

Article

Endoscopic Biopsy Assessment of Neoplastic Prevalence in Dogs with Chronic Diarrhoea and Non-Suggestive Ultrasound Findings

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Abstract: Chronic diarrhoea is a frequent complaint in dogs. Abdominal ultrasonography is frequently utilised in cases of dogs with chronic diarrhoea. The prevalence of neoplasia in dogs with chronic diarrhoea for which ultrasonographic findings are not suggestive of neoplasia has not been reported. This study aimed to list the histologic diagnosis of endoscopic gastroduodenal biopsies in this specific population. The medical records of 115 dogs with chronic diarrhoea for which an abdominal ultrasound was not suggestive of a neoplastic process and had undergone endoscopic biopsies were reviewed. Cases were excluded if an abdominal ultrasound revealed a focal intestinal mass, loss of intestinal wall layering, or a mass lesion in another location. Dogs that had undergone previous treatment with immunosuppressants were also excluded. Histologic findings revealed neoplastic features in 3 out of 115 cases (2.6%) and non-neoplastic conditions in 112 cases (97.4%). In conclusion, the prevalence of neoplastic disease in this population was very low. This is valuable information when considering the diagnostic approach in patients which meet the population criteria and which would historically have had endoscopy and biopsy recommended with the main goal of excluding neoplasia but have moderate–high anaesthetic risk, limited access to endoscopy and/or when financial constraints are present (Figure 1).

Keywords: dog; diarrhoea; endoscopy; abdominal ultrasonography; enteropathy; lymphoma



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1. Introduction

Diarrhoea is a frequent complaint in small animal medicine [1–3]. It can be a manifestation of extra-gastrointestinal disease, such as hypoadrenocorticism [4], liver disease, chronic kidney disease, or pancreatitis, or due to gastrointestinal diseases *per se*, such as chronic inflammatory enteropathy (CIE), neoplasia, or infectious processes, among others [1,3,5]. Diarrhoea can also be classified based on its duration: acute versus chronic (lasting longer than three weeks, although this may vary depending on the bibliographic source) and by its anatomical origin (small versus large bowel) [5].

In many cases of chronic diarrhoea, CIE and neoplasia remain the main differential diagnoses after initial investigations. CIE is a common cause of persistent or recurrent gastrointestinal signs in dogs, including diarrhoea. According to recent classification suggestions, different entities are recognized, such as food-responsive enteropathy (FRE),

microbiota-related modulation-responsive enteropathy (MrMRE), and immunosuppressant-responsive enteropathy (IRE) [5]. However, distinction between these disorders is challenging, with histopathology providing information as to the underlying type and severity of inflammation, but not a certainty of a response to treatment. The diagnostic approach is tailored to each case, but common diagnostic steps include biochemistry, imaging, endoscopy, and gastrointestinal biopsies. Additionally, therapeutic trials are frequently used to differentiate between the various types of CIE [1–3]. Neoplasia can cause similar signs to CIE; the most common neoplasms affecting the canine gastrointestinal tract are lymphoma, carcinoma, leiomyoma, and stromal tumours [6].

Although the diagnostic utility of ultrasound in patients with chronic diarrhoea was put into question in a previous study (reported to be vital or beneficial only in 15% of cases) [6,7], abdominal ultrasonography is still frequently utilised when approaching dogs with chronic diarrhoea. This imaging modality has certain strengths, such as high accessibility when compared to other imaging modalities and provision of information regarding multiple differential diagnoses of diarrhoea. In some cases, abdominal ultrasonography may reveal features suggestive of neoplasia, such as intestinal mass lesions or loss of wall layering. However, an overlap between imaging findings in neoplastic conditions and other processes has been described, and it is also recognised that some cases of gastrointestinal neoplasia have an unremarkable ultrasonographic appearance [7,8].

Endoscopy is considered an important cornerstone of diagnosis in gastrointestinal pathology due to its relatively non-invasive nature and the ability to obtain histopathological biopsies. Histopathology may help characterise the severity and underlying inflammatory cell type in cases of CIE, but a key reason for many clinicians to perform endoscopy and biopsy is for the attempted exclusion of neoplastic processes which have not been detected by ultrasonography.

