Gastric carcinoma in canines and humans, a review*S. Hugen [a #], R.E. Thomas [b], A.J. German[c], I.A. Burgener[a], P.J.J. Mandigers[a]*

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Abstract:

Gastric carcinoma (GC) is the most common neoplasm in the stomach of dogs. Although incidence in the general population is reported to be low, breed-specific GC has a high incidence. Median age at presentation ranges from 8 to approximately 10 years. The disease is mostly located in the lesser curvature and antropyloric region of the stomach. Unfortunately, diagnosis is usually made when the disease is at an advanced stage and, therefore, prognosis is poor. Due to similarities in clinical presentation, diagnosis, histology and prognosis, canine GC may serve as a valuable model for human GC. Extensive pedigrees of canine gastric carcinoma cases could reveal insights for human gastric carcinoma. Putative species differences include the role of *Helicobacter* in pathogenesis, the wide array of genetic data and screening available for humans, and treatment protocols that are available for human GC.**Introduction**:

The overall prevalence of gastric carcinoma (GC) in dogs is low although, in a small number of breeds, a higher incidence has been reported [1]. The familial occurence of canine GC, combined with the narrow genetic basis of our current purebred populations offers opportunities to investigate the genetic background of (familial) human gastric carcinoma. Potentials advantages for such comparative research includes the fact that dogs share the same environment as humans, the fact that within pedigrees genetic variance is reduced compared to man, and the fact that lifespan is relatively shorter [2]. This paper gives an overview of the current knowledge of the clinical and genetic characteristics of GC in dogs and humans. It will address the complete scope of aetiology, clinical presentation, diagnosis, therapy and prognosis and genetics of canine and human gastric carcinoma, but will not be an in-depth review of human gastric carcinoma.

Aetiology

Human gastric carcinoma ranks as the fifth most prevalent cancer worldwide, and is the third cause of cancer-related death in men and fifth in women[3]. Cancer of the gastro-oesophageal junction (GEJ) is considered a separate group with different epidemiology and aetiology and is outside the scope of this review [4, 5]. The aetiology of human gastric carcinoma is complex and incompletely understood. Besides hereditary cancer syndromes, known risk factors include smoking, alcohol consumption, high salt and fat consumption, obesity, low fruit and vegetable consumption, ageing, low economic status, other gastric diseases, and *Helicobacter pylori* infection [6, 7]. *H. pylori* infection is the best studied of these and causes a three-to-six fold increase in gastric cancer risk. About 1 - 3 % of people infected with *H. pylori* develop gastric cancer. It causes chronic active inflammation, mucosal damage and altered gene expression and epigenetic changes in multiple genes, eventually leading to carcinogenesis [8-11].

The intestinal type (IGC) and diffuse type (DGC) of gastric carcinoma are believed to result from distinct pathogenetic pathways. The IGC form develops after stepwise progression from chronic gastritis to atrophic gastritis, metaplasia, dysplasia to intestinal type carcinoma.Diffuse gastric carcinoma however is thought to arise *de novo* by downregulation of *CDH1*[7, 12]. Early stages of DGC are characterised by, often multiple, foci of superficial signet ring carcinoma in situ [12-14]. Multiple hereditary cancer syndromes increase risk of gastric carcinoma. Hereditary diffuse gastric cancer (HDGC) carries

a cumulative lifetime risk of up to 70% in men and 56 % in women of developing gastric carcinoma for mutation carriers [15, 16]. *H. pylori* infection does not appear to be associated with HDGC [17]. Other, rare, hereditary cancer syndromes increasing the risk of gastric carcinoma are: Lynch syndrome, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), familial adenomatous polyposis, Li-Fraumeni syndrome and Peutz-Jeghers syndrome [18-20].

