

Original Article

A histopathological study on spontaneous gastrointestinal epithelial tumors in dogs

Tsubasa Saito¹, Kazumi Nibe², James K. Chambers¹, Mizuho Uneyama¹, Ko Nakashima³, Koichi Ohno⁴, Hajime Tsujimoto⁴, Kazuyuki Uchida^{1*}, and Hiroyuki Nakayama¹

¹Laboratory of Veterinary Pathology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

²Japan Animal Referral Medical Center, 2-5-8 Kuji, Takatsu-ku, Kawasaki, Kanagawa 213-0032, Japan

³Japan Small Animal Medical Center, 2-27-4 Nakatomi-minami, Tokorozawa, Saitama 359-0003, Japan

⁴Laboratory of Veterinary Internal Medicine, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

Abstract: The present study evaluated the histopathological features, biological nature, anatomical location, sex, age and breeds of dogs affected by spontaneous gastrointestinal epithelial tumor. Biopsy samples of gastrointestinal tumors, from 95 dogs were examined and classified according to the WHO histological classification. A total of 131 samples, including 38 gastric, 13 small intestinal, and 80 large intestinal tumors were examined. The study observed that Jack Russell Terriers and Miniature Dachshunds were the breeds with the highest predisposition for gastrointestinal tumors. Gastric tumors included 5 adenomas, 30 adenocarcinomas (12 tubular, 2 papillary, 4 tubulopapillary and 12 signet-ring cell carcinomas) and 3 undifferentiated carcinomas. Intestinal tumors included 35 adenomas, 57 adenocarcinomas (43 acinar, 4 papillary, 7 mucinous and 3 signet-ring cell carcinomas), and 1 undifferentiated carcinoma. The study did not detect any difference among the incidence rates of invasion/metastasis in the tubular (44%), papillary (33%) and tubulopapillary (25%) adenocarcinomas. Additionally, the tubular (acinar), papillary and tubulopapillary adenocarcinomas were further divided into 48 polypoid and 17 non-polypoid types, based on their growth patterns. Invasion/metastasis was detected in 21% of the polypoid type and 100% of the non-polypoid type of adenocarcinomas. A correlation was detected between the occurrence of invasion/metastasis and the type of histopathological growth pattern in adenocarcinomas. The study demonstrated that Jack Russell terriers and Miniature Dachshunds are the most common breeds affected by gastrointestinal tumors and the entire group of the canine adenocarcinomas with non-polypoid growth pattern has greater malignant potentials, compared to the adenocarcinomas with polypoid growth patterns. (DOI: 10.1293/tox.2019-0076; J Toxicol Pathol 2020; 33: 105–113)

Key words: dog, gastric tumor, histopathology, intestinal tumor, spontaneous epithelial tumor

Introduction

Spontaneous canine gastrointestinal tumors are rather common in veterinary medicine and such tumors are believed to be a suitable model, for their human counterparts. This is because various types of mutations of Adenomatous polyposis coli gene (APC), a tumor suppressor gene, are commonly found in human and canine colorectal tumors^{1, 2}. APC gene-mutated or -transgenic mice are most widely used for investigating the tumorigenesis of this particular tumor. These rodent models may reflect the pathogenesis of APC-associated gastrointestinal tumors, but may not explain the

pathological features seen in human tumors. Thus, research on spontaneous canine gastrointestinal tumors will provide useful information, which can provide assistance in understanding the tumorigenesis of their human counterparts. Histopathological classification of canine gastrointestinal tumors was based on the WHO histological classification of tumors in domestic animals³. Despite the presence of well-described morphological characteristics in the classification, to date, the biological and/or clinicopathological features of canine gastrointestinal tumors have not yet been established properly.

There are two major concepts to explain the carcinogenesis of alimentary tract tumors in humans, especially in the colorectum: the adenoma-carcinoma sequence^{4–6} and *de novo* carcinoma theories^{7–10}. Carcinogenesis, by the adenoma-carcinoma sequence, progresses from benign precursor lesions⁶. This theory indicates a progressive malignant transformation, induced by stepwise genetic alterations². The concept is mainly based on the phenomenon of frequent occurrence of colorectal carcinoma in adenomatous lesions. On the other hand, *de novo* carcinogenesis is characterized by primary tumor lesions, which exhibit a flat or dome-

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*Corresponding author: K Uchida

(e-mail: auchidak@mail.ecc.u-tokyo.ac.jp)

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shaped appearance. Since small carcinomatous lesions occur without any antecedent adenomatous elements in their vicinity, it can be assumed that these malignant lesions do not originate from precursor adenomatous lesions^{10–12}. In addition, flat-shaped tumor lesions are reported to be highly malignant, even though they are very small in size^{13, 14}.