It is the authors' hypothesis that the prevalence of neoplasia in dogs with chronic diarrhoea without mass lesions (gastrointestinal and non-gastrointestinal), areas with loss of intestinal wall layering or lymphadenomegaly, is low. The aim of this study was to list the histopathologic diagnoses of endoscopic gastroduodenal biopsies in this specific population. We consider that this information could be useful when discussing the benefits versus risks of pursuing endoscopy in these patients with their carers and may be particularly relevant in animals for which endoscopy is not a viable economic option. A second hypothesis is that dogs with a neoplastic diagnosis would have additional clinical signs more frequently than cases with non-neoplastic diagnoses.

2. Materials and Methods

2.1. Data Collection

This was a retrospective study where the medical records of dogs with chronic diarrhoea that presented to a referral hospital in the United Kingdom between 2010 and 2020, were reviewed.

Dogs were included if they had presented with chronic—longer than 3 weeks—small intestinal or mixed diarrhoea without mass lesions, areas with loss of intestinal wall layering, or lymphadenomegaly, and for which endoscopic biopsies of the stomach and duodenum were available. It was also a requirement for the dog to have an unremarkable faecal analysis. Diarrhoea was considered small intestinal in nature when the frequency of defecation was not increased, there was an absence of tenesmus or dyschezia, or the presence of mucus or fresh blood, based on the description by the carer. The duration of the diarrhoea was recorded from the history provided by the carer. The population was also subclassified according to the presence or absence of protein-losing enteropathy (PLE). PLE was defined as a patient with a clinical diagnosis of enteropathy and hypoalbuminaemia

and an absence of other causes of hypoalbuminaemia. Albumin levels were classified as low (serum albumin levels below 25 g/L) or normal (serum albumin levels between 25 and 40 g/L).

Abdominal ultrasound was performed by a European or American board-certified radiologist or a resident under supervision. Cases were excluded if the abdominal ultrasound revealed a focal intestinal mass, loss of intestinal wall layering (except in cases where this was presumed secondary to evidence of ultrasonographically identified ulceration) or a mass lesion not related to the gastrointestinal tract. Dogs that had undergone previous treatment with immunosuppressants were also excluded.

The presence or absence of the following ultrasonographic features was recorded: transverse dimension, presence of jejunal lymphadenomegaly (size and characteristics), and presence of speckles/striations. The definition of jejunal lymphadenomegaly was based on previous studies, where lymphadenomegaly was considered present when the lymph node had a thickness of more than 5–6 mm, with a maximum thickness range of 1.6–8.2 mm (median 3.9 mm) and a width range of 2.6–14.7 mm (median 7.5 mm) [9]. The definition of intestinal wall thickening was based on previous studies where the data indicate norms for the jejunum of <4.1 mm for dogs up to 20 kg, <4.4 mm for dogs between 20 and 39.9 kg, and <4.7 mm for dogs over 40 kg. Regarding the duodenum, the data indicate norms for the duodenum: <5.1 mm for dogs up to 20 kg, <5.3 mm for dogs between 20 and 29.9 kg, and <6.0 mm for dogs over 30 kg [10].

Gastroduodenoscopy was performed by a European or American board-certified internal medicine specialist or resident under supervision under general anaesthesia. The protocol for endoscopic biopsies was based on the guidelines from the World Small Animal Veterinary Associations International Gastrointestinal Standardisation Group [11]. All samples were taken with a flexible endoscope (different manufacturers were used over the study period), and a minimum number of 8–10 samples were obtained from the stomach and duodenum for each case. Regarding the specific location in each organ, biopsies were taken from different areas. In the duodenum, samples were taken from distal to proximal. In the stomach, samples were taken from the pylorus, pyloric antrum, body, lesser curvature and fundus. Each sample was then retrieved and unfolded from biopsy forceps and placed on a non-absorbent sponge which was then placed in 10% buffered formalin [12].

