

This is the peer reviewed version of the following article:

Desmas, I; Burton, JM; Post, G; Kristal, G; Kirstal, O; Gauthier, M; Borrego, JF; Di Bella, A; Lara-Garcia, A (2016), Clinical presentation, treatment and outcome in 31 dogs with presumed primary colorectal lymphoma (2001-2013). *Veterinary and Comparative Oncology*. doi: 10.1111/vco.12194

which has been published in final form at <http://dx.doi.org/10.1111/vco.12194>.

This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

The full details of the published version of the article are as follows:

TITLE: Clinical presentation, treatment and outcome in 31 dogs with presumed primary colorectal lymphoma (2001-2013)

AUTHORS: Desmas, I; Burton, JM; Post, G; Kristal, G; Kirstal, O; Gauthier, M; Borrego, JF; Di Bella, A; Lara-Garcia, A

JOURNAL TITLE: *Veterinary and Comparative Oncology*

PUBLISHER: Wiley

PUBLICATION DATE: 29 March 2016 (online)

DOI: 10.1111/vco.12194

1 **Clinical presentation, treatment and outcome in 31 dogs with presumed primary colorectal**
2 **lymphoma (2001-2013).**

3 Isabelle Desmas, DVM, MVetMed ¹; Jenna Burton, DVM, MS, DACVIM (Oncology)²; Gerald Post,
4 DVM, MEM, DACVIM (Oncology)³; Orna Kristal, DVM, DACVIM (Oncology)⁴; Meredith
5 Gauthier, DVM, DACVIM (Oncology) ⁵; Juan F. Borrego, DVM, DACVIM (Oncology)⁶; Andrea Di
6 Bella, DVM, CertSAM, Dip.ECVIM-CA (Medicine)⁷; Ana Lara-Garcia, DVM, PhD, MSc, PgCert
7 Med Ed, Dip. ACVIM & ECVIM-CA (Oncology)¹.

8 ¹ Royal veterinary College, Hatfield, Hertfordshire, UK

9 ² Animal Cancer Center, Veterinary Teaching Hospital, Colorado State University, Fort Collins, CO,
10 USA

11 ³ The Veterinary Cancer Center , CT , USA-

12 ⁴ Chavat Daat Veterinary Speciality Center, Beit Berl, Israel

13 ⁵ Mississauga Oakville Veterinary Emergency Hospital and Referral Services, Oakville, Ontario,
14 Canada

15 ⁶ School of Veterinary Medicine, University of Madison-Wisconsin, Wisconsin, USA

16 ⁷ Vets Now Referrals, Chatham, Kent, UK

17

18 Presented in abstract form at the Veterinary Cancer Society congress, Las Vegas, USA, October 2012.

19 Address to corresponding author is Isabelle Desmas at Davies Veterinary Specialists Manor Farm

20 Business Park, Higham Gobion, Hitchin, Hertfordshire SG5 3HR, UK –

21 idesmas@vetspecialists.co.uk

22

23

24

25 The objective of this multicenter retrospective study was to describe clinical presentation, treatment,
26 outcome, and determine prognostic factors for dogs with presumed primary colorectal lymphoma
27 (PCRL). Thirty-one dogs were included. The predominant features of PCRL were high grade (n=18)
28 and immunophenotype B (n=24). Most dogs were substage b (n=25) with higher prevalence of
29 haematochezia (n=20). One dog had surgery only. Thirtydogs received chemotherapy; amongst them
30 13 had surgery or radiotherapy. Progression free survival (PFS) was 1318 days and disease-related
31 median survival time (MST) 1845 days. Fourteen dogs were alive at the end of the study with a
32 median follow-up time of 684 days (3- 4678 days). Younger dogs had longer PFS (p=0.031) and
33 disease-related MST (p=0,01).Presence of haematochezia corresponded with longer PFS (p=0.02).
34 Addition of local treatment to chemotherapy did not significantly improve the outcome (p=0.584).
35 Canine PCRL has considerably longer PFS and MST than other forms of non-Hodgkin's lymphoma.

36 Keyword: canine, lymphoma, chemotherapy, colorectal

37 Abbreviations

38 AL: Alimentary Lymphoma

39 CI: Confidence Interval

40 CR: Complete Response

41 GI: Gastrointestinal

42 MST: Median Survival Time

43 PCRL: Primary Colorectal Lymphoma

44 PFS: Progression Free Survival

45 PR: Partial Response

46 **Introduction**

47 Canine gastrointestinal (GI) lymphoma, also named alimentary lymphoma (AL), is second in
48 frequency to the multicentric form and accounts for 5-7% of all canine lymphomas.¹ In human
49 medicine, AL is defined according to Dawson's criteria² (Figure 1), in which the lymphoma is
50 considered alimentary only if the predominant lesion lies within the GI tract, with lymph node
51 involvement confined to the lymph node chain draining that specific GI segment. In veterinary
52 medicine, this definition historically has been extended and AL in general is described as the primary
53 infiltration of neoplastic lymphocytes in the GI tract with or without additional extra-GI involvement
54 confined to the abdominal cavity.³ Most of the dogs affected by AL present late in the course of the
55 disease with severe GI clinical signs and have rapid progression with a worse outcome than the
56 multicentric form⁴: median survival time for canine AL ranges from 0.5 to 2.5 months,^{4,5} versus 10 to
57 12 months for the multicentric form.¹ This difference in prognosis can be attributed to the negative
58 prognostic factors carried by the most common presentation of canine GI lymphoma: T-cell
59 immunophenotype, high grade and substage b.^{4,5,6,7} However dogs with AL typically do worse than
60 dogs with multicentric lymphoma carrying similar negative prognostic factors so it is unknown if
61 there are additional inherent features of AL, such as specific morphologic subtype that could account
62 for its poorer prognosis. Chemotherapy and supportive care are the standard of treatment for AL in
63 dogs. A specific chemotherapy protocol (VELCAP-SC: vincristine, L-asparaginase,
64 cyclophosphamide, doxorubicin, prednisolone - short, consolidated) for canine AL resulted in an
65 overall median survival time of 77 days for the whole population and of 117 days for the
66 chemotherapy responders.⁴

67 Primary large intestinal lymphoma can arise primarily from the colon, the rectum or both. In human
68 medicine, it is referred to as primary colorectal lymphoma (PCRL) regardless of the segment of large
69 intestine it is originating from. Canine PCRL is a rare presentation of AL, which has been sparsely
70 described in the veterinary literature within case series reporting information about response and
71 outcome for all GI locations.^{3-6,8} When specific information for dogs with large intestinal lymphoma
72 has been reported in those studies, a better outcome than other GI locations has been observed^{3-5,8,9}
73 with remission times up to 54 months (Table 1). A recent case series of 11 dogs with rectal lymphoma
74 treated with surgery (7/11) and/or chemotherapy (8/11) described a mean survival time of 1697 days,

75 with a median not reached¹⁰. This data suggests that PCRL could have a better prognosis than AL in
76 other locations. Such difference in prognosis could have implications in veterinary practice as some
77 owners or veterinarians might be reluctant to treat dogs diagnosed with PCRL due to the currently
78 described overall poor prognosis for AL. Questions that remain unanswered at the moment are: if
79 studies with a higher number of patients would corroborate a distinct prognosis and a specific clinical
80 presentation for canine PCRL; which prognostic factors are associated with this presentation and
81 which therapeutic approach would have the best outcome. The purpose of the present multi-center
82 retrospective study is to provide further information to answer those questions.