The aim of the present study was to explain the clinicopathological and histopathological features of canine gastrointestinal epithelial tumors. Biopsy samples of canine gastrointestinal epithelial tumors were classified according to the “WHO histological classification of tumors in domestic animals.” The results obtained from this study may provide beneficial knowledge regarding the histopathological nature, age, sex, breed and tumor location of spontaneous canine tumors.

Materials and Methods

Cases

A total of 131 biopsy samples of gastrointestinal epithelial tumors (38 gastric, 13 small intestinal, and 80 large intestinal tumors) from 95 dogs were collected through endoscopy or surgical excision, at three institutions (Veterinary Medical Center of the University of Tokyo, Japan Small Animal Medical Center and Japan Animal Referral Medical Center), between 2013 and 2016. We recorded the breed, age, and sex of the study subjects, as well as the anatomical locations, presence of metastasis/invasion and histopathological classification of the lesions.

Histological examinations

All the samples were fixed in 10% neutral buffered formalin and routinely embedded in paraffin. The tissue sections, which were four-micrometers in thickness, were stained with hematoxylin and eosin (HE) stains. The specimens were examined by three pathologists: one pathologist was certified by the Japanese Society of Toxicologic Pathology (Tsubasa Saito) and the other two pathologists were certified by the Japanese College of Veterinary Pathology (James K. Chambers and Kazuyuki Uchida). Each lesion was classified according to the “WHO histological classification of tumors of the alimentary system of domestic animals”³. In addition, histological patterns of adenocarcinoma (excluding signet-ring cell carcinomas and mucinous adenocarcinomas) were classified into polypoid growth (PG) type and non-polypoid growth (NPG) type, according to the histological classifications of human intestinal tumor¹¹. Briefly, they defined PG carcinomas as those with marked intramucosal proliferation and NPG carcinomas as those without protuberant intramucosal growth.

Results

Age, sex, and breed of the cases

The average ages of the canine patients with gastric, small intestinal, and large intestinal tumors were 9.8 years, 11.9 years and 9.3 years, respectively (Table 1 and 2). The average ages of canine patients with gastric adenoma (7.6 years) and large intestinal adenoma (8.5 years) were observed to be lesser, compared to the average ages of canine

Table 1. Histopathological Diagnosis and Age, Sex and Location of Canine Gastric Epithelial Tumors

	WHO										Total	
	Benign			Malignant						SCC		UND
	Adenoma			Adenocarcinoma								
	Tub*	Pap*	Tub-Pap*	Tub*	Pap*	Tub-Pap*	MUC	SRC				
Age (years)	9.0 ± 2.4	-	2	9.6 ± 2.6	8.5 ± 0.7	10.5 ± 2.5	-	10.4 ± 2.1	-	11.0 ± 1.0	9.8 ± 2.5	
Range	(6–12)			(6–15)	(8–9)	(8–14)		(7–13)		(10–12)	(2–15)	
Sex												
Male	3	0	1	7	2	2	0	6	0	1	22	
Female	1	0	0	5	0	2	0	6	0	2	16	
Location												
Cardia	1	0	0	3	0	0	0	0	0	1	5	
Fundus	0	0	0	3	0	0	0	0	0	1	4	
Body	1	0	0	4	0	0	0	4	0	1	10	
Angular	0	0	0	5	0	1	0	5	0	3	14	
Pylorus	3	0	1	5	2	3	0	8	0	1	23	
Growth pattern												
Polypoid	4	0	1	5 [1]	2 [1]	4 [1]	-	-	-	-	16 [3]	
Non-polypoid	0	0	0	7 [7]	0	0	-	-	-	-	7 [7]	
Total	4	0	1	12 [8]	2 [1]	4 [1]	0	12 [12]	0	3 [3]	38	

Tub, tubular adenocarcinoma; Pap, papillary adenocarcinoma; Tub-Pap, tubulopapillary adenocarcinoma; MUC, Mucinous adenocarcinoma; SRC, Signet-ring cell carcinoma; SCC, Squamous cell carcinoma; UND, Undifferentiated carcinoma; -, not applicable; *, Tubular, papillary, tubulopapillary type of adenocarcinoma, and adenoma were further divided into polypoid growth or non-polypoid growth types based on their growth patterns. Number of cases showing invasion or metastasis is enclosed in bracket. Age are presented as the mean ± standard deviation values.

patients with malignant tumors (10.1 years in gastric carcinoma and 10.0 years in large intestinal carcinoma).