Endoscopic biopsies were evaluated by European or American board-certified anatomic pathologists. Only cases where the biopsies were considered of good quality according to the pathologist were included. Histologic diagnoses were divided into neoplastic and non-neoplastic categories. The non-neoplastic group included lymphoplasmacytic enteritis (LPE), characterised by inflammation composed exclusively of lymphoplasmacytic cells; eosinophilic enteritis (EE), defined by purely eosinophilic inflammation; and mixed-cell enteritis (ME), which involved mixed inflammatory components, including combinations such as neutrophilic-lymphoplasmacytic, neutrophilic-eosinophilic, or eosinophilic-lymphoplasmacytic. Cases without inflammatory abnormalities were classified as normal histology (N) following the guidelines of the WSAVA International Gastrointestinal Standardisation Group [11,13].

The following data were also collected in a spreadsheet from each case: sex, age, breed, body weight, duration of the diarrhoea (in weeks) and the presence (and nature) of other clinical signs. The results of additional investigations were also reviewed. When available, haematology, biochemistry, basal cortisol and serum cobalamin concentrations were recorded. The presence of anaemia was classified as mild (PCV 30–40%), moderate (PCV 20–30%) and severe (PCV <20%). Anaemia was also classified as non-regenerative (reticulocyte count $0\text{--}80 \times 10^3/\mu\text{L}$) or regenerative (reticulocyte count $>80 \times 10^3/\mu\text{L}$). Leukocytosis was classified as neutrophilia [mild ($12\text{--}30 \times 10^3/\mu\text{L}$), moderate ($30\text{--}60 \times 10^3/\mu\text{L}$) or severe

($>60 \times 10^3/\mu\text{L}$), eosinophilia ($>1.8 \times 10^3/\mu\text{L}$) or lymphocytosis ($>6.8 \times 10^3/\mu\text{L}$). Thrombocytopenia was categorised as a marked decrease ($<10\text{--}30 \times 10^3/\mu\text{L}$), a moderate decrease ($30\text{--}100 \times 10^3/\mu\text{L}$), or a mild decrease ($>100 \times 10^3/\mu\text{L}$). Thrombocytosis was defined as a platelet count exceeding $440 \times 10^3/\mu\text{L}$. The biochemistry parameters which were recorded were albumin (reference range 25–39 g/L), total proteins (reference range 57–80 g/L), total calcium (reference range 2.1–2.8 mmol/L), cholesterol (reference range 3.3–9.1 mmol/L), ALT (reference range 12–85 U/L), DGGR lipase (reference range 8–63 U/L), urea (reference range 2.8–8.3 mmol/L), and creatinine (reference range 41–123 mmol/L). The basal cortisol was considered not supportive of hypoadrenocorticism when values were above 55 nmol/L. An ACTH stimulation test was performed if basal cortisol was below <55 nmol/L. The serum concentration of cobalamin was classified following the reference range of the Gastrointestinal Laboratory in Texas A&M University Veterinary Medicine & Biomedical Science. It was defined that hypocobalaminemia values below <251 ng/L were considered normal in the reference range of 251–908 ng/L, and it was considered increased above 908 ng/L [14].

The survival to discharge and the one-year survival time from the diagnosis were also recorded.

2.2. Statistical Analysis

The statistical analysis, including percentage calculations, was performed using Microsoft Excel (Microsoft® Excel for Mac Version 16.89 (24090815)). No specific statistical tests were applied in this study.

3. Results

3.1. Study Population

During the study period, 115 dogs were enrolled in the study. The median age of all dogs was 7 years (range 7 months to 14 years). There were 49 females (9 intact, 40 neutered) and 66 males (17 intact, 49 neutered). The breeds included in this study are summarised in Table 1. The breeds that were most frequently encountered were the Jack Russel Terrier ($n = 10$), Labrador Retriever ($n = 8$), and Staffordshire Bull Terrier ($n = 7$).

Table 1. Dog breeds.