Similar to human GC, the aetiology of canine gastric carcinoma is complex and poorly understood, but it is believed that both environmental and genetic factors play a role [1, 21]. Long-term administration of N-Nitrosamines can lead to induction of gastric carcinoma, although the relevance of this in clinical settings in unclear [22]. The strong breed predisposition and familial occurrence described for several canine breeds, including the Belgian Shepherd dog, indicates the importance of genetic factors in the aetiology of gastric cancer [1, 21, 23]. In addition, some very small subgroups of canine gastric cancer may have different aetiologies. For example few cases of hypertrophic gastritis (Ménétriers-like disease) progressing into superficial signet-ring-type gastric carcinoma are reported [24, 25]. In the Norwegian Lundehunde, atrophic gastritis, characterised by reduction in parietal cells and hyperplasia of neuroendocrine cells, is reported to be associated with gastric tumour development. In these dogs, hypergastrinaemia secondary to atrophy may be important in carcinogenesis [26, 27]. Unlike in humans, precursor lesions are not frequently described in dogs that develop gastric carcinoma and no convincing relationship could be demonstrated between gastric polyps that are sporadically identified, *Helicobacter*, and gastric carcinoma [28]. *H. pylori* is infrequently found in the stomach of dogs, likely due to the different glycosylation profile and the ability of different strains to adhere to specific host glycan receptors [29]. However, different 'Non-*Helicobacter-pylori*-type *Helicobacter* species (NHPH) are frequently encountered in the stomach of both healthy dogs and those showing signs of gastrointestinal disease [30, 31]. The pathogenic significance of these *Helicobacter* species remains controversial in dogs, since a clear relationship between NHPH and gastritis has not been established [32]. Therefore, a possible role in the aetiology of gastric carcinoma is questionable.

Clinical presentation of gastric carcinoma

Humans

Incidence of gastric carcinoma is particularly high in Eastern Asia with Central and Eastern Europe and South America second and third. Stomach cancer rates are approximately twice as high in males as in females [33]. The vast majority of gastric carcinomas arise sporadically. Familial clustering is apparent in less than 15% of cases and most of these are not associated with a definitive germline mutation [34], and hereditary cancer syndromes are associated with less than 3% of gastric cancer cases [35, 36]. It is only in cases with mutations in germ cells, that the risk of GC is constitutionally passed on to the progeny.

The epidemiology and predominant location of gastric carcinoma varies geographically due to a complex of genetic and environmental factors [7, 37]. Carcinomas in the body or the corpus of the stomach are typically located along the greater or lesser curvature [38]. Similarly, the location of the tumour in hereditary forms of gastric carcinoma also appears to vary with racial and geographical differences [17]. Gastric carcinoma patients are typically middle-aged to older with most patients aged between 50 and 70 years at presentation. Patients younger than 30 years of age are rarely seen [39].

Clinical signs of gastric carcinoma in humans tend to emerge late in the development of the disease. Therefore, the cancer is often at an advanced stage at presentation [40] and more than half the patients have lymph node metastasis at first clinical presentation or surgery [41].

Dogs

According to a recent Norwegian survey, canine GC accounts for only 0.16% of all reported canine cancer cases [1]. This is in accordance with earlier reports in which GC cases accounted for less than 1% of all canine tumours [42, 43]. However, GC is the most common neoplasm in the stomach of dogs compared to the less frequently seen leiomyo(sarco)ma, gastro-intestinal stromal tumours (GIST) and lymphoma [44-48]. An increased prevalence of gastric carcinoma is present in several dog breeds with breed predispositions reported for the Staffordshire bull terrier, Rough Collie [49], Bouvier des Flandres, Standard poodle, Norwegian elkhound [1], Hovawart and Chow-Chow [45, 47] and, most convincingly, in the Belgian shepherd, Tervueren and Groenendael [1, 21, 23, 50].

Gastric carcinoma is typically a disease of middle aged to older dogs. Median age at presentation ranges from 8 to approximately 10 years [45, 49, 51-54], although there are anecdotal reports of cases less than 5

years of age [52]. Comparable to humans, GC seems to occur more frequently in male than female dogs. Seim-Wikse et al. reported a statistically different odds ratio (OR) for males versus females of 2.3, with only a male to female ratio of 1.2:1 [1]. However, there are other ratios reported varying from 1.4:1 to 2.75:1 [21, 45, 47, 53]. This variation might be explained by the use of relatively small numbers of dogs in these studies as well as phenotypical diversity. There are indications that the male: female ratio is different in different subtypes of gastric adenocarcinoma [43].