Large intestinal tumors were observed to be more frequent in the male canine patients, compared to the females: the male/female ratio was 51/26 (Table 2). However, there was no significant gender predilection observed in the incidence of gastric or small intestinal tumors (Table 1 and 2).

Jack Russell terriers and Miniature Dachshunds were the most commonly affected breeds, with regards to with gastric (Table 3) and intestinal (Table 4) tumors, respectively. These tumors were observed to have a tendency to occur in multiple regions throughout the gastrointestinal tract. No cases of signet-ring cell carcinoma, mucinous adenocarci-

noma, or undifferentiated carcinoma were detected in Jack Russell terriers.

Anatomical location of the tumors

In the current study, the most common anatomical location, for gastric tumors, was the angular and the pyloric regions (Table 1). There were no particular areas in the small intestine, where tumors developed frequently (Table 2). However, adenoma and adenocarcinoma were observed to have a tendency to develop in the lower parts of the large intestine, such as the colorectal junction and the rectum (Table 2).

Table 2. Histopathological Diagnosis and Age, Sex and Location of Canine Intestinal Epithelial Tumors

		WHO							Total	
		Benign	Malignant					ASC		UND
		Adenoma*	Adenocarcinoma			SRC				
		Aci*	Pap*	MUC						
Small intestine										
Age (years)		-	11.0 ± 5.3	13	10.8 ± 1.5	11	-	NR	11.9 ± 3.1	
	Range		(6–18)		(9–13)				(6–18)	
Sex										
	Male	0	4	0	2	0	0	0	6	
	Female	0	0	1	3	1	0	0	5	
	No recorded	0	1	0	0	0	0	1	2	
Location										
	Duodenum	0	1	0	1	0	0	0	2	
	Jejunum	0	1	0	1	1	0	0	3	
	Ileum	0	2	1	2	0	0	0	5	
	No recorded	0	1	0	1	0	0	1	3	
Growth pattern		0								
	Polypoid	0	2	1 [1]	-	-	-	-	3 [1]	
	Non-polypoid	0	3 [3]	0	-	-	-	-	3 [3]	
Total		0	5 [3]	1 [1]	5 [5]	1 [1]	0	1 [1]	13	
Large intestine										
Age (years)		8.5 ± 2.2	10.8 ± 2.9	9.3 ± 2.3	5	6.5 ± 2.1	-	-	9.3 ± 2.8	
	Range	(4–14)	(5–15)	(8–12)	-	(5–8)	-	-	(4–15)	
Sex										
	Male	26	24	1	0	0	0	0	51	
	Female	9	12	2	1	2	0	0	26	
	No recorded	0	2	0	1	0	0	0	3	
Location										
	Cecum	0	0	0	0	0	0	0	0	
	Colon	3	6	2	0	1	0	0	12	
	Colorectal junction	14	5	1	0	1	0	0	21	
	Rectum	18	25	0	1	0	0	0	44	
	No recorded	0	2	0	1	0	0	0	3	
Growth pattern										
	Polypoid	35	31 [5]	3	-	-	-	-	69 [5]	
	Non-polypoid	0	7 [7]	0	-	-	-	-	7 [7]	
Total		35	38 [13]	3	2 [2]	2 [2]	0	0	80	

Aci, Acinar adenocarcinoma; Pap, papillary adenocarcinoma; MUC, Mucinous adenocarcinoma; SRC, Signet-ring cell carcinoma; ASC, Adenosquamous carcinoma; UND, Undifferentiated carcinoma; -, not applicable; NR, not record; *, Tubular, papillary type of adenocarcinoma, and adenoma were further divided into polypoid growth or non-polypoid growth types based on their growth patterns. Number of cases showing invasion or metastasis is enclosed in bracket. Age are presented as mean ± standard deviation values.