Cases/Breed	Number of Females	Number of Male
West highland white terrier	2	2
Shetland Sheepdog	0	1
Clumber spaniel	0	1
Whippet	1	0
Miniature schnauzer	0	1
Lhasa Apso	2	0
Border collie	1	5
English Pointer	0	1
French bulldog	2	0
German Shepherd	1	4
Lurcher	0	2
Jack Russel terrier	5	5
Labrador	4	4
Staffordshire bull terrier	4	3
Pug	2	2
Cocker spaniel	3	2
Chihuahua	0	3

Table 1. *Cont.*

Cases/Breed	Number of Females	Number of Male
Cavalier King Charles	0	2
Cockapoo	1	0
Goldendoodle	1	0
Siberian Husky	1	1
Leonberger	0	1
Golden Retriever	1	2
Caim Terrier	1	0
Rottweiler	2	3
Newfoundland	0	1
Old English mastiff	1	0
Cross breed	3	1
Patterdale terrier	0	1
Miniature pincher	1	0
Rhodesian ridgeback	1	0
Hungarian Vizsla X	0	1
Dachshund	1	1
Border terrier	1	0
Whippet	0	1
Springer spaniel	1	3
Rough collie	0	1
Sharpei	1	0

3.2. Clinical Signs

All the patients included in the study had diarrhoea as per the inclusion criteria. Diarrhoea was the only clinical sign in 16/115 of dogs (14%), and 99/115 of the dogs (86%) in the study had additional clinical signs. The median duration of diarrhoea was 24 weeks (range 3–208 weeks). In dogs with additional clinical signs, listed in Table 2, the most common sign was vomiting (87/99 cases [88%]), followed by weight loss (38/99 cases [38%]), and inappetence (34/99 cases [34%]). Other clinical signs included abdominal pain (ten of ninety-nine cases [10%]) and regurgitation (eight of ninety-nine cases [8%]).

Table 2. Clinical signs were reported at the initial presentation.

Clinical Sign	Number of Cases	Percentage
Vomiting	87/99	88%
Weight loss	38/99	38%
Inappetence	34/99	34%
Abdominal pain	10/99	10%
Regurgitation	8/99	8%
Other clinical signs:	10/99	10%
Bloating	5/10	50%
Gagging and retching	1/10	10%
PU/PD	2/10	20%
Haematochezia	2/10	20%

3.3. Haematology and Serum Biochemistry

Haematology was performed in 97/115 (84%) and revealed parameters out of the reference range in 31/97 (32%) of the cases. The most common findings were neutrophilia in 21/31 (68%) of the cases. Mild neutrophilia was identified in 14/21 (67%) of the cases. Moderate neutrophilia was identified in seven out of twenty-one (33%) of the cases. There were no cases with severe neutrophilia. Neutropenia was identified in one of thirty-one (3.2%) of the cases. Anaemia was present in five out of thirty-one (16%) of the cases, where

mild anaemia was present in four out of five (80%) of cases and moderate anaemia was present in one out of five (20%) of cases. Of these, regenerative anaemia was identified in three out of five (60%) of the cases, while non-regenerative anaemia was observed in two out of five (40%) of the cases. Thrombocytosis was identified in eight of thirty-one (26%) of the cases, and mild thrombocytopenia was identified in two of thirty-one (6.5%) of the cases (Table 3).

Table 3. Haematology at initial presentation.

Haematology	Cases	Percentage		Cases	Percentage
Neutrophilia	21/31	68%	Mild	14/21	67%
			Moderate	7/21	33%
			Severe	0/21	0%
Neutropenia	1/31	3.2%			
Anaemia	5/31	16%	Mild	4/5	80%
			Moderate	1/5	20%
			Regenerative	3/5	60%
			Non-regenerative	2/5	40%
Thrombocytosis	8/31	26%			
Thrombocytopenia	2/31	6.5%			

Biochemistry was performed in 96/115 (83%) of the cases and revealed parameters out of the reference range in 71/96 (74%) of the cases. The most common abnormalities were hypoalbuminaemia (42/71, 59% of the cases), hypoproteinaemia (32/71, 45% of the cases) and hypocholesterolaemia (26/71, 37% of the cases). Total hypocalcaemia was identified in nine of seventy-one (13% of the cases). Increased ALT (twelve of seventy-one, 17% of the cases), DGGR lipase (seven of seventy-one, 9.8% of the cases), cholesterol (six of seventy-one, 8.5% of the cases), and urea (four of seventy-one, 5.6% of the cases). All cases had creatinine within the reference range (Table 4).