83

84 **Material and methods**

85 Case selection:

86 Dogs were presumed to have PCRL if they had absence of peripheral lymphadenopathy, a cytologic
87 or histologic diagnosis of lymphoma had been made based on examination of a mass or diffuse
88 intestinal wall infiltration of rectum, colon, or both and the main clinical signs at presentation were
89 associated to large intestinal involvement. Dogs with concurrent abdominal lymphadenopathy,
90 hepatomegaly and splenomegaly were eligible for inclusion. Exclusion criteria included presence of
91 gross disease in other areas of the GI-tract evidenced by abdominal imaging or direct visualization at
92 surgery.

93 The American College of Veterinary Internal Medicine Oncology Diplomate list serve was used to
94 recruit cases for this retrospective study for which a diagnosis of PCRL was established. Medical
95 records of dogs diagnosed with PCRL-between 2000 and 2013 at the Queen Mother Hospital for
96 Animals, Royal Veterinary College, London, United Kingdom; The College of Veterinary Medicine,
97 Washington State University, Pullman, Washington State, USA; East Bay Veterinary Specialists,
98 Walnut Creek, California, USA; Animal Cancer Center, Colorado State University, Fort Collins,
99 Colorado, USA; The Hope Center for advanced Veterinary Medicine, Vienna, Virginia, USA; The
100 Veterinary Cancer Center, Norwalk, Connecticut, USA; School of Veterinary Medicine, Purdue

101 University, West Lafayette, Indiana, USA; Chavat Daat Veterinary Speciality Center, Beit Berl,
102 Israel; Veterinary Medical Center, Michigan State University, East Lansing, Michigan, USA;
103 Mississauga Oakville Veterinary Emergency Hospital and Referral Services, Oakville, Ontario,
104 Canada; School of Veterinary Medicine, University of Madison-Wisconsin, Wisconsin, USA;
105 Veterinary Specialty Center at Veterinary Emergency Service, Middleton, Wisconsin, USA;
106 Southwest Veterinary Oncology, Gilbert, Arizona, USA; Alta Vista Animal Hospital , Ottawa,
107 Ontario, Canada; Veterinary Medical Center, Ohio State University, Columbus, Ohio, USA; Animal
108 Specialty and Emergency Center (ASEC), Los Angeles, California, USA; Vets Now Referrals, Blue
109 Bell Hill, Kent, UK; were retrospectively reviewed.

110 Medical records review:

111 Data abstracted from the medical record included signalment, date and weight at diagnosis, presenting
112 clinical signs, duration of the clinical signs, prior treatment(s), location of disease, method of
113 diagnosis (cytology or histopathology), lymphoma grade and immunophenotype, results of clinical
114 staging performed including physical examination findings, imaging technique used (thoracic
115 radiographs, abdominal ultrasound, colonoscopy or CT scan) and bone marrow aspirate results,
116 laboratory test results (including complete blood count, serum biochemical profile, urinalysis and
117 faecal analysis when available), treatment modality (surgery, radiation therapy protocol,
118 chemotherapy protocol(s)), response to therapy, date and cause of death or last follow-up visit.
119 Necropsy results were recorded when available. Results of clinicopathological testing were classified
120 as normal or abnormal by comparison with established reference ranges for the participating
121 institution where the test was performed.
122 Histological reevaluation was performed for all cases for which samples were available. Lymphoma
123 grading was performed with grading system employed at the discretion of the pathologist reviewing
124 the slides for cases with histopathology and according to cell size for those with cytological
125 diagnosis.¹¹⁻¹³ Immunohistochemistry or immunocytochemistry was performed using antibodies
126 against CD3 and CD79 for all cases for which samples were available and in which

127 immunophenotyping had not been performed. Immunophenotyping was also performed with PCR for
128 antigen receptor re-arrangement (PARR) in some cases.

129 Dogs were clinically staged at diagnosis according to the World Health Organization (WHO) criteria
130 for canine lymphoma.¹ Dogs were further classified as substage a (having no clinical signs) or
131 substage b (having systemic signs or clinical signs associated to the gastrointestinal presentation of
132 lymphoma with potential impact on systemic status, as previously described for assessment of
133 substage in canine AL). Clinical signs included in the b substage category were haematochezia,
134 tenesmus, diarrhoea, vomiting, lethargy, or decreased appetite. Haematochezia, tenesmus, vomiting,
135 and diarrhoea were considered local clinical signs; lethargy and decreased appetite were considered
136 systemic signs. Information regarding exact anatomic location and extent of the disease was gathered
137 from the physical examination and staging test results.

138 Therapeutic modality was recorded for each patient. When surgery was performed, information
139 regarding the type and extent of surgery (i.e. excisional or incisional biopsy, date of procedure, and
140 regional lymph node(s) removal) was recorded. Only dogs that had an excisional surgery were
141 considered to have had surgery as a treatment. Surgical technique was recorded when available. For
142 patients that were treated with radiation therapy, type and protocol (dose, number and frequency of
143 fractions) were recorded. For chemotherapeutic treatments, information regarding protocols
144 (induction and rescue) including drug, dose, administration frequency and protocol duration, was
145 recorded. For descriptive purposes, the first chemotherapy protocol used was categorised as: CHOP
146 type protocol, doxorubicin single agent, COP type protocol, lomustine-based protocol, prednisolone
147 and chlorambucil or prednisolone alone. CHOP protocols could be of different length (19 or 25
148 weeks) and sometimes included L-asparaginase, or epirubicin instead of doxorubicin; the COP type
149 protocols sometimes included a dose of cytarabine (COAP protocol).

150 Response to treatment was classified according to remission status recorded by the veterinarian
151 providing the data using the following categories: complete response (CR), partial response (PR),
152 stable disease, and progressive disease. Response to treatment was mainly determined based on results
153 of clinical examination and assessment of progression of clinical signs. When available, follow-up
154 abdominal ultrasound examinations were used to assess for changes in internal organs. Complete

155 response was defined as resolution of all clinical signs and disappearance of all clinical evidence of
156 disease on the basis of physical examination (via rectal and abdominal palpation) or follow-up
157 abdominal ultrasound examination. Partial response was defined as (\geq) 50 and ($<$) 100% reduction in
158 size of measurable disease on the basis of physical examination (via rectal and abdominal palpation)
159 or follow-up abdominal ultrasound examination associated or not with improvement of the clinical
160 signs. No response was defined as no changes or deterioration in clinical signs, and less than 50%
161 reduction, increase in the size of measurable disease or appearance of new lesions on the basis of
162 physical examination (via rectal and abdominal palpation) or follow-up abdominal ultrasound
163 examination.¹⁴ When surgery was performed prior to chemotherapy, only dogs with residual
164 macroscopic disease were included in the assessment of response to chemotherapy.