As in humans, clinical signs of gastric cancer in dogs are usually mild to absent during the early stages of the disease. The most common clinical signs are vomiting (40-95% of cases), anorexia (48-52%) weight loss (23-52%), and lethargy (25-28%) [45, 47, 54]. Gualtieri et al found no strong relationship between the extent of gastric wall involvement of the tumour and the severity of vomiting. Haematological and biochemical changes are typically absent or small and may consist of mild anaemia, increased liver enzymes, hypoglycaemia, hyperproteinaemia, hypalbuminaemia and prolonged clotting times [45, 47].

Metastasis has classically been reported to occur at a high rate, and has typically reached 70-90% by the time of diagnosis [43, 45, 49, 54]. A possible explanation for this could be that the early stage of the disease is often missed due to the mild nature of the clinical signs meaning that veterinary advice is not sought. The most common site of metastasis is the regional lymph nodes. More distant sites frequently reported are the liver, lung, duodenum, adrenal glands, pancreas, omentum and spleen. In a few more recent smaller studies metastasis percentage at presentation was lower [47, 55-57]. It is unclear if this is due to lesser malignancy in these cases, earlier presentation or the diagnostic protocol used.

The primary tumour in canine gastric carcinoma is most often located in the lesser curvature and pyloric region of the stomach but can extend throughout the stomach [21, 43, 45, 54, 57]. The gastric wall is often markedly thickened and contains abundant fibrous tissue. This scirrhous aspect of the tumour can make the stomach wall non-distensible, a condition sometimes referred to as *linitis plastica*. Ulceration of the mucosal surface is present in about half of the cases and may be characterized by a necrotic centre with a raised rim [43, 45, 49].

Diagnosis

In humans, different diagnostic guidelines vary with the geographic location. However, when gastric carcinoma is suspected, endoscopy with multiple biopsies is recommended consistently in all national and international guidelines [58, 59]. Over 90% of tumour cases are diagnosed by endoscopy [60], partially in conjunction with methods to improve visualization of the mucosa in endoscopy such as confocal endomicroscopy or narrow band imaging, to detect vascular patterns, to improve sensitivity and specificity [61, 62]. There is broad consensus that staging is mandatory for decision making: This can be performed by physical examination, clinicopathological testing (e.g. complete blood count, tests of liver and kidney function), and advanced imaging such as abdominal/pelvic CT (possibly combined with PET-CT) and either CT or radiography of the thorax. However, throughout Europe, endoscopic ultrasonography is the method of choice for the detection of locoregional metastasis and to assess tumour infiltration depth. Laparoscopy, with or without peritoneal wash to detect malignant cells cytologically, is recommended to exclude occult metastasis in surgical candidates [59, 63, 64].

In dogs, the clinical signs, signalment and family history are often sufficient to include GC as a differential diagnosis. Furthermore, in breeds with a strong breed predisposition and a large database of confirmed cases, family history may contribute to the suspicion of gastric carcinoma. Abdominal radiographs may show thickening of the gastric wall, loss of (cranial) abdominal detail, cranial abdominal mass effect, or no specific findings [45, 47]. However, this type of diagnostic investigation is now less commonly performed because of the advent of ultrasonography and CT.

Abdominal ultrasonography enables the morphological assessment of the stomach wall, abdominal lymph nodes, and other possible metastatic sites. This may enable a tentative diagnosis of gastric carcinoma to be made and can direct further diagnostic work-up. The majority of gastric carcinomas are ultrasonographically sessile masses involving all layers of the stomach, and may extend through the serosal surface. Evidence of ulceration and lymphadenopathy may also be apparent, but ultrasonography has relatively poor sensitivity for detection of such lesions. Further, dogs with gastric carcinoma share many ultrasonographic features with dogs that have gastric lymphoma [46, 65]. Although ultrasonography is a valid tool in the diagnostic approach of gastric carcinoma, recent studies found only 50-58% compatibility of ultrasonography in clinical cases of stomach cancer [47, 66].