Table 4. Serum biochemistry at initial presentation.

Biochemistry	Cases	Percentage
Hypoalbuminaemia	42/71	59%
Hypoproteinaemia	32/71	45%
Hypocholesterolemia	26/71	37%
Hypocalcaemia	9/71	13%
Increased ALT	12/71	17%
Hypercholesterolaemia	6/71	8.5%
Increased DGGR	7/71	9.8%
Increased Urea	4/71	5.6%

3.4. Serum Cobalamin

Serum cobalamin concentrations were available in 106/115 (92%) of the cases. From these cases, 48/106 (46%) had decreased values, and 48/106 (46%) cases had normal values. Increased values of cobalamin were seen in 10/106 of the cases (9%) (Table 5).

Table 5. Serum cobalamin concentrations at initial presentation.

Cobalamin	Cases	Concentration	Cases	Percentage
Available	106/115	Low	48/106	46%
		Normal	48/106	46%
		Increased	10/106	9%
No available	9/115			

3.5. Protein-Losing Enteropathy Diagnosis

Protein-losing enteropathy was diagnosed in eight of one hundred and fifteen (7%) of the cases. The mean serum albumin concentration was 14.3 g/L (reference range 25–40 g/L).

3.6. Basal Cortisol

Basal cortisol was measured in 83/115 (72%) of the cases. It was above 55 nmol/L in 70/83 (84%) of the cases. An ACTH stimulation test was performed in 13/83 (16%) of the cases.

3.7. Abdominal Ultrasonographic

Abnormal ultrasonographic findings were identified in 52/115 (45%) of cases. The following features were reported: mucosal speckles (14/52 cases [27%]), mucosal striations (10/52 cases [19%]), lymphadenomegaly (14/52 cases [27%]), and thickening of the intestinal wall (17/52 cases [33%]). Among the cases with intestinal wall thickening, twelve out of seventeen (71%) of cases had diffuse thickening, while five out of seventeen (29%) of the cases had localised thickening, with three out of five (60%) in the jejunum and two out of five (40%) in the duodenum (Table 6).

Table 6. Abdominal ultrasonographic findings.

Ultrasonographic Findings	Cases	Percentage
Mucosal speckles	14/52	27%
Mucosal striations	10/52	19%
Lymphadenomegaly	14/52	27%
Thickening of the intestinal wall	17/52	33%
Diffuse thickening	12/17	71%
Localised thickening	5/17	29%
Jejunum	3/5	60%
Duodenum	2/5	40%

The thickening of the intestinal wall was also subjectively classified as mild (thirteen out of seventeen cases [76%]), moderate (fourteen out of seventeen cases [23%]), or severe (zero out of seventeen [0%]) based on the board-certified radiologist's assessment during the examination, relying on their experience and judgement, as there are no universally established thresholds or specific measurements to objectively define these categories.

3.8. Histologic Findings

Histologic findings revealed neoplastic features in 3 out of 115 cases (2.6%) and non-neoplastic conditions in 112 cases (97.4%). In the non-neoplastic cases, the type of inflammation was classified as lymphoplasmacytic enteritis (LPE, 46/115 cases, [40%]), eosinophilic enteritis (EE, 5/115, [4%]), or mixed-cell enteritis (ME, 60/115 cases, [52%]). Normal histology was seen in one case (1/115, [0.9%]) (Table 7).

Table 7. Histologic findings in duodenal samples.