165 Statistical analysis:

166 Categorical data are presented either as percentages or ratios. Continuous data are presented as
167 median (range). Survival time was defined as the time from diagnosis until natural death or
168 euthanasia. Deaths due to disease progression were considered events for the disease-related median
169 survival time. Dogs that were lost to follow-up, still alive at the end of the study period or died from
170 causes unrelated to the lymphoma were censored. In addition, overall survival time was also
171 calculated. Due to the small number of patients that died from lymphoma, this variable included all
172 deaths as events (related to lymphoma or unrelated) with dogs lost to follow-up or still alive at the end
173 of the study period being censored. Progression free survival was defined as the time from initiation
174 of treatment to event. For this variable the date of relapse was considered as the endpoint for dogs
175 when this occurred. Dogs that had not relapsed during the study period were censored at the last date
176 they were contacted or evaluated by the vet or the date of death free of disease.

177 After statistical description of the patient population, survival analysis using Kaplan-Meier product
178 limit method was conducted to estimate disease-related median survival time (MST), median overall
179 survival time, and progression free survival (PFS), for the whole population of PCRL patients.
180 Disease-related MST and PFS of dogs distributed in groups on the basis of various potential risk

181 factors (univariate analysis) was also calculated. Exploratory statistical analysis for each categorical
182 risk factors (age, location of the disease, involvement of organs other than the large intestine,
183 substage, number of clinical signs present, type of clinical signs (local vs systemic), grade,
184 immunophenotype, treatment type, chemotherapy protocol) used the logrank test to compare
185 estimated PFS and disease-related MST between categories. Multivariate analysis was not performed
186 due to the small number of animals in each group and high censorship of dogs in the study. A value of
187 $p \leq 0.05$ was considered significant. All calculations were performed with the aid of a standard
188 statistical software^a.

189 **Results**

190 Signalment: Thirty-one dogs met the inclusion criteria for this study and consisted of 17 spayed
191 females and 14 males (12 neutered and 2 intact). The median age at diagnosis was 5 years (range 1.5-
192 13.5 years old). Median weight was 23.8 kg (range 5.9-52.1 kg). The most common breeds were cross
193 breeds (7 dogs; 22.6%), and Labrador retrievers (4 dogs; 12.9%).

194 Clinical signs at diagnosis: Presenting clinical signs were known for 29 of 31 dogs. Twenty-five
195 (80.64%) dogs had clinical signs at presentation associated with the disease and were considered
196 substage b. Haematochezia was the most common presenting clinical sign (n = 20; 64.5%) with 13 of
197 these dogs presenting additional clinical signs. Other reported clinical signs included: tenesmus in
198 35.6 % (n=11), diarrhea in 25.8 % (n=8), narrow diameter of faeces in 12.9% (n=4), vomiting in 3.4%
199 (n=1), lethargy in 3.4% (n=1). Eighteen dogs (58%) had simultaneously 2 to 4 different clinical signs
200 and 7 dogs (22.5%) had one clinical sign at presentation. Presence of a rectal mass was described on
201 physical examination in 35.6 % (n=11) and rectal prolapse in 9.68% (n=3). The median duration of
202 clinical signs was 21 days (range 1-120 days) for the 28 dogs for which this information was
203 available.

204 Staging and location of the disease: As per inclusion criteria, none of the dogs had peripheral
205 lymphadenopathy identified on physical examination. Imaging was performed in 29 patients: 2 dogs
206 had imaging of thorax and abdomen as well as bone marrow evaluation, 19 had imaging of the thorax

207 and abdomen, 7 dogs had only abdominal imaging and 1 had only thoracic imaging. Abdominal
208 imaging consisted of ultrasonography in 24 dogs, radiographs in 2 and computed tomography in 2.
209 Thoracic imaging was performed in 2 dogs with CT scan and in 20 with radiographs. Dogs that did
210 not have abdominal imaging had direct evaluation of the GI tract via laparotomy or endoscopy.

211 A solitary mass was found in 23 patients (17 rectal masses of which 4 dogs also had regional lymph
212 node involvement, 6 colonic masses of which 5 dogs also had regional lymph node involvement).
213 Multiple masses were identified in 5 patients, with 1 dog having multiple masses in the rectum, 1 dog
214 with multiple masses in the colon, and 3 dogs having masses occurring in both areas. Three dogs were
215 determined to have lymphoma diffusely throughout the colorectal region. Regional lymphadenopathy
216 was present in 12 dogs with lymphoma confirmed by lymph node cytology for 8 dogs. Splenic
217 aspirates were performed in 2 dogs and liver aspirates in 4 dogs. Liver involvement was confirmed in
218 1 dog based on cytology.

219 Immunophenotype and grade: Three cases were diagnosed via cytology and 28 by histopathology.
220 Histological or cytological assessment of lymphoma grade was reported for 29 cases (94%) and 2
221 cases were reported to be low grade lymphoma, 9 were intermediate grade lymphoma, and 18 high
222 grade lymphoma (Table 2). Slides of 22 cases were obtained for review by a pathologist (7 different
223 pathologists reviewed all the slides with 2 of them reviewing a total of 16 slides- KS and BP), in those
224 confirmation of diagnosis and grade was performed. None of the cases which had a grade previously
225 done and for which histopathology slides were reviewed had a change in their grade.

226 Immunophenotype was available for 26 patients (84%). It was performed via immunohistochemistry
227 for 23 dogs and this took place at the time of pathology review for 12 cases. Immunophenotype was
228 determined by immunocytochemistry for 2 dogs and PARR for 1 dog. There were 24 B-cell
229 lymphomas, 1 T-cell lymphoma and 1 non-B non-T cell lymphoma. (Table 2).

230 Treatment and response to treatment: All dogs received therapy, and all but one (that had only
231 surgery) received chemotherapy as part of the treatment plan. Seventeen patients (55.5%) received
232 chemotherapy as a sole treatment and thirteen (42%) received chemotherapy in addition to local

233 treatment. Nine dogs (29%) had surgery prior to adjuvant chemotherapy. Four dogs (13%) had
234 chemotherapy combined with radiation therapy. These cases received radiation therapy with photons;
235 protocols comprised hypofractionated regimens for 3 dogs (2 dogs received 2 fractions of 6 Gy and
236 one dog received one fraction of 6 Gy) and the fourth dog was treated with a hyperfractionated
237 protocol (19 fractions of 1.5 Gy). One dog (2.5%) had surgery alone.