Table 3. Histopathological Diagnosis and Breeds of Dogs of Canine Gastric Epithelial Tumors

Breed	Benign			Malignant							Total	(%)
	Adenoma			Adenocarcinoma					SCC	UND		
	Tub	Pap	Tub-Pap	Tub	Pap	Tub-Pap	MUC	SRC				
Jack Russell terrier	2	0	1	4	2	3	0	0	0	0	12	31.6
Miniature Dachshund	0	0	0	1	0	1	0	6	0	1	9	23.7
French Bulldog	0	0	0	3	0	0	0	0	0	0	3	7.9
Mix	0	0	0	1	0	0	0	2	0	0	3	7.9
Belgian Shepherd Dog	0	0	0	1	0	0	0	1	0	0	2	5.3
English Cocker Spaniel	0	0	0	0	0	0	0	1	0	1	2	5.3
Leonberger	0	0	0	1	0	0	0	1	0	0	2	5.3
Maltese	2	0	0	0	0	0	0	0	0	0	2	5.3
Miniature Schnauzer	0	0	0	0	0	0	0	1	0	0	1	2.6
Shih Tzu	0	0	0	0	0	0	0	0	0	1	1	2.6
West Highland White terrier	0	0	0	1	0	0	0	0	0	0	1	2.6
Total	4	0	1	12	2	4	0	12	0	3	38	100.0

Tub, tubular adenocarcinoma; Pap, papillary adenocarcinoma; Tub-Pap, tubulopapillary adenocarcinoma; MUC, Mucinous adenocarcinoma; SRC, Signet-ring cell carcinoma; SCC, Squamous cell carcinoma; UND, Undifferentiated carcinoma.

Table 4. Histopathological Diagnosis and Breeds of Dogs of Canine Intestinal Epithelial Tumors

Breed	Benign		Malignant					Total	(%)
	Adenoma	Aci	Adenocarcinoma			ASC	UND		
			Pap	MUC	SRC				
Small intestines									
Miniature Dachshund	0	1	1	1	0	0	0	3	23.1
Jack Russell terrier	0	2	0	0	0	0	0	2	15.4
Miniature Schnauzer	0	0	0	2	0	0	0	2	15.4
American Cocker Spaniel	0	0	0	1	0	0	0	1	7.7
Chinese Crested Dog	0	0	0	0	1	0	0	1	7.7
Mix	0	0	0	1	0	0	0	1	7.7
Papillon	0	1	0	0	0	0	0	1	7.7
Not recorded	0	1	0	0	0	0	1	2	15.4
Total	0	5	1	5	1	0	1	13	100.0
Large intestines									
Miniature Dachshund	25	20	1	0	0	0	0	46	57.5
Jack Russell terrier	0	8	2	0	0	0	0	10	12.5
Boston terrier	2	1	0	0	0	0	0	3	3.8
French Bulldog	3	0	0	0	0	0	0	3	3.8
Border Collie	1	1	0	0	0	0	0	2	2.5
Lakeland terrier	0	2	0	0	0	0	0	2	2.5
Mix	0	0	0	1	1	0	0	2	2.5
Papillon	1	1	0	0	0	0	0	2	2.5
Shetland Sheepdog	1	1	0	0	0	0	0	2	2.5
Welsh Corgi	1	0	0	0	1	0	0	2	2.5
Belgian Shephrd Dog (Tervueren)	0	1	0	0	0	0	0	1	1.3
Toy Poodle	0	1	0	0	0	0	0	1	1.3
Yorkshire Terrier	1	0	0	0	0	0	0	1	1.3
Not recorded	0	2	0	1	0	0	0	3	3.8
Total	35	38	3	2	2	0	0	80	100.0

Aci, Acinar adenocarcinoma; Pap, papillary adenocarcinoma; MUC, Mucinous adenocarcinoma; SRC, Signet-ring cell carcinoma; ASC, Adenosquamous carcinoma; UND, Undifferentiated carcinoma.

Histopathological classification of gastric tumors

The 38 gastric tumors, involved in the current study, included five adenomas, thirty adenocarcinomas and three undifferentiated carcinomas. There were no cases of mucinous adenocarcinoma or squamous cell carcinoma. Adenoma lesions displayed a focal polypoid growth pattern, composed of tubulopapillary structures (Fig. 1A) and were further classified into four tubular adenomas and one tubulopapillary adenoma; on the other hand, no cases of papillary adenoma were detected (Table 1). The tubulopapillary structures were composed of single-layered columnar epithelial tumor cells, with a slightly enlarged and unevenly located nucleus (Fig. 1B). The 30 adenocarcinomas were further classified into 12 tubular adenocarcinomas, two papillary adenocarcinomas, four tubulopapillary adenocarcinomas and 12 signet-ring cell carcinomas (Table 1). A disorganized cell layer, with loss of cellular polarity, anisokaryosis, and prominent nucleoli were observed in the lesions of papillary, tubulopapillary (Fig. 1C and D) and/or tubular (Fig. 1E and F) adenocarcinoma. Papillary lesions were observed to be accompanied by a fibrovascular stalk, whereas tubular lesions were accompanied by irregular branching tubules. All adenomas (5/5), papillary adenocarcinomas (2/2), tubulopapillary adenocarcinomas (4/4) and less than half of the tubular adenocarcinomas (5/12) exhibited polypoid growth. Submucosal invasion or metastasis was detected in 27% (3/11) of the PG type adenocarcinomas and 100% (7/7) of the NPG type adenocarcinomas. Lesions of signet-ring cell carcinoma displayed a focal proliferation, just beneath the mucosal epithelium, occasionally. The tumor cells, which possessed abundant intracytoplasmic mucin (Fig. 1G), commonly invaded into the deep mucosa or the submucosa and often metastasized into the regional lymph nodes. Undifferentiated carcinomas did not show any tubular or papillary structures; however, a diffuse invasive growth of pleomorphic tumor cells, with irregular-shaped nuclei and prominent nucleoli, was observed frequently (Fig. 1H).