Histologic Findings	Cases	Percentage
Lymphoplasmacytic enteritis	46/115	40%
Eosinophilic enteritis	5/115	4%
Mixed-cell enteritis	60/115	52%
Lymphoma	3/115	2.6%
Normal	1/115	0.9%

3.9. Clinical Overview of the Cases with a Neoplastic Diagnosis

In the neoplastic group, the histologic diagnosis was large cell lymphoma in all cases. The breeds affected were a Golden Retriever (female, neutered, 8 years), a Rottweiler (male, neutered, 8 years), and a Cocker Spaniel (female, neutered, 9 years). The duration of clinical signs was 3 weeks for the Cocker Spaniel, 4 weeks for the Golden Retriever, and 24 weeks for the Rottweiler. Clinical signs included vomiting ($n = 3/3$), weight loss ($n = 2/3$, and inappetence ($n = 2/3$). Abdominal ultrasonography showed mild jejunal lymphadenopathy in the Cocker Spaniel and mild jejunal ulceration in the Rottweiler. There were no ultrasonographic abnormalities reported in the Golden Retriever.

The serum albumin concentration was low in all three cases. The Cocker Spaniel had a serum albumin level of 15 g/L (reference range: 25–40 g/L), the Golden Retriever had a level of 17 g/L (reference range: 25–40 g/L), and the Rottweiler's serum albumin concentration was 23 g/L (reference range: 25–40 g/L).

Serum cobalamin concentrations were low in the Golden Retriever and Cocker Spaniel, measuring 198 ng/L and less than 150 ng/L, respectively (reference range: 251–908 ng/L). The Rottweiler had normal cobalamin concentration levels at 298 ng/L (reference range: 251–908 ng/L).

3.10. Survival One Year from the Diagnosis

Survival data one year post-diagnosis was available for 66 of the 115 cases (57%); the remaining cases were lost to follow-up at that stage. Of the cases where this information was available, 52 dogs (79%) were still alive one year after diagnosis. The reason for non-survival was recorded in 13/14 cases, with the most commonly recorded reason being euthanasia due to failure to respond to treatment (10 out of 13 cases, 77%). The other reasons recorded were complications from aspiration pneumonia in two dogs and the diagnosis of large cell lymphoma in two dogs (Table 8).

Table 8. Survival one year from the diagnosis.

	Cases	Percentage	One Year Survival	Cases	Percentage
Available	66/115	57%	YES	52/66	79%
			NO	14/66	21%
No available	49/115	43%			

Within the neoplastic group, the Golden Retriever and Rottweiler were euthanised following the diagnosis of large cell lymphoma, while the Cocker Spaniel was lost to follow-up.

4. Discussion

This study describes the histopathological findings of gastrointestinal endoscopic biopsies in dogs with chronic diarrhoea and where abdominal ultrasound did not reveal any mass lesion, loss of intestinal wall layering or lymphadenomegaly. The study design

and inclusion criteria were chosen in order to assess a specific population of animals in a very specific but common clinical scenario. It is the authors' clinical impression that in most cases from this population—where endoscopy is commonly performed—the histology reveals inflammatory disease only. This subjective assessment was the basis for the hypothesis and the aim for the current study.

In the present study, the number of cases for which the histology revealed neoplasia was low, being reported only in 2.6%, confirming the main hypothesis of the study.

Regarding our second hypothesis, which proposed that dogs with a neoplastic diagnosis would exhibit additional clinical signs more frequently than those with non-neoplastic diagnoses, this could not be confirmed due to the low number of neoplastic cases. The primary clinical signs observed in the neoplastic group, apart from diarrhoea, were vomiting, weight loss, and inappetence. In the non-neoplastic group, the most common clinical sign, aside from diarrhoea, was vomiting, followed by weight loss and inappetence.

When a veterinary surgeon and carer face a decision regarding the performance of a test, multiple factors must be taken into account. These include the clinical benefit, the associated risks, and, in the carer's case, the economic cost. The clinical benefit of a test should be weighed against the risk and cost by the veterinary surgeon and the carer.

Clinical benefits may include the confirmation of a diagnosis, additional information with an impact on the treatment or diagnostic approach, or prognostic information. In the type of population that the study sample represents, according to the current data, the likelihood of revealing a diagnosis other than CIE is low. Gastroduodenoscopy and histology in cases of chronic diarrhoea can provide a diagnosis, characterise further the type of inflammation (types and severity) and provide prognostic information. However, even though characterisation of the inflammation is listed as a reason to perform endoscopy by some authors and textbooks, the current scientific evidence does not support a different approach for each type [15,16]. Consequently, the clinical benefit of this histological characterisation remains to be proven. Histopathology can also help identify primary lymphangiectasia and neoplasia. For the former, a diet trial with a low-fat diet can be trialled, and it is an option for food-responsive enteropathy but also lymphangiectasia. As previously discussed, the number of cases in this study where neoplasia was diagnosed in this population was low.

