: The mean age of patients overall was 10.41 years, and 9.97, 10.55, and 12.00 years for adenoma, epithelioma, and carcinoma, respectively. There was no statistically significant association between this type of histological malignancy and the mean age of occurrence (P=0.538). The sex distribution of these patients was: castrated males (32%), intact females (25%), spayed females (20%), intact males (14%), and unknown (9%). The most frequently presented breeds involved were shih-tzu (34%), Maltese (13%), cocker spaniel (11%), schnauzer (9%), Yorkshire terrier, Pekingese, and crossbreed (5%, respectively).

Tumors were all located on the eyelid, due to its anatomic origin. The mean size of these tumor was 0.87 cm in diameter, ranging from 0.1 mm to 1.5 cm in diameter.

The reported clinical signs in 16 cases included a progressive increase in size (>1 month; 31%), sudden increase in size (≤1 month), hemorrhage and inflammation (19% each), and recurrence and rupture (6% each).

Follicular tumors

Trichoblastoma: The mean age of occurrence for trichoblastoma was 8.58 years, ranging from 4 months to 18 years. The sex distribution was: castrated males (38%), intact females (27%), intact males (16%), spayed females (12%), and unknown (7%). The most affected breeds were Maltese (28%), shih-tzu (25%), poodle (20%), Yorkshire terrier (15%), and cocker spaniel (12%).

Locations of lesions involved the head (except the ear and lip, 49%), neck (12%), limb (10%), ear (7%), foot (7%), dorsal skin (4%), abdominal skin (2%), and the lip, axillary skin, flank, inguinal skin, and thoracic skin (1% each). In 3% of cases, the location of the lesion was unknown. The size of trichoblastoma was reported in 48 cases and varied from 0.25 to 7 cm in diameter, with a mean size of 2.08 cm in diameter.

Reported clinical signs in 31 cases included sudden increase in size (≤1 month, 26%), progressive increase in size (>1 month, 26%), no change in size over 1 year (19%), sudden occurrence (within 1 month, 10%), hemorrhage (6%), rupture, recurrence, and repeated enlarging and regression (3% each).

Infundibular keratinizing acanthoma: The mean age of occurrence of infundibular keratinizing acanthoma (IKA) was 8.32 years, ranging from 8 months to 19 years. The sex distribution was castrated males (28%), spayed females (22%), intact females (22%), intact males (17%), and unknown (11%). The five most common breeds involved were Maltese (24%), shih-tzu (20%), Yorkshire terrier (13%), Pekingese (12%), crossbreed (11%).

Table 3: Breed wise distribution of tumors

Breed	Number	Percentage %	Breed	Number	Percentage %
Shih-tzu	438	20	Chihuahua	25	1
Maltese	346	16	Jindo	24	1
Cocker spaniel	196	9	Miniature pinscher	24	1
Schnauzer	175	8	Beagle	23	1
Yorkshire terrier	153	7	Pug	23	1
Crossbreed	152	7	Labrador retriever	22	1
Poodle	154	7	Spitz	22	1
Dachshund	45	2	Alaskan malamute	21	1
Pekingese	43	2	Others	78	4
Golden retriever	42	2	Not Applicable	124	6
Pomeranian	42	2		2172	100

Table 4: Incidence of the five most presented tumors

Tumor	Tumor type		No.	Percentage %
Sebaceous gland and modified sebaceous gland tumors (n=478)	Sebaceous gland tumor (n=217)	Adenoma	117	45
		Epithelioma	89	
		Carcinoma	11	
	Hepatoid gland tumor (n=205)	Adenoma	106	43
		Epithelioma	39	
		Carcinoma	60	
	Meibomian gland tumor (n=56)	Adenoma	16	12
		Epithelioma	39	
		Carcinoma	1	
Follicular tumors (n=385)	Trichoblastoma		162	42
	Infundibular Keratinizing Acanthoma		123	32
	Pilomatricoma		69	18
	Trichoepithelioma		31	8
Lipoma and liposarcoma (n=337)	Lipoma		329	98
	Liposarcoma		8	2
Cutaneous histiocytoma (n=216)	N/A*		N/A*	N/A*
Mast cell tumor (n=195)	Subcutaneous	N/A*	43	22
	Cutaneous	Low-grade	113 (74%)	78
		High-grade	39 (26%)	

* N/A: Not applicable.

Locations of tumors were the foot (21%), dorsal skin (19%), limb (13%), tail (11%), head (8%), flank (7%), eyelid (3%), neck (3%), hip, abdominal skin, axillary skin, perianal skin, and auricle (2% respectively). The penile and thoracic skin was affected in 1% each, and the location of lesions was unknown in 4% of cases. The size of IKAs varied from 0.3 to 11 cm in diameter, and the mean diameter was 2.25 cm.

Clinical signs in 45 cases were reported as inflammation (49%), multiple masses (>3 masses; 18%) progressive increase in size (>1 month, 16%), sudden increase in size (<1 month, 7%), sudden occurrence (within 1 month; 4%), rupture (4%), and recurrence (2%).