CT scans are very helpful in assessing stomach wall, lymph nodes, and other indications of metastasis [47, 56], but challenges in interpreting the morphology of the stomach wall persist, most commonly due to gas artefacts or incomplete distension. This can be overcome by using Helical Hydro CT, which offers enhanced contrast and stomach extension; indeed, in a recent feasibility study, imaging results corresponded well with histology of gastric and lymph node biopsies [57].

Endoscopy is the diagnostic method of choice for GC [44, 45, 67], since the epithelial origin of the lesions typically makes for a high rate of diagnostic accuracy [50]. However, in some cases it can be difficult to differentiate changes associated with gastric carcinoma from inflammation [68]. Diagnostic methods to improve the evaluation of gastric mucosa in endoscopy are not routinely used, but may be available in the future to aid *in vivo* diagnosis of (early) gastrointestinal disease [69].

Exploratory coeliotomy is the gold standard for diagnosing GC, but is highly invasive. Its main benefits are the fact that it enables full thickness gastric biopsies to be acquired, and also a complete evaluation of abdominal metastasis. A further advantage of coeliotomy is the potential that simultaneous surgical removal can also be considered if indicated.

Histology

Ninety percent of human gastric cancers are adenocarcinomas, and these are subdivided by histological appearance using a scheme referred to as the Laurén classification into diffuse and intestinal types [70] or classified according to the WHO-guidelines according to the most dominant histological pattern. The WHO classification recognises 4 main types: (i) Tubular adenocarcinomas with prominent dilated or slit-like and branching tubules. Tumour cell morphology is columnar, cuboidal, or flattened by intraluminal mucin; (ii) papillary adenocarcinomas, well-differentiated exophytic tumours with elongated processes lined by cylindrical or cuboidal cells and a fibrovascular connective tissue core; (iii) mucinous adenocarcinomas in which extracellular mucin pools constitute over 50% of the tumour The tumour cells can form glands of columnar mucous-secreting epithelium or irregular cell clusters. Occasional scattered signet ring cells may be present but do not dominate ; and, (iv) signet-ring cell carcinomas where > 50% of the tumour consists of malignant cells containing intracytoplasmic mucin

and the nuclei may be displaced against cell membranes [38]. Histological subtyping is important because of differences in likely pathogenesis, diagnostic testing, therapy and prognosis [14, 59, 71-73]. The term 'early gastric cancer' (ECG) is used for a carcinoma limited to the mucosa or the mucosa and submucosa. In addition, 'precursor lesions' may be recognised in asymptomatic patients and in tissue surrounding cancerous lesions Chronic atrophic gastritis and intestinal metaplasia and dysplasia commonly precede and/or accompany gastric carcinoma of the intestinal type, although only a small portion of these patients progress to develop gastric cancer [38, 74].

In dogs, surgical or endoscopic biopsies are mostly assessed according to a scheme adapted from the human WHO classification with six major types based on predominant histological growth pattern: Papillary, tubular, tubulopapillary, mucinous, signet ring or undifferentiated. The other classification system commonly used is the 'Laurén' classification with the intestinal type tumours forming poorly- to well-differentiated glands and the diffuse type of GC being composed of poorly cohesive cells and lacking glandular structures. The diffuse type tumour will often contain cells with large amounts of intracytoplasmic mucin called signet ring cells [70, 75]. Classification according to the Laurén scheme, with less subgroups gives more power to often small case sets and allows for easier translation to human medicine. The clinical and prognostic significance of the subtypes, irrespective of Laurén or WHO-classification systems, in canine GC has not been clearly demonstrated so far [53].