Endoscopic score, clonal rearrangement test, lacteal dilation, and histology have been reported as negative prognostic indicators [17–19], which may represent an important factor for some carers. However, for some other carers, obtaining this information might not justify pursuing endoscopy—particularly as there is currently no evidence to adjust the treatment even if negative prognostic factors are present.

The risks involved in gastrointestinal endoscopy include general anaesthesia, which varies for each patient; recent studies report an anaesthetic-related mortality rate of 0.69% [19,20] and the risk of gastrointestinal perforation [21,22].

Finally, cost is an important factor in carer decision-making. For example, in the authors' institution, the cost of a gastroduodenoscopy is approximately £1640, and a colonoscopy is approximately £1460. Even if endoscopy would ideally be performed in every case to confirm a suspected diagnosis of CIE, exclude neoplasia and tailor the management of the case, sometimes contextualised medicine is required due to economic or anaesthetic factors or comorbidities. As such, it is important to have evidence to support reasonable alternative diagnostic and treatment approaches that might be considered different from the gold standard.

It is also fundamental to bear in mind that a neoplastic process can still be present in cases where a mass lesion, loss of intestinal wall layering, or lymphadenomegaly have not been reported in ultrasound. For example, the sonographic appearance of gastroin-

testinal lymphoma in dogs is highly variable and overlaps with that of normal intestines, other neoplastic conditions, and enteritis [8]. In one study, five out of thirteen (26.7%) of histopathologically confirmed lymphoma cases did not exhibit any sonographic abnormalities [8]. In another study, lymphoma had no intestinal ultrasonographic abnormalities in five out of sixty-five (7.7%) cases [23]. Information regarding large or small cell lymphoma was not specified in these studies. Small cell lymphoma, in particular, can be difficult to diagnose. Previous literature recommends performing immunohistochemistry and PCR for Antigen Receptor Rearrangements (PARR) in addition to histology to differentiate it from chronic inflammatory enteropathy [24]. Abdominal ultrasound did not show abnormalities in the gastrointestinal tract or abdominal lymph nodes in dogs with small cell lymphoma in five out of thirteen (38%) cases in this study [24]. When considering our study population, failing to identify small cell lymphoma represents a main concern when considering not performing endoscopy. While ultrasound of many other types of neoplasia often reveals a mass lesion, these are uncommon findings in dogs with small cell lymphoma [24,25]. Differentiating between inflammation and small cell lymphoma can be crucial, as the prognosis for the latter can be good with chemotherapy [24].

Regarding the frequency of gastrointestinal lymphoma, one study reported this neoplasia in five out of one hundred and thirty-six cases (4%) in dogs with chronic diarrhoea, making it the most frequent neoplastic disease [1]. In another recent study investigating the prevalence of inflammatory enteropathy versus lymphoma in dogs undergoing gastroduodenoscopy, 2% of cases were diagnosed with lymphoma [26]. However, it is worth noting that the study populations in these studies met different inclusion criteria compared to the present population (which was selected based on ultrasonographic findings and the presence of chronic diarrhoea).

In our patients with a histological diagnosis of neoplasia, all were diagnosed with large cell lymphoma, supporting the idea that it is a common neoplasia of the gastrointestinal tract [24]. All cases had concomitant clinical signs and low serum albumin. In a previous study of intestinal lymphoma, hypoalbuminaemia was present in only 38 out of 69 (55%) cases [23]. In the present study, all cases with protein-losing enteropathy (PLE) had inflammatory histology. Consequently, albumin levels do not seem useful for distinguishing between neoplasia and inflammation in determining the need for endoscopy for a final diagnosis. However, it is important to highlight that the number of cases with neoplasia on histology was low, and no clinical differences between the neoplastic and inflammatory groups could be established.