238 Out of the ten patients that had surgery, nine dogs (29%) presented with a solitary mass. The
239 remaining dog had a solitary mass removed from the rectum and was found to have diffuse disease in
240 the colon at later staging. Two dogs also had lymph node involvement and one of them had the lymph
241 nodes biopsied at the same surgery. Eight dogs (25.8%) had surgery performed by the referring vet
242 prior to referral and there was no evidence of previous diagnosis based on cytology or biopsy for the
243 two remaining dogs so it is likely that surgery in the 10 patients was performed as a mean to obtain a
244 diagnosis as well as therapeutic procedure. Due to the retrospective nature of the study, the primary
245 intent of performing surgery could not be ascertained. Type of surgery was recorded for 2 patients:
246 one had mucosal resection and one had end-to-end anastomosis. The latter procedure was performed
247 because the dog was initially referred for a rectal polyp previously diagnosed on endoscopic biopsies
248 performed by the referring vet and lymphoma was diagnosed on the surgical histopathology. Eight
249 patients out of the 28 diagnosed via histopathology (25.8%) had endoscopic biopsies.

250 The distribution of induction chemotherapy protocols used was as follows: 18 (58.1%) patients
251 received a CHOP type protocol, 5 dogs (16%) had a COP type protocol, 3 (10%) had a lomustine-
252 based protocol (lomustine / vincristine / cyclophosphamide; lomustine / prednisolone or lomustine /
253 prednisolone/ L-asparaginase respectively), 1 dog (2.5%) had doxorubicin single agent and
254 prednisolone, 1 dog (2.5%) had chlorambucil and prednisolone , and 2 dogs (5%) received only
255 prednisolone. The response rate to chemotherapy for the 22 dogs that had gross disease at the start of
256 chemotherapy (only one of the dogs that had surgery had gross residual disease at the start of
257 chemotherapy) was available in the records of 19 dogs (86%). The overall response rate was 100%
258 with 18 dogs (95%) having a complete response and 1 dog (5%) a partial response.

259 The estimated PFS was 1318 days, since 71% of dogs were censored the confidence interval (CI) is
260 not available. Nine patients had a relapse during the follow up period and reinduction with a
261 chemotherapy protocol was attempted in 8 of them (six dogs received one additional protocol, one
262 dog received 2 and one received 5 additional protocols). Chemotherapy protocols used for reinduction
263 comprised: lomustine/prednisolone with or without L-asparaginase, CHOP, COP,
264 vincristine/chlorambucil, doxorubicin single agent or vincristine single agent. Two dogs were
265 euthanized the same day that the chemotherapy was resumed. Response was available for 5 out of the
266 6 remaining dogs and all had a complete response. The median remission duration for these 5 dogs,
267 after the first reinduction protocol was initiated, was 411 days (range 298-938).

268 Outcome: At the end of the study period, 14 dogs were still alive, 5 dogs were lost to follow up, 7
269 dogs died of lymphoma, and 5 dogs died of unrelated causes (1 intramuscular hemangiosarcoma, 1
270 suspected osteosarcoma, 1 chronic kidney disease, 2 unknown cause). Only one dog underwent
271 necropsy and disseminated lymphoma was found to be the cause of his death. The median follow-up
272 time was 684 days (range 3-4678 days). The estimated disease-related MST where only dogs that died
273 from lymphoma were considered as events was 1845 days (Figure 2). Since 77.5% of dogs were
274 censored, the CI was not available. The estimated overall MST, where dogs that died from any causes
275 were considered as events, was 1548 days (95% CI: 886- 2210). MST calculated only for those 7
276 patients that died of lymphoma was 643 days (range 399-1845 days) and for the 5 patients dying of
277 unrelated causes was 789 days (range 465-4678 days). The 1, 2, and 4 year overall survival rates for
278 all dogs in this study were 100, 50, and 25 %, respectively.

279 Prognostic factors:

280 There was no statistically significant association between gender, number of presenting clinical signs
281 (one versus multiple), type of clinical signs (systemic versus local), location of the disease (solitary vs
282 multiple/diffuse), involvement of organs other than intestines, immunophenotype (B vs others), grade
283 (high vs others), treatment (chemotherapy alone versus chemotherapy plus a local treatment) (Figure
284 3), chemotherapy treatment (CHOP/doxorubicin-based protocol versus others or CHOP vs others) and

285 either PFS or disease-related MST. The disease-related MST for dogs receiving chemotherapy alone
286 was 1845 days (95 % CI: 855-2835) versus a median that could not be reached for dogs receiving
287 chemotherapy plus a local treatment and the difference between these medians was not statistically
288 significant (p-value 0.584) (Figure 3). When substage was analysed it was not a statistically
289 significant risk factor for disease-related MST (p-value = 0.345) but substage b was found to have a
290 significantly positive impact on PFS (p-value = 0.001), with a PFS that was not reached for dogs
291 categorized as substage b (95% CI: 0-2331.5) versus a PFS of 271 days for dogs without clinical signs
292 at diagnosis. The presence of haematochezia at diagnosis was not a statistically significant risk factor
293 for disease-related MST (p-value = 0.147) but was found to have a significantly positive impact on
294 PFS (p-value = 0.02), with a PFS of 1141 days for dogs without haematochezia (95% CI: 0-2331.5)
295 versus a PFS that was not reached for dogs with haematochezia at presentation. Dogs younger than 7
296 years had longer PFS than dogs older than 7 years (836 days for older dogs, 95% CI: 537-1135 versus
297 a PFS not reached for younger dogs, p-value = 0.031 and 0.01 respectively) but a similar disease-
298 related MST was present in both groups.

299

300 **Discussion**

301 The primary goal of the current study was descriptive, as PCRL has not previously been described in
302 a large case series in the veterinary literature and just few sparse cases of colorectal lymphoma have
303 been reported (Table 1). The current study showed that PCRL occurs primarily in middle-aged dogs
304 with no sex or breed predisposition. Results of this study suggested that PCRL is typically high grade
305 and B cell immunophenotype with most dogs presenting as substage b. The majority of dogs (23/31;
306 74.2%) presented with a solitary mass and 13/31 (43.7%) had evidence of involvement of abdominal
307 extra GI organs (liver or regional lymph nodes). The disease features of dogs with PCRL described in
308 this study are consistent with cases previously reported.^{3-5,8,10,15}

309 Results of the present study suggest that dogs with PCRL treated with chemotherapy, with or without
310 additional local therapy, had a very good prognosis as demonstrated by a high response rate, long

311 PFS, and long MST. This is in agreement with previous published results ^{3-5,8,10,15}, and in contrast to
312 the reported low response rate (56%) ⁴ and short survival time (13-77 days) for dogs with diffuse GI
313 tract lymphoma of other locations.^{4,5} The CI could not be calculated for disease-related MST, despite
314 a median follow-up time of almost 2 years, as 14 (45%) of the dogs in this study were still alive at the
315 time of writing. Therefore it is possible that the PFS and survival time for dogs with PCRL might be
316 even longer than has been estimated in our study. For a more accurate determination of disease-
317 related MST, the population in this study would require follow up beyond 2 years. The possibility of
318 additional deaths unrelated to lymphoma for dogs currently alive and in complete remission besides
319 the 5 already recorded, could continue adding censored dogs to the statistical analysis which will
320 make it difficult to reach a defined value for PFS and disease-related MST. We considered that the
321 improved prognosis of dogs with PCRL found in this study, particularly in comparison to previously
322 published outcomes of dogs with AL lymphoma, warranted communication to the veterinary
323 community despite availability only of estimated statistical parameters via the Kaplan Meier method.