Histopathological classification of intestinal tumors

The current study involved 93 intestinal tumors: 13 small intestinal tumors and 80 large intestinal tumors (Table 2). Tumors of the small intestine were histologically classified into six adenocarcinomas (five acinar and one papillary adenocarcinoma), five mucinous adenocarcinomas, one signet-ring cell carcinoma and one undifferentiated carcinoma. No cases of adenoma or adenosquamous carcinoma were detected in the small intestine. A half (3/6) of the adenocarcinomas exhibited polypoid growth: acinar (2/5) and papillary (1/1) types. Submucosal invasion or metastasis was detected in 33% (1/3) of PG type adenocarcinomas and 100% (3/3) of NPG type adenocarcinomas.

The 80 large intestinal tumors, in the current study, were histologically classified into 35 adenomas, 41 adenocarcinomas (38 acinar and three papillary adenocarcinomas), two mucinous adenocarcinomas and two signet-ring cell carcinomas. No cases of adenosquamous carcinoma or

undifferentiated carcinoma were detected in the large intestine. Adenoma showed a focal polypoid growth, composed of papillary and/or tubular structures (Fig. 2A). A single layer of the columnar epithelium consisted of epithelial tumor cells, with slightly enlarged and unevenly located nuclei (Fig. 2B). The most common type of intestinal adenocarcinoma (Fig. 2C–E), observed in the current study, was the acinar adenocarcinoma (tubular carcinoma). The lesion was composed of multi-layered acinar tubular structures and the nuclei of the tumor cells were heterogeneous and irregularly-shaped, with prominent nucleoli (Fig. 2D), or the basement membrane of the neoplastic glands were not clear (Fig. 2F). Most of the colorectal adenocarcinomas (34/41), including 31 acinar and three papillary types, showed the polypoid growth pattern (Fig. 2C), whereas the only tumor that showed the non-polypoid growth pattern (7/41) was the acinar adenocarcinoma (Fig. 2E). Submucosal and muscular invasion was detected in 18% (6/34) of the PG type adenocarcinomas and 100% (7/7) of the NPG type adenocarcinomas. Mucinous adenocarcinoma and signet-ring cell carcinoma showed lesions, which were predominantly seen in the submucosa. Mucinous adenocarcinoma showed severe mucinous lesions in the submucosa, with sporadically formed irregular glandular structures (Fig. 2G and H). Intracytoplasmic mucin was observed in the tumor cells of signet-ring cell carcinoma. Mucinous adenocarcinoma and signet ring cell carcinoma were occasionally observed in the same specimen. In undifferentiated carcinoma, the tumor cells that lacked the cytological features of the typical epithelial tumor and had a high nuclear-cytoplasmic ratio with indistinct cellular borders were observed within the mucosa, submucosa and the muscular layer. This lesion was accompanied by partial lesions that displayed tubular, signet-ring and mucinous differentiations.

Discussion

Canine gastrointestinal epithelial tumors have attracted the interest of human tumorigenesis researchers because spontaneous gastrointestinal tumors are rare in experimental animals. However, the biological behaviors and clinicopathological and histopathological features of canine tumors are not yet well known. In canine medicine, gastrointestinal polyps are frequently detected, during endoscopic examinations. The present study, we reviewed 131 canine gastrointestinal epithelial tumors. While, information on the average age, location of tumor lesions, or predisposition towards a particular gender is already well-established^{15–17}, the present study revealed that in Japan, gastrointestinal epithelial tumors occur more frequently in Jack Russell Terriers and Miniature Dachshunds. Previous reports on the subject revealed diverse results, with some authors stating that there was no predisposition towards any particular breed, in canine gastric neoplasms^{15, 18}, whereas others showed that Belgian Shepherd Dogs¹⁹, Collies¹⁵, German Shepherds^{15, 20} and West Highland White terriers²⁰ have increased risks of gastric or intestinal carcinoma. However, Jack Russell Ter-