Biomarkers

In human medicine, the search for prognostic or predictive biomarkers for gastric carcinoma is important in the field of personalised medicine. Indeed, a number of candidate biomarkers have been discovered. HER-2 is a proto-oncogene encoded by the ERBB2 gene, and is a tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family [76]. It is an important predictive biomarker for gastric carcinoma [77]. HER-2 testing is recommended in both American, European and Asian gastric cancer guidelines in patients with metastatic or recurrent gastric cancer under consideration for palliative chemotherapy. When score of immunohistochemical staining for HER-2 is 3+, targeted therapy is

indicated [58, 64, 78-80]. The c-Met proto-oncogene encodes the c-Met receptor. High MET gene amplification and expression in gastric cancer serve as an independent negative prognostic factor. C-Met has also been identified as a possible therapeutic target. A third potential biomarker with possible predictive value is the ligand of PD-1, an immune-inhibitory receptor of the CD28 family which plays a role in tumour immune escape [77].

The tyrosine kinases HER-2 and EGFR (Her-1) have recently been investigated in canine gastric adenoma and carcinoma. HER-2 positivity (3+ staining) was present in 11 of 19 gastric tumours, independent of histological subtype or malignancy. EGFR expression was present in 42% of samples and significantly more in intestinal-type than diffuse-type tumours [81]. The potential implication of these proteins as predictive or prognostic biomarkers needs further investigation and confirmation with gene expression studies[82].

Recently, serum gastrin expression was investigated as a possible biomarker in dogs with gastric carcinoma. This was prompted by a case report of high gastrin in a cattledog with hypergastrinaemia and mucinous gastric carcinoma, and the confirmed association between atrophic gastritis and gastric neoplasia in Norwegian Lundehunde [27]. However, serum gastrin was not useful as a single biomarker [52]. In the search for a biomarker to aid diagnosis of GC in dogs, HER-3 expression and CDX-2 expression have also been investigated. The transmembrane glycoprotein HER-3 is overexpressed in various human cancers including stomach cancer [83, 84]. The nuclear transcription factor CDX-2 is a reliable immunohistochemical marker for human gastrointestinal adenocarcinoma and metastases [85, 86]. Marked HER-3 expression and CDX-2 expression was demonstrated in the canine gastric adenocarcinomas and the lymph node metastasis, and both HER-3 expression and CDX-2 expression was not detected in normal canine gastrointestinal tissues [55]. Thus, complementing standard histological examination of tissue samples with immunohistochemistry may improve diagnostic accuracy and better identify metastasis [55, 56].

Therapy and prognosis

In humans, treatment of gastric cancer is highly dependent on clinical staging and varies in invasiveness according to national and international guidelines. Early gastric cancer lesions can be treated by

endoscopic resection and have a favourable prognosis. Indeed, national screening programmes in Japan and Korea have identified many more patients with early gastric cancer in these countries [58, 87]. Screening may encompass double contrast radiography studies followed by upper endoscopy, or only upper endoscopy [88].

For all patients with advanced gastric cancer without distant metastasis, curative surgery is the aim. Margins of > 5 cm for diffuse gastric cancer and 2-3 cm for intestinal type cancer should be maintained and depending on the grade of cancer D1 lymph nodes (perigastric nodes directly attached along the lesser curvature and greater curvatures of the stomach) or D2 lymph node (D1 plus nodes along the left gastric artery, common hepatic artery, celiac trunk, splenic hilus, and splenic artery) resection is performed [89, 90].

In people carrying a mutation for HDGC, prophylactic total gastrectomy is offered in early adulthood, typically at an age 5 years younger than the youngest affected family member [73, 91].

Peri-operative chemotherapy has been widely adopted as standard care throughout the world. Although in north America chemoradiotherapy is often the first choice, where 5-FU and Leucovorin are combined with radiotherapy[78]. Much used protocols include ECF (epirubicin, cisplatin and 5-FU) or ECX (epirubicin, cisplatin and capecitabine) in Europe and the UK [64, 92] and S-1 sometimes with addition of cisplatin or capecitabine plus oxaliplatin in Asia[58, 93]. For non-resectable disease, palliative chemotherapy is used, with the addition of trastuzumab in HER2 positive patients [64, 78, 80].