324 A subsequent goal of our study was to evaluate outcome with different treatment modalities for dogs
325 with PCRL. No statistical difference was found between PFS or survival of dogs receiving
326 chemotherapy only versus chemotherapy plus local treatment with surgery or radiation. Patients that
327 received chemotherapy only had a PFS of 1318 days and a disease-related MST of 1845 days, and the
328 PFS and disease-related MST were not reached for patients that had chemotherapy combined with
329 local treatment, however, this difference in outcome was not statistically significant. This finding
330 shows that chemotherapy alone was effective to treat a localized presentation of lymphoma and
331 surgery or radiation therapy, which carry some morbidity, might delay start of medical anticancer
332 treatment, and increase total cost of therapy, are not necessarily required to achieve a good outcome.

333 In this study surgery was performed mainly in cases with presumed solitary large intestine masses
334 primarily to achieve a diagnosis and we lack information documenting if alternative diagnostic
335 procedures were previously attempted unrewardingly or why surgery was elected by referring vets as
336 a diagnostic tool above other diagnostic modalities. It is possible that the differential diagnosis of
337 PCRL and its implications in the therapeutic approach were not considered due to its rarity in

338 comparison to other types of colorectal neoplasia for which surgery is routinely recommended. The
339 findings in this study support consideration of PCRL as a differential for solitary colorectal masses
340 and when possible the use of low invasive diagnostic techniques such as cytology or incisional biopsy
341 prior to treatment planning. Due to the retrospective nature of the study, treatment groups were not
342 randomised and there is a possibility that surgery had been selected more often for dogs with more
343 advanced diseases and that multimodality treatment would be more beneficial than a single treatment
344 for advanced disease. On the contrary surgery may also have been elected more often for dogs with
345 isolated disease, and it might have made a difference in the outcome of PCRL patients, as this has
346 been described for solitary lesions of lymphoma in other locations.¹⁶⁻¹⁸

347 In this study there was no difference in PFS or survival time based on the type of chemotherapy
348 protocol used to treat dogs with PCRL. We have to be very cautious in the interpretation of our data
349 considering that, due to the small number of dogs in the present study, only two chemotherapy groups
350 could be defined (doxorubicin-based protocol vs others). Still, it is important to consider that these
351 results describe that less intense chemotherapy protocols, often chosen when facing client economic
352 or time constraints or when clients seek therapies with potentially lower prevalence of adverse effects,
353 seem to achieve similar PFS and survival times than with CHOP type protocols. This finding
354 correlates with a previous studies where an overall survival time of approximately 4.5 years was
355 reached in 9 dogs with rectal lymphoma receiving either a low dose COP protocol or a truncated (6
356 weeks) CHOP protocol¹⁰.

357 Age greater than 7 years was associated with a significantly decreased prognosis as compared to dogs
358 younger than 7 years. Since most dogs had long PFS, it is possible that older patients were more likely
359 to succumb to concurrent or subsequent morbidities than younger dogs. Decreased owner motivation
360 to re-start treatment at relapse in older dogs is also a possible reason that these dogs had a shorter
361 disease-related MST as compared to younger dogs, but this would not explain the shorter PFS
362 experienced by dogs older than 7 years.

363 Canine lymphoma patients with systemic signs or clinical signs associated to their presentation with a
364 systemic impact (substage b) are known to have a worse prognosis.^{1,19-21} Dogs with AL are often
365 substage b at diagnosis mainly due to clinical signs associated to local disease and it is possible that
366 they often are less responsive to therapy due to clinical signs being surrogate markers of more
367 advanced disease.^{5,14} GI signs, particularly upper GI signs such as anorexia and vomiting, are often
368 perceived as poor quality of life by owners, leading to an early decision of euthanasia during the
369 course of treatment. In the present study, although most dogs presented with clinical signs associated
370 to PCRL, their symptoms did not appear as severe in nature as GI signs of dogs with diffuse small
371 intestinal or gastric lymphoma. We decided to consider haematochezia, tenesmus, and diarrhoea as
372 markers of systemic illness due to the possible associated systemic discomfort and pain and potential
373 impact in quality of life. Being this a retrospective study with limited recorded information about
374 severity of clinical signs and impact on the dogs' general status, grading of GI signs at presentation
375 according to the VCOG criteria²² was not possible and precluded a comparison with previous studies
376 about canine AL. Interestingly in this study there was no difference in outcome for dogs with systemic
377 versus local signs and substage did not have an impact in survival time. Although PFS of dogs
378 without clinical signs was shorter than for dogs with substage b (271 days versus not reached), these
379 results could have been biased due to the small number of dogs in the substage a group or potential
380 missing data regarding patient's clinical signs. More information is needed to ascertain how best to
381 apply the current canine lymphoma staging system to extranodal forms like PCRL and to identify its
382 value in determining prognosis.

383 The presence of haematochezia at diagnosis was found to have a positive impact on the PFS
384 compared to other signs. For the 20 dogs presenting with haematochezia, the PFS was not reached,
385 compared with 1141 days for 9 dogs without haematochezia but with other clinical signs. It is not
386 clear why haematochezia would have a positive impact on the prognosis. Perhaps this was more
387 alarming for owners than diarrhoea and its observation might have led to earlier diagnosis and
388 treatment. On the other hand, we can also assume that other signs reported (diarrhoea, rectal prolapse,
389 tenesmus) might be associated with more advanced disease and decreased outcome, however 13/20

390 cases with haematochezia also had additional clinical signs. This result could also be secondary to a
391 statistical bias; a larger population would help to determine if the presence or absence of
392 haematochezia truly has an impact on prognosis.

393 In previous studies on canine AL, the immunophenotype was most commonly of T-cell origin.^{5,6,8,23-25}
394 We report here that colorectal lymphoma is most commonly of B-cell origin, raising a clear
395 distinction from other GI locations. The B-cell phenotype in canine high-grade lymphoma generally is
396 associated with a better response to conventional chemotherapy protocols, compared with the T
397 immunophenotype.^{19,26} In the current study, 77% of the dogs were of immunophenotype B, there were
398 only 2 cases of known non-B immunophenotype with outcomes comparable to the ones with
399 immunophenotype B (survival times 491 and 1273 days) and 5 cases with unknown
400 immunophenotype (Table 2). We did not find any impact of immunophenotype on outcome but the
401 low number of dogs with non-B phenotype included in the study clearly precludes knowing the real
402 impact of this factor in PCRL.