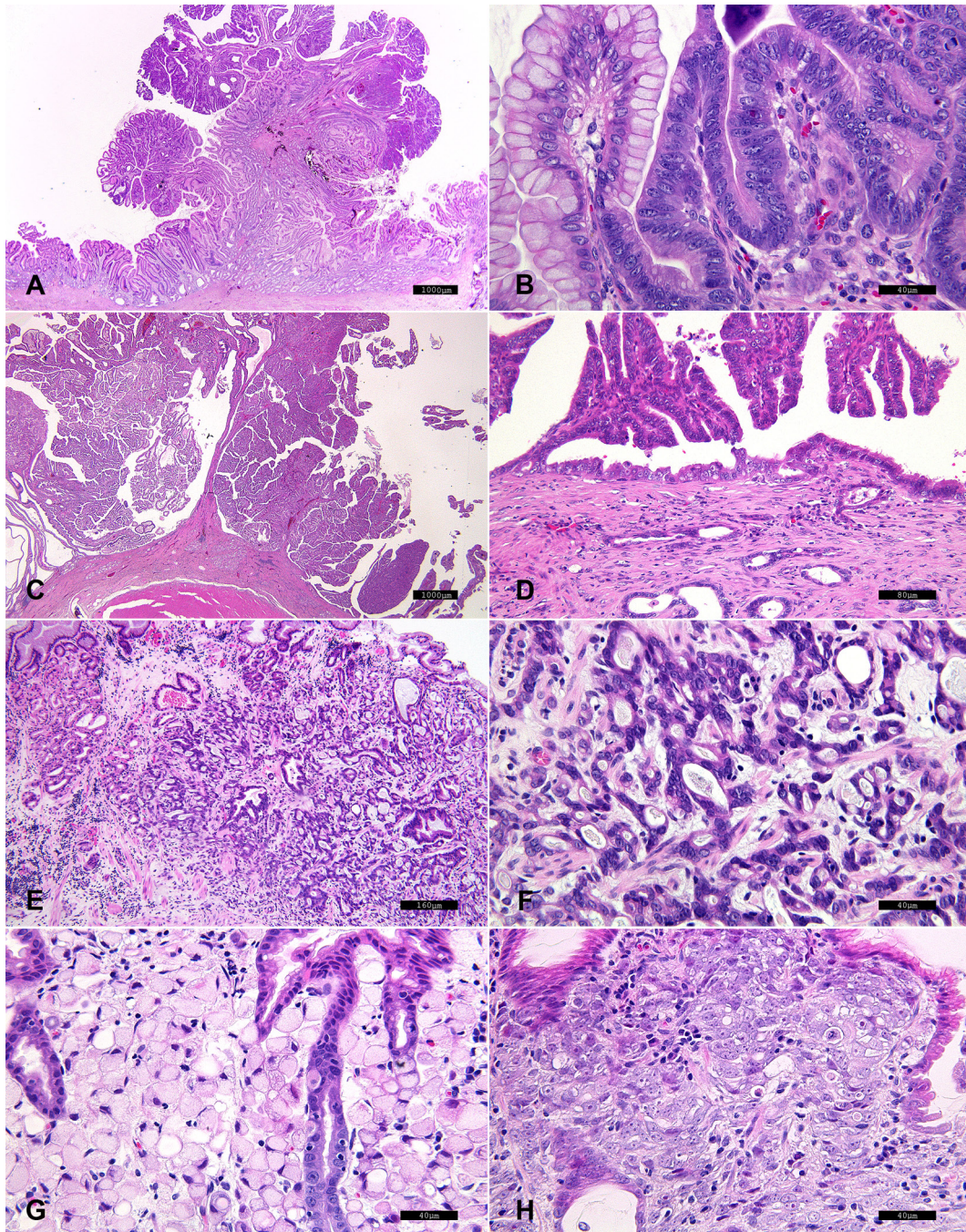


Fig. 1. Canine gastric epithelial tumors; HE stained. (A) Tubulopapillary adenoma with polypoid proliferation. Bar=1,000 μ m. (B) Higher magnification of Fig. 1A; tumor cells of tubulopapillary adenoma on the right. Bar=40 μ m. (C) Polypoid proliferation of tubulopapillary adenocarcinoma with focal submucosal invasion. Bar=1,000 μ m. (D) Higher magnification of Fig. 1C; focal invasion of malignant papillary adenocarcinoma cells to the muscularis. Bar=80 μ m. (E) Non-polypoid growth of tubular adenocarcinoma within the lamina propria. Bar=160 μ m. (F) Higher magnification of Fig. 1E; tumor cells of tubular adenocarcinoma with irregular tubular structures. Bar=40 μ m. (G) Tumor cells of signet-ring cell carcinoma, with eccentric nuclei due to abundant intracytoplasmic mucin. Bar=40 μ m. (H) Tumor cells of undifferentiated carcinoma without specific differentiation. Bar=40 μ m.