Pilomatricoma: The mean age of occurrence was 7.47 years, ranging from 2 to 13 years, although the age of two cases was unknown. Sex distribution of populations were castrate males (39%), intact females (25%), spayed females (17%), and intact males (12%). The sex of 7% of cases were unknown. Breeds of dogs with the most representation were Maltese (42%), schnauzer (25%), poodle (19%), crossbreed (7%) and Yorkshire terrier (7%).

Locations of occurrence were the dorsal skin (35%), limb (16%), neck (9%), flank (7%), foot and abdominal skin (6% respectively), head (except ear and lips, 4%), axillary skin, tail (4% respectively), inguinal skin, auricle, thoracic skin (1% each). The location of 6% of these tumors was not applicable. The mean diameter of pilomatricoma was 2.5 cm, and varied from 0.3 to 20 cm.

Clinical signs of from 26 cases included a progressive increase in size (31%), inflammation (19%), a sudden increase in size (15%), calcification inside the mass (15%), osteolysis and hypertrophy of bone on radiography (8%), multiple nodules (over 20 sites throughout the skin), hemorrhage, and keratinization of epithelium (4% each).

Trichoepithelioma: The mean of age patients with this tumor type was 10.2 years and ranged from 1 to 17 years; the age of four cases was unknown. The sex distribution of these patients was: intact females (29%), castrated males (23%), intact males (19%), spayed females (13%), and unknown (16%). Breeds of patients frequently presented were schnauzer (23%), cocker spaniel, Maltese, and shih-tzu (13% each), golden retriever and crossbreed (10% respectively).

The site of the tumor was the dorsal skin (26%), limb (19%), head (13%), neck and tail (10% respectively), flank, thorax, foot, and abdominal skin (3% each). The location of 10% of tumors was unknown. The size of tumors ranged from 0.5 to 9 cm, with a mean size of 3.77 cm.

Clinical signs from nine cases included inflammation (33%), sudden occurrence, sudden increase in size, no change in size, recurrence, rupture, and adherence to muscle (11% each).

Lipoma and Liposarcoma: The mean age of patients were 8.74 years, ranging from 9 months to 16 years, except 18 cases with unknown age information. The sex distribution of patients was: castrated males (35%), spayed females (24%), intact females (17%), intact males (11%), and unknown (13%). The most common breeds included Maltese (18%), shih-tzu (16%), schnauzer (14%), poodle (10%), and cocker spaniel (9%).

The locations of tumor occurrence were the limbs (19%), thoracic skin (17%), dorsal skin (15%), abdominal skin (11%), flank (9%), axillary skin (8%), neck (7%), inguinal area (4%), perianal skin, foot, head (2% respectively), tail (1%) and peri-vulvar skin (1%). Location of 2% of lesions were not applicable. The mean size of the tumor in the 103 cases with information reported was 4.3 cm in diameter, ranging from 0.3 to 20 cm. Relatively massive tumors (≥10 cm) were reported in 14 cases.

The reported clinical signs from 130 dogs included inflammation (39%), multiple masses (>3 masses; 19%), sudden increase in size (≤1 month; 12%), progressive increase in size (>1 month; 12%), local invasiveness to the muscle (7%), sudden occurrence (≤1 month; 3%), recurrence, pain, no change in size (2% each), ulceration, pruritus, necrosis, and calcification (1% each).

Cutaneous histiocytoma: CD18 was used to reveal the origin of neoplastic cells in histologically ambiguous cases (Figure 3A). The mean age of dogs with cutaneous histiocytoma was 4.9 years, ranging from 5 months to 17 years. The sex distribution of patients was as follows: castrated males (41%), intact females (20%), intact males (17%), spayed females (13%) and unknown (9%). The breeds which had high frequency were Maltese (13%), shih-tzu (13%), poodle (12%), Yorkshire terrier (9%), cocker spaniel, and schnauzer (8% respectively).

Tumors located in the head (32%), foot (19%), limb (16%), ear, neck and dorsal skin (6% each), flank, perianal area, axillary skin, abdominal skin and thoracic skin (2% respectively). In 5% of cases, location of lesion was not applicable. In 67 cases with a reported tumor size, the mean size of the mass was 1.15 cm in diameter, ranging from 0.2 to 5 cm in diameter.

Reported clinical signs were a sudden increase in size (≤1 month; 43%), progressive increase in size (>1 month), inflammation (17% each), pruritus (10%), hemorrhage (7%), repeated enlarging and regression, recurrence, and alopecia (2% each).

Mast cell tumor: In tumors lacking typical features of mast cell tumor, CD117 was used as for differential marker (Figure 3B). The mean age of patients was 9.22 years, ranging from 6 months to 17 years. The sex of these dogs included castrated males (27%), spayed females (25%), intact females (24%), intact males (14%), and unknown (10%). Breeds that comprised a high proportion were Maltese (20%), poodle (15%), shih-tzu (10%), crossbreed (9%), and schnauzer (8%).