403 The most common grade for lymphoma found in this study was high (58% of the dogs) and was not a
404 significant prognostic factor in our population. The grading was performed based on the National
405 Cancer Institute working formulation with separation of the patients into 3 categories: low,
406 intermediate, and high grade.¹¹⁻¹³ Recent studies advise for classification of canine lymphomas
407 according to the WHO classification^{7,28} in order to standardise future study populations as this may
408 have a prognostic significance.²⁷ This would be extremely interesting for canine PCRL in order to
409 further characterize and describe this anatomical presentation. However, in this retrospective study,
410 the limited availability of initial tissue samples and absence of immunophenotype for some dogs has
411 precluded this classification. Other studies that classified their patients according to the working
412 formulation into low, intermediate, and high grade¹³ found that grade had prognostic significance.¹² In
413 our study, there were too few dogs in the low or intermediate grade category and perhaps this could
414 have an impact on the statistical significance. Interestingly, despite most dogs having high grade B
415 cell lymphoma, their disease-related MST was much longer (1845 days) than that of dogs affected by
416 the multicentric form of same grade and immunopenotype (MST reported in literature of 162-308

417 days¹²), reinforcing the fact that anatomic site seems to be a better predictor of outcome than
418 previously published prognostic factors.

419 Information available for staging of dogs included in this study was limited due to its retrospective
420 nature and staging performed was quite heterogeneous due to the high number of participating
421 institutions. This was unfortunately unavoidable when trying to compile a large case series of PCRL
422 due to its low prevalence. Staging was not complete for all dogs and different imaging modalities
423 were used. In addition, even imaging techniques used routinely for staging in veterinary oncology
424 such as abdominal ultrasound or computed tomography have limitations for detection of lymphoma.
425 Also aspirates of liver and spleen were not routinely performed despite knowledge that neoplastic
426 infiltration is possible even with a normal imaging appearance²⁹. In this study, twelve dogs had
427 evidence of regional lymphadenopathy and one hepatic involvement without impact on PFS or
428 survival time. It is very possible that a higher number of dogs had a higher stage of disease than
429 recorded leading to erroneous staging classification of cases (stage migration)³⁰ and this could explain
430 the lack of statistical difference. On the other hand, given the overall long PFS and survival times for
431 all patients, it could also be thought that possibly under-staged dogs had a good outcome. Based on
432 this study's data it seems that presence of complete staging would not have provided any further
433 prognostic information for dogs with PCRL. However, as there is not established standard treatment
434 for PCRL, it would be advisable that complete staging would be performed to outweigh potential
435 advantages versus morbidity/cost if considering local therapy prior to chemotherapy or as solely
436 therapy in PCRL.

437 Human primary AL are classified as confined to the GI tract, with no other evidence of systemic
438 involvement (see figure 1). They are most often of B cell origin⁸, which is comparable to our study
439 findings, but opposite to the immunophenotype of canine AL⁶. PCRL is a rare disease in human
440 medicine³¹ with controversy about what the standard of care should be for its treatment.³¹ Long
441 survivals have been described with 83% of the patients alive and free of disease at 10 years after a
442 combination of surgery and chemotherapy.³² but shorter prognosis with a 5 year survival rate of 47%
443 has also been reported.³³ In people, the two most frequent histologic subtypes of PCRL are mucosa-

444 associated lymphoid tissue (MALT) lymphoma and diffuse large B cell lymphoma with both PCRL
445 types carrying very different prognosis. The MALT form, of low grade and B-cell origin, can be cured
446 after surgical resection and/or a short course of chemotherapy. The prognosis is more guarded for the
447 diffuse large B cell lymphoma which carries a high relapse rate (33-75%).³⁴ Interestingly, although
448 most cases of canine PRCL in our population were high grade and B-cell origin the biologic
449 behaviour seems to differ from the high grade form of human PRCL.

450 The limitations of this study are inherent to its retrospective design and include small sample size,
451 variable staging and treatment regimens, and lack of standardized follow-up. The small population
452 due to the rarity of the disease limited the statistical power of our analyses and prognostic factors
453 associated with PFS and disease-related MST may not have been identified due to the variations in
454 staging and treatment protocols. Of the factors analysed, few were found to be prognostic indicators in
455 exploratory univariate analysis. Unfortunately, multivariate analysis could not be carried out as too
456 many dogs were censored mostly due to long survival, loss of follow-up, or death from unrelated
457 cause. Evaluation of a larger sample size, prospectively, over a longer period of time including
458 standardized comprehensive staging and standardized therapy would be ideal and may permit
459 determination of additional characteristics and identify risk factors for PCRL. This would be
460 challenging, requiring even further collaboration than the one required for this study (with 18
461 institutions collaborating in 4 countries) due to the low prevalence of this presentation of canine
462 lymphoma. It needs to be reinforced that larger number of dogs and longer follow-up may still not
463 reach statistical significance if most patients do not demonstrate events linked to their lymphoma
464 (relapse or death) as they would remain censored from the whole population should they remain in
465 remission or die from other causes.

466 In conclusion, results of the present study describe canine PCRL as a rare disease often of high grade
467 and B-cell immunophenotype that when treated with chemotherapy results in prolonged PFS and
468 survival times regardless of chemotherapy protocol type or addition of local treatment modalities.
469 Results of this study suggest that PCRL has a greatly improved outcome compared to previously
470 published outcomes of dogs with AL. Therefore, attempts to differentiate dogs with PCRL from dogs

471 with diffuse GI lymphoma should be pursued in order to better guide owners regarding treatment and
472 associated prognosis. Veterinarian awareness of this specific presentation of canine lymphoma will
473 likely have an important impact on the treatment decision process for owners of dogs with PCRL.

474

475 Footnotes

476 a. (SPSS version 19.0 for Windows, SPSS Inc, Chicago, Ill).

477

478

479 Acknowledgements: Ken Smith (Royal Veterinary College, UK), Ruby Chang (Royal Veterinary
480 College, UK), Barbara Powers (Colorado State University, USA), Kevin Choy (Washington State
481 University, USA), Steve Atwater (East Bay Veterinary specialists, USA), Alexander Simunek
482 (Veterinary cancer center, USA), Michael Childress (Purdue university, USA), Conor J McNeill (The
483 Hope Center for advanced veterinary medicine, Vienna, Virginia, USA), Paulo Vilar (Michigan State
484 University, USA), Kai Shiu (Veterinary Specialty Center at Veterinary Emergency Service, USA),
485 Lynda Beaver (Southwest Veterinary Oncology, USA), Guillermo Couto and Sandra Barnard (Ohio
486 State University, USA), Sue Downing (Animal Specialty and Emergency center, USA), Lina Bravo
487 (Alta Vista Hospital, Canada).