riers and Miniature Dachshunds were not considered by any of these reports. In the current study, Jack Russell Terriers were frequently observed to develop 'multiple polyp' lesions throughout the gastrointestinal tract, especially in the stomach and rectum, from an early age (two years). The gas-

trointestinal polypoid lesions, observed in in this breed, are similar to the lesions seen in human familial adenomatous polyposis (FAP). FAP is known to form a considerable number of gastrointestinal polyps in young patients²¹⁻²⁴, while several authors have also reported patients with relatively

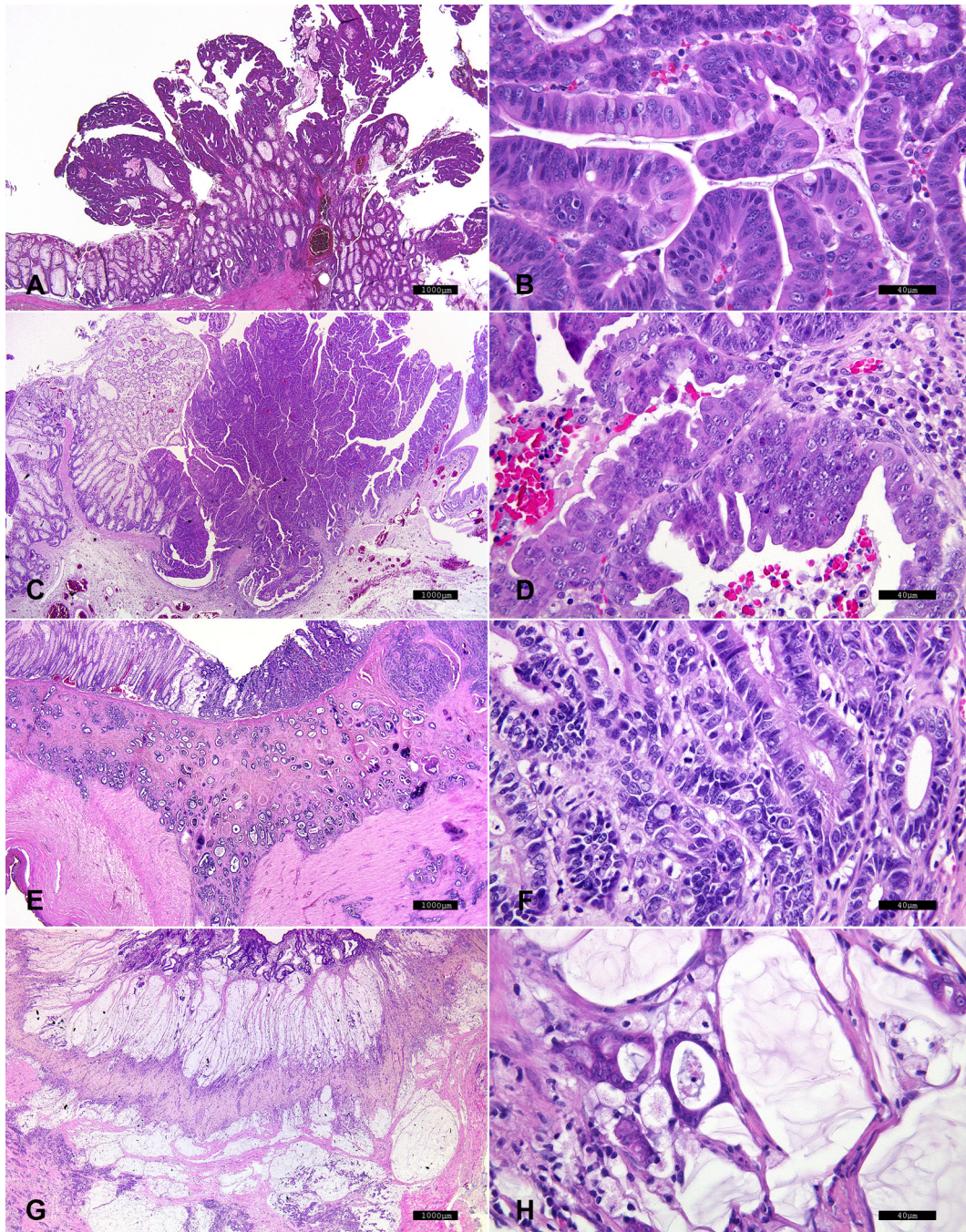


Fig. 2. Canine intestinal epithelial tumors; HE stained. (A) Colorectal adenoma with polypoid proliferation. Bar=1,000 μm . (B) Higher magnification of Fig. 2A; tumor cells of colorectal adenoma with a slight atypia. Bar=40 μm . (C) Polypoid proliferation of papillary adenocarcinoma with focal submucosal invasion. Bar=1,000 μm . (D) Higher magnification of Fig. 2C; tumor cells of papillary adenocarcinoma with anisokaryosis and prominent nucleoli. Bar=40 μm . (E) Non-polypoid growth of acinar adenocarcinoma in the mucosa and invasion into the submucosa. Bar=1,000 μm . (F) Higher magnification of Fig. 2E; tumor cells of acinar adenocarcinoma with irregular tubular structures. Bar=40 μm . (G) Mucinous adenocarcinoma, with abundant mucin within the submucosa and muscularis. Bar=1,000 μm . (H) Higher magnification of Fig. 2G; tubular structures and signet-ring cells, with excess mucin in the lesion of mucinous adenocarcinoma. Bar=40 μm .

fewer polyps^{25, 26}. The age and location of polypoid lesions in the present Jack Russell terrier cases were similar to those reported in human FAP^{22, 24, 26}; however, the high incidence of gastric tumors may be a characteristic unique to the breed

of Jack Russell terriers. In contrast, the large intestine is of importance, while considering the tumorigenesis of gastrointestinal tumors in Miniature Dachshunds because the breed frequently develops inflammatory polyposis in the

colorectum^{27, 28}. A previous study, by the authors, showed that inflammatory polyposis in Miniature Dachshunds may subsequently develop into adenoma or adenocarcinoma²⁹. Hence, these two breeds of dog could possibly provide useful information as models in the study of tumorigenesis of gastrointestinal tumors.