The only potentially curative treatment option for gastric carcinoma in the dog is surgical resection. Malignancies should be resected with wide margins of 1-2 cm of apparently normal tissue around the tumour. Unfortunately, in many cases, the extent and location (especially when the lesser curvature is involved) precludes such dissection. Tumours in the antropyloric region may be resected by partial gastrectomy and gastroduodenostomy [45]. Pylorectomy with gastroduodenostomy has a poor long-term survival time in dogs with malignant neoplasia. Median overall survival time of dogs with malignant neoplasia and metastasis was only 33 days (95% CI 14-578) [68]. Surgical resection in 10 cases of gastric adenocarcinoma resulted in a median survival time of 72 days (range 3 months to 4 years) [45]. Survival after surgical resection alone in 8 dogs resulted in a short survival of between 2 days and 10 months [54].

Chemotherapy alone or adjuvant chemotherapy after surgical resection has been described in small case studies and case reports only and may be of limited additional value in advanced disease. Chemotherapy protocols used include carboplatin, doxorubicin, doxorubicin combined with cyclophosphamide and 5-fluorouracil, followed by cisplatin and 5-fluorouracil in combination with cyclophosphamide [47, 54, 56, 94]. In a report of three cases, survival time was 9 weeks, 9 weeks and 7.5 months, respectively [54]. In other reports of a single case, survival time after surgery and adjuvant chemotherapy was 81 days and in 114 days, respectively [47, 94].

Total gastrectomy has been performed sporadically in dogs with gastric carcinoma, but ethical questions remain in performing this extensive surgery in dogs with such advanced disease, because of post-operative quality of life and expected prognosis with metastatic disease [45, 95].

Surgery with adjuvant chemotherapy of gastric adenocarcinoma confined to the mucosa or submucosa may have a more favourable prognosis [56]. Poor prognosis of dogs with gastric carcinoma is likely influenced by late presentation. Recent evaluation of more than 80 biopsies at the Department of Pathobiology, Faculty of Veterinary Medicine, Utrecht University, has shown that it is not always possible to determine the extent of neoplastic infiltration into the muscular layers based on the scant tissue collected during endoscopic biopsy (unpublished observations). This additional uncertainty further complicates the decision as to whether or not surgery is indicated. Furthermore, the less well organised diffuse-type or signet ring- type tumours are considered to have a less favourable prognosis then the more glandular tumours. There are indications that these tumours might metastasise earlier [96]. To the authors knowledge there are currently no screening programs in dogs.

Genetics

Humans

In humans, most cases of gastric cancer are sporadic without evidence of germline mutations, and arise as a result of the complex interplay between environmental risk factors and (acquired) genetic factors. These genetic factors may be the result of somatic gene mutations, single nucleotide polymorphisms (SNPs) in known candidate genes, chromosomal and microsatellite instability, or changes in miRNA profile or epigenetic landscape. Through numerous studies, a multitude of genes and genomic regions

have been implicated in gastric cancer and disease progression. For example, APC, TP53, NME1 have been implicated with loss of heterozygosity [97]. Microsatellite instability is found in up to 38% of sporadic gastric cancer cases and high microsatellite instability is associated with better prognosis [98, 99]. SNPs in inflammatory genes have also been extensively studied, particularly in genes involved in the host response to *H. pylori* infection [100, 101]. A positive association between IL1 markers and increased risk of gastric cancer have also been confirmed by several meta-analyses [102, 103]. However, ethnical and geographical factors, histological subtype (diffuse vs intestinal), and anatomical location of the tumour are also of importance in this association [35, 104]. Another gene with an established gene polymorphism increasing gastric cancer risk is IL17A [105, 106]. The host response to *H. pylori* infection and its' influence on gastric cancer development is also reflected in the MUC1 polymorphism, with the G allele conveying an almost 30% reduced risk of gastric cancer [107].