Serum cobalamin levels were low in approximately half of the cases, emphasising that this is a common vitamin deficiency in dogs with chronic diarrhoea. Previous studies on hypcobalaminemia in dogs with CIE reported a frequency of 19% to 38% [1,27–29]. In a study of alimentary cell lymphoma, 40% of cases had hypcobalaminemia [24,25]. In our study, hypcobalaminemia was reported in two out of three cases of neoplasia. However, it is important to note that some authors recommend supplementation when serum cobalamin is below 400 ng/L [14], and by these criteria, all three of those patients would benefit from supplementation. As with serum albumin, serum cobalamin levels do not appear to be useful in increasing suspicion of either neoplasia or inflammation.

This study has several limitations. First, its retrospective design and the fact that abdominal ultrasound, endoscopy and histopathology studies were performed by different board-certified specialists could have affected the described data and outcomes. Despite attempts to standardise the assessment of ultrasonographic features, a degree of subjectivity remains unavoidable. Only gastroduodenoscopy was performed, and it could be argued that the performance of colonoscopy might have provided additional diagnostic information, and a diagnosis of neoplasia could have been missed with the study approach.

Previous studies have shown discrepancies between duodenal and ileal biopsies [30–32]; however, in most cases, these discrepancies were related to the type and severity of inflammation [30]. Only in two cases was neoplasia found in the duodenum but not in the ileum [32].

In the hospital where this study was conducted, it was common practice to perform only upper gastrointestinal endoscopy in this type of population (dogs with chronic diarrhoea where the ultrasound was not highly suggestive of neoplasia), unless significant large intestinal signs were present. Full-thickness biopsies would have strengthened the current conclusions, as neoplastic conditions could have been underdiagnosed [33]. However, these were not performed based on the clinicians' judgement. The inclusion of follow-up information attempts to compensate for this limitation, as previous studies have reported median survival times of 7 or 127 days for dogs with small cell lymphoma without treatment or with only prednisone, respectively [24]. In another study on dogs with intestinal lymphoma, the median survival time was 62 days [23].

Furthermore, the sample size of the group was another potential limitation, as it may not be representative of the general canine population, and the study population was also drawn from a single referral hospital. Only cases that underwent endoscopy were included, which could have impacted the results. Also, the sample heterogeneity in terms of breeds and ages represents an additional limitation, which could have affected the findings. Therefore, caution should be exercised when generalising these results to all dogs with chronic diarrhoea. Future studies with larger, more standardised populations are needed to address these limitations.

5. Conclusions

In conclusion, although even larger studies are required, the likelihood of neoplasia seems to be very low in dogs with chronic diarrhoea and specific abdominal ultrasound findings.

We believe this information is of interest, as the study sample represents a common presentation of canine patients and clinical scenarios where endoscopy is strongly recommended and commonly performed. The study results are valuable when discussing the diagnostic approach with carers, particularly in patients with moderate–high anaesthetic risk, difficult access to endoscopy and/or when economic funds are limited; in summary, when contextualised medicine is necessary. That being said, the authors recognise that histopathology remains the gold standard for diagnosis of gastrointestinal disorders, and careful consideration of all factors must be explained to the carer prior to performing endoscopy.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/sci7020039/s1>.

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Informed Consent Statement: This study was based on the retrospective use of historic data collected in the normal course of veterinary clinical practice, where informed owner consent was given at the time for the anonymous use of medical records. For this study, the data were anonymised to ensure no patient or owner could be identified as a result of publication. Thus, to adhere to the RCVS ERP Guidelines and RCVS/BVA Ethical Review Working report, the authors ensured that informed consent was obtained from owners regarding the anonymous use of medical records and maintained the anonymisation of all the personal data regarding the patients and owners during the construction of this manuscript (Supplementary Materials).

Data Availability Statement: The data are contained within the article. The data presented in this study are available in the tables and figures in the article “Endoscopic Biopsy Assessment of Neoplastic Prevalence in Dogs with Chronic Diarrhoea and Non-Suggestive Ultrasound Findings”.

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