488 **References**

- 489 1. Vail DM ME, Young KM. Canine lymphoma and lymphoid leukemia in Withrow's
490 and MacEwen's small animal oncology. 4th ed. Philadelphia: WB Saunders, 2007.
- 491 2. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the
492 intestinal tract. Report of 37 cases with a study of factors influencing prognosis. *Br J Surg*
493 1961;49:80-89.
- 494 3. Couto CG, Rutgers HC, Sherding RG, Rokjo J.. Gastrointestinal lymphoma in 20
495 dogs. A retrospective study. *J Vet Intern Med* 1989;3:73-78.
- 496 4. Rassnick KM, Moore AS, Collister KE, Northrup N.C., Kristal O., Chretin J.D.et al.
497 Efficacy of combination chemotherapy for treatment of gastrointestinal lymphoma in dogs. *J Vet*
498 *Intern Med* 2009;23:317-322.
- 499 5. Frank JD, Reimer SB, Kass PH, Kiupel M.. Clinical outcomes of 30 cases (1997-
500 2004) of canine gastrointestinal lymphoma. *J Am Anim Hosp Assoc* 2007;43:313-321.
- 501 6. Coyle KA, Steinberg H. Characterization of lymphocytes in canine gastrointestinal
502 lymphoma. *Vet Pathol* 2004;41:141-146.
- 503 7. Vezzali E, Parodi AL, Marcato PS, Bettini G. Histopathologic classification of 171
504 cases of canine and feline non-Hodgkin lymphoma according to the WHO. *Vet Comp Oncol*
505 2010;8:38-49.
- 506 8. Miura T, Maruyama H, Sakai M, Takahashi T., Koie H., Yamaya Y.et al. Endoscopic
507 findings on alimentary lymphoma in 7 dogs. *J Vet Med Sci* 2004;66:577-580.

508 9. Holt PE, Lucke VM. Rectal neoplasia in the dog: a clinicopathological review of 31
509 cases. *Vet Rec* 1985;116:400-405

510 10. Van den Steen N, Berlato D, Polton G, Dobson J., Stewart J., Maglennon G. et al.
511 Rectal lymphoma in 11 dogs: a retrospective study. *J Small Anim Pract* 2012;53:586-591.

512 11. Greenlee PG, Filippa DA, Quimby FW, Patnaik A.K., Calvano S.E., Matus R.E. et al.
513 Lymphomas in dogs. A morphologic, immunologic, and clinical study. *Cancer* 1990;66:480-490.

514 12. Valli VE, Kass PH, San Myint M., Scott F.. Canine lymphomas: association of
515 classification type, disease stage, tumor subtype, mitotic rate, and treatment with survival. *Vet Pathol*
516 2013;50:738-748.

517 13. Dhaliwal RS, Kitchell BE, Ehrhart E, Valli V.E., Dervisis N.G.. Clinicopathologic
518 significance of histologic grade, pgg, and p53 expression in canine lymphoma. *J Am Anim Hosp*
519 *Assoc* 2013;49:175-184.

520 14. Dank G., Rassnick K.M., Kristal O., Rodriguez C.O., Clifford C.A., Ward R. et al.
521 Clinical characteristics, treatment, and outcome of dogs with presumed primary hepatic lymphoma:
522 18 cases (1992-2008). *J Am Vet Med Assoc* 2011; 239: 966-971.

523 15. Holt PE, Lucke VM. Rectal neoplasia in the dog: a clinicopathological review of 31
524 cases. *Vet Rec* 1985;116:400-405.

525 16. Berlato D, Schrempp D, Van Den Steen N, Murphy S.. Radiotherapy in the
526 management of localized mucocutaneous oral lymphoma in dogs: 14 cases. *Vet Comp Oncol*
527 2012;10:16-23.

528 17. Kessler M, Kandel-Tschiederer B, Pflighaar S, Tassani-Prell M. Primary malignant
529 lymphoma of the urinary bladder in a dog: long term remission following treatment with radiation and
530 chemotherapy. *Schweiz Arch Tierheilkd* 2008;150:565-569.

531 18. Spugnini EP, Citro G, Mellone P, Dotsinsky I, Mudrov N., Baldi A.
532 Electrochemotherapy for localized lymphoma: a preliminary study in companion animals. *J Exp Clin*
533 *Cancer Res* 2007;26:343-346.

534 19. Simon D, Moreno SN, Hirschberger J, Moritz A., Kohn B., Neumann S. et al.
535 Efficacy of a continuous, multiagent chemotherapeutic protocol versus a short-term single-agent
536 protocol in dogs with lymphoma. *J Am Vet Med Assoc* 2008;232:879-885.

537 20. Simon D, Nolte I, Eberle N, Abbrederis N., Killich M., Hirschberger J. Treatment of
538 dogs with lymphoma using a 12-week, maintenance-free combination chemotherapy protocol. *J Vet*
539 *Intern Med* 2006;20:948-954.

540 21. Sorenmo K, Overley B, Krick E, Ferrara T., Lablanc A., Shofer F.. Outcome and
541 toxicity associated with a dose-intensified, maintenance-free CHOP-based chemotherapy protocol in
542 canine lymphoma: 130 cases. *Vet Comp Oncol* 2010;8:196-208.

543

544 22. Vail DM, Michels GM, Khanna C, Selting K.A., London C.A. Response evaluation
545 criteria for peripheral nodal lymphoma in dogs (v1.0)--a Veterinary Cooperative Oncology Group
546 (VCOG) consensus document. *Vet Comp Oncol* 2010;8:28-37.

547 23. French RA, Seitz SE, Valli VE. Primary epitheliotropic alimentary T-cell lymphoma
548 with hepatic involvement in a dog. *Vet Pathol* 1996;33:349-352.

549 24. Gieger T. Alimentary lymphoma in cats and dogs. *Vet Clin North Am Small Anim*
550 *Pract* 2011;41:419-432.

551 25. Ozaki K, Yamagami T, Nomura K, Narama I. T-cell lymphoma with eosinophilic
552 infiltration involving the intestinal tract in 11 dogs. *Vet Pathol* 2006;43:339-344.

553 26. Ruslander DA, Gebhard DH, Tompkins MB, et al. Immunophenotypic
554 characterization of canine lymphoproliferative disorders. *In Vivo* 1997;11:169-172.

555 27. Frantz AM, Sarver AL, Ito D, Phang T.L., Karimpour-Fard A., Scott M.C. et al.
556 Molecular profiling reveals prognostically significant subtypes of canine lymphoma. *Vet Pathol*
557 2013;50:693-703

558 28. Ponce F, Marchal T, Magnol JP, Turinelli V., Ledieu D., Bonnefont C. et al. A
559 morphological study of 608 cases of canine malignant lymphoma in France with a focus on
560 comparative similarities between canine and human lymphoma morphology. *Vet Pathol* 2010;47:414-
561 433.

562 29. Crabtree AC, Spangler E, Beard D, Smith A. Diagnostic accuracy of gray-scale
563 ultrasonography for the detection of hepatic and splenic lymphoma in dogs. *Vet Radiol Ultrasound*
564 2010;51:661-664.