The PSCA gene, encoding prostate stem cell antigen identified with a Genome Wide Association Study (GWAS) was shown in multiple patient cohorts to hold a polymorphic genetic variation increasing the risk of gastric cancer development. PSCA was revealed to have a role in the inhibition of epithelial cell proliferation [108, 109]. A high level of evidence for association with risk of developing sporadic gastric carcinoma was confirmed for polymorphisms of PSCA and MUC1, in addition to MTX1, PRKAA1, PLCE1, TGFBR1, PKLR, GSTP1, CASP8 and TNF [110]. In addition to these and other risk-conferring genetic factors, a large number of nonsynonymous somatic mutations are present in gastric adenocarcinomas. Frequently mutated genes include TP53, genes of cell adhesion pathways, chromatin remodelling genes and, in diffuse type carcinomas specifically, RHOA – a RAS homology family member [111, 112].

Hereditary diffuse gastric cancer is an autosomal dominant condition caused by a germline mutation in the CDH1 gene. HDGC is a clinical diagnosis based on the criteria of the International Gastric Cancer Linkage Consortium, characterized by early-onset, multigenerational DGC and lobular breast cancer[17]. The CHD1 gene encodesE-cadherin an important cell adhesion molecule. The mutation is most frequently heterozygous and can take many forms and involve both coding and non-coding regions[16]. Loss of function of the remaining allele can be caused by genetic and epigenetic changes such as

promoter hypermethylation and loss of heterozygosity [113]. CHD1 mutations explain about 10-40% of hereditary diffuse gastric cancer cases [17, 91, 114].

A truncating allele in the related protein alpha-E Catenin was identified in a Dutch family with HDGC without CDH1 mutation through exome sequencing [115]. Alpha-E-catenin acts together with β-catenin in connecting the cytoplasmic domain of E-cadherin to the cytoskeleton. Mutations in the catenin gene family however did not appear to be of more widespread importance in CDH1-negative HDGC families[116].

Recently, novel germline mutations in non-CHD1 hereditary gastric cancer have been identified. Multiple genetic mutations in the mitogen-activated protein kinase kinase kinase (MAP3K6) were described in patients with familial gastric cancer from different families [117]. And candidate mutations in BRCA1, STK11, SDHB, PRSS1, ATM, MSR1 and PALB2 were identified in individual CDH1 negative HDGC family members [16]. However, in the majority of families with hereditary gastric cancer, the underlying genetic cause remains unknown.

Dogs

Depending on the patient population at a given research institute, most cases of canine gastric carcinoma are likely to be spontaneous or familial. For instance in the Netherlands, sporadic cases are rare, and the majority of cases occur in interrelated dogs (unpublished observation). Sporadic cases of GC arise through acquired somatic mutations during life, possibly in conjunction with environmental risk factors and epigenetic events. These mutations likely include cell cycle proteins [53]. *KRAS* exon 2 status has been evaluated in canine gastric adenomas and adenocarcinomas in one recent study. The *KRAS* gene encodes a small protein involved in signal transduction between transmembrane receptors (like the EGF-receptor superfamily) and the nucleus [118] and was mutated in one of 14 canine gastric carcinoma cases [81].

In familial canine gastric carcinoma, germline mutations are thought to be passed on through generations with environmental and epigenetic factors contributing to disease expression. However, to date no known mutations in dogs with GC have been published.

Conclusion

Similar to human GC, canine GC is a heterogeneous disease with limited treatment options and a poor prognosis. Whilst it is appreciated that genetic and environmental factors play an important role in cases of gastric carcinoma, much remains unknown about the aetiology. Given the frequent occurrence of familial, presumed hereditary, cases of canine gastric carcinoma in some regions, an opportunity exists for research into the genetics of gastric carcinoma. Extensive pedigrees of canine gastric carcinoma cases may provide a valuable model for human hereditary gastric carcinoma. And due to the unique characteristics of inbred dog populations a far smaller number of animals and DNA markers is needed [119]. For a better prognosis of canine GC in the future and to take advantage of the vast amount of research conducted in humans, it is important to identify cases as early as possible in the course of the disease. A possible benefit for cost-effective screening patients with increased risk of canine familial gastric cancer remains to be investigated.

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