The location of tumors included the limb (31%), foot (9%), abdominal skin, flank, dorsal skin (7% each), head except the ear and lip (6%), neck (5%), axillary skin, inguinal skin, perianal region, thoracic skin and ear (4% respectively), tail (3%), penile skin, lip, and foot (1% each). Two percent of tumors did not an have identified locations. The mean size of tumors was 3.34 cm in diameter, in the reported 68 cases, ranging from 0.5 to 20 cm in diameter.

Reported clinical signs were a sudden increase in size (≤1 month; 21%), multiple masses (>3 masses; 19%), progressive increase in size (>1 month; 13%), inflammation (12%), recurrence (9%), hemorrhage (8%), local invasiveness to the muscle (7%), pruritus and repeated enlargement and regression (5% each).

DISCUSSION

Although there were some differences between the findings in this study and those of previous reports, tumors showing the highest frequency were generally similar between studies (Pakhrin *et al*., 2007; Graf *et al*., 2018; Machado *et al*., 2018). This may reflect that specific cell populations are particularly vulnerable to tumorigenic stimulation. However, there might be a bias in the frequency of tumors, as many clinicians may not submit their sample for histopathological analysis if they consider that the tumor is evidently benign based on gross morphology or pre-surgical cytology, for example, lipoma. Indeed, in a previous study which analyzed 25,996 cases of skin tumors, lipoma formed the highest portion (Villamil *et al*., 2002). Interestingly, in geographical regions with higher levels of solar radiation than Korea, such as Zimbabwe and Grenada, common tumor types differed markedly. In Zimbabwe, squamous cell carcinoma accounted for the most, while in Trinidad, Grenada, and South Africa, hemangiosarcoma comprised the high proportion of canine skin tumor types (Mukaratirwa *et al*., 2005; Chikweto *et al*., 2011; Suepaul *et al*., 2019; Tompkins *et al*., 2019). This may reflect the inductive effect of ultraviolet radiation on hemangiosarcoma or squamous cell carcinoma, as suggested in previous studies (Nikula *et al*., 1992; Pirie *et al*., 2006; Kim and He, 2014), and furthermore, natural environments could be influencing factors for canine tumor etiology.

Tumors mostly occurred in the limbs (19%) in the present study, in agreement with a previous study by Aleksic *et al*. (2005). This could simply be because the limbal skin occupies a large amount of skin area; similarly, truncal skin also comprises a large area of skin, and in previous studies, most tumors arose from the truncal skin (Mukaratirwa *et al*., 2005; Chikweto *et al*., 2011).

Although genetic predisposition has been shown in several studies (Goldschmidt and Goldschmidt, 2017; Graf *et al*., 2018), dogs with breed susceptibility are not commonly raised in some countries including Korea, thus those reports could not be a practical source of information. Therefore, further studies are needed to investigate based on differences not only in genetic predisposition, but also in cultural differences such as the preference for specific breeds, to provide more helpful information for clinicians and owners. However, studies focusing on genetic predilection are still precious, because they could show valuable insights on the etiology of tumors (Dobson, 2013). In addition, as there are a few popular breeds with genetic susceptibility in Korea, for example, Schnauzer to melanoma and hair follicle tumor, it could be useful information for owners raising those breeds.

Interestingly, in tumors, which have a low-intermediate-high level of malignant progression, such as sebaceous gland tumors or hepatoid gland tumors, there was a statistically significant association between tumor malignancy and the mean age of patients. It coincides

with facts proved in previous studies (Sorenmo *et al*., 2009; Pastor *et al*., 2018). This may suggest that environmental toxin exposure or genetic mutations may accumulate in the individuals' bodies, and when a major "hit" occurs, it provokes the malignant progression of the tumor due to the accumulated burden on the cells. However, because scientific evidence to support this hypothesis is little, further research is necessary.

In this study, the most commonly reported clinical sign was inflammation. The type of inflammation and whether ulceration was involved were not detailed from clinician's reports. However, as ulceration and typical pyogranulomatous inflammation was prominent in majority of histological sections with reported clinical signs of inflammation, the greatest possibility seems to be due to self-trauma. However, as inflammation could promote tumorigenesis and tumor progression (Hensler and Mueller, 2013; Neagu *et al*., 2019), it might suggest the correlation between skin tumorigenesis and inflammation in canine species, as other kinds of cancer in dogs (Morrison, 2011). In addition, this study provides evidence that a rapid or progressive increase in mass size or multiple nodules throughout the body can be indirect indicators for tumor.

Conclusions: The present study shows general incidence of canine skin tumors in Korea and further detailed data including location of tumor, clinical signs, and sex, breed, age of patients with most common skin tumors.

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Authors contribution: SHK and WSC has designed the study, interpreted data, drafted and revised the manuscript. BJS, SHC, HYL analyzed histopathological and statistical data. MKB collected data and prepared dataset for statistical analysis. JHS supervised the project and critically revised the manuscript.

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