According to the “WHO histological classification of tumors of the alimentary system of domestic animals,” malignant intestinal epithelial tumors are classified into acinar (tubular) adenocarcinoma, papillary adenocarcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma, undifferentiated carcinoma and adenosquamous carcinoma³. Although there have been a few reports on canine gastrointestinal squamous cell carcinoma^{30, 31}, the tumor was not detected in the present study. Moreover, these tumors frequently display mixed histopathological features within a specimen and hence, it would be difficult to make a differential diagnosis between acinar and papillary adenocarcinomas, based on the cell morphology alone. Thus, the histological growth pattern is of importance, while diagnosing an adenocarcinoma. The current study focused on the histologic growth patterns of adenocarcinomas, namely polypoid growth pattern and non-polypoid growth pattern. Invasion and/or metastasis were detected in 21% (10/48) of the PG type adenocarcinomas and 100% (17/17) of the NPG type adenocarcinomas.

Considerable research has been performed on the topic of human polypoid and non-polypoid lesions. Adenocarcinomas with the non-polypoid pattern of growth are considered as “*de novo* carcinomas,” from a histogenesis perspective and are different from adenocarcinomas with the polypoid growth pattern, indicative of an adenoma-carcinoma sequence¹¹. The *de novo* carcinoma theory is based on the recognition of small lesions of colorectal cancer of the superficial type, forming NPG type or depressed lesions^{11, 13, 32, 33}, which often lack adenomatous components³⁴. NPG type adenocarcinomas frequently infiltrate into the submucosa and readily permeate the lymphatics and veins^{11, 13, 14, 32, 35}, growing rapidly and resulting in advanced carcinomas³⁴. These histological and biological characteristics may be similar between humans and canines.

In conclusion, the present study provided the status of the occurrence of canine gastrointestinal tumors in Japan; reported the Jack Russell terriers and Miniature Dachshunds as the most susceptible breeds and explained the histopathological features of the tumors. Histological growth patterns are important, in order to understand the histopathological and biological features of canine gastrointestinal tumors. In particular, most of the canine adenocarcinomas with non-polypoid growth pattern have a higher malignant potential, when compared to canine adenocarcinomas with polypoid growth pattern.

Disclosure of Potential Conflicts of Interest: The authors declare that they have no conflicts of interest.

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