565 30. Flory AB, Rassnick KM, Stokol T, Scivani P.V., Erb H.N.. Stage migration in dogs
566 with lymphoma. *J Vet Intern Med* 2007;21:1041-1047.

567 31. She WH, Day W, Lau PY, Mak K.L., Yip A.W. Primary colorectal lymphoma: Case
568 series and literature review. *Asian J Surg* 2011;34:111-114.

569 32. Aviles A, Neri N, Huerta-Guzman J. Large bowel lymphoma: an analysis of
570 prognostic factors and therapy in 53 patients. *J Surg Oncol* 2002;80:111-115.

571 33. Lai YL, Lin JK, Liang WY, Huang Y.C., Chang S.C. Surgical resection combined
572 with chemotherapy can help achieve better outcomes in patients with primary colonic lymphoma. *J*
573 *Surg Oncol* 2011;104:265-268.

574 34. Park H, Chung JW, Kim AJ, Park S.Y., Rim M.Y., Jang Y.R. et al. A Case of Rectal
575 Mucosa-associated Lymphoid Tissue Lymphoma Diagnosed by Endoscopic Unroofing Technique.
576 *Korean J Gastroenterol* 2012; 59: 428-432.

577
578
579

580

581

582

583

584

585

586

587

588

589

590

591

592

593

594

595

596

597

598

599
600
601
602
603

Table 1: Cases of rectal lymphoma in the veterinary literature (LN: lymph node, NA: not available)

Cases (n)	Location	Diagnostic method	Immuno-phenotype	Treatment type	Survival	Ref.
1	Large intestine	NA	NA	Chemotherapy: COAP protocol	>54 months	3
7	Rectum	histology	NA	Surgery	5 weeks, 1 dog had no relapse after 8 months, 1 relapsed but was still alive at 18 months	9
6	Large intestine	5 histology 1 cytology	NA	4 chemotherapy only (type NA) 2 surgery + chemotherapy (NA)	61 days (0-2520 days)	5
1	Colon	histology	T	VELCAP-SC protocol	NA	4
1	Rectum	histology	NA	COP protocol	> 356 days	8
11	Rectum	histology	10 B	6 surgery + chemotherapy (CHOP/COP) 1 surgery alone 3 chemotherapy (CHOP/COP or prednisolone) 1 no treatment	1697 days	10

604
605
606
607
608

609 Table 2: Location, extension, histologic characteristics, and treatment data of dogs with colorectal
 610 lymphoma.

Data	Number of cases
Aspect	23 solitary masses 5 multiple masses 3 diffuse disease
Location	18 rectal disease 7 colonic disease 6 colorectal disease
Staging	12 lymph node involvement 1 liver involvement
Substage	29 substage b 2 unknown
Immunophenotype	24 B 1 T 1 non B non T 5 non available
Grade	18 high 9 intermediate 2 low 2 non available
Treatment	1 surgery 17 chemotherapy 9 chemotherapy + surgery 4 chemotherapy + radiotherapy
Chemotherapy protocol	18 CHOP 5 COP 1 doxorubicin 3 lomustine 1 chlorambucil + prednisolone 2 prednisolone

611

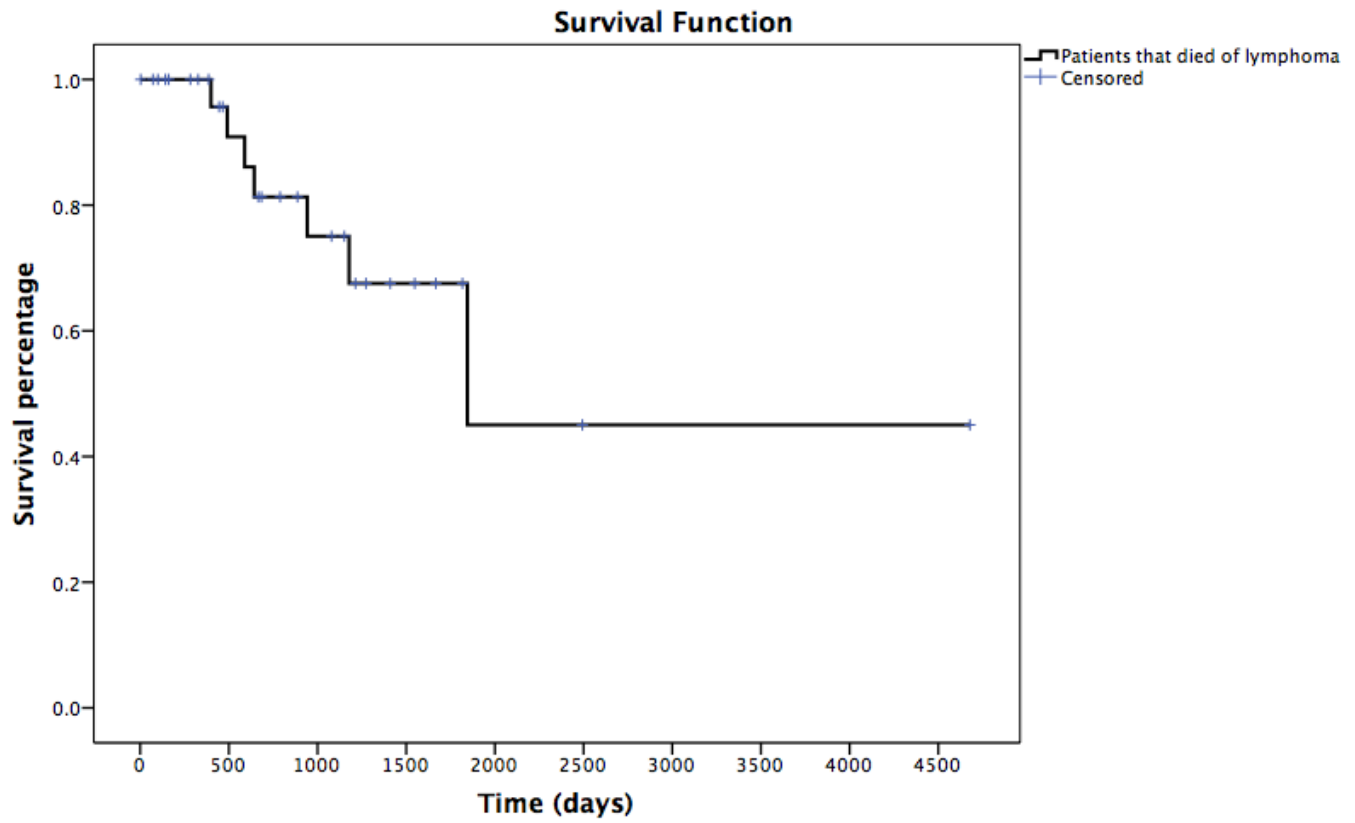
612

613 Figure 1: Criteria of inclusion for human primary gastrointestinal lymphoma

614
615
616
617
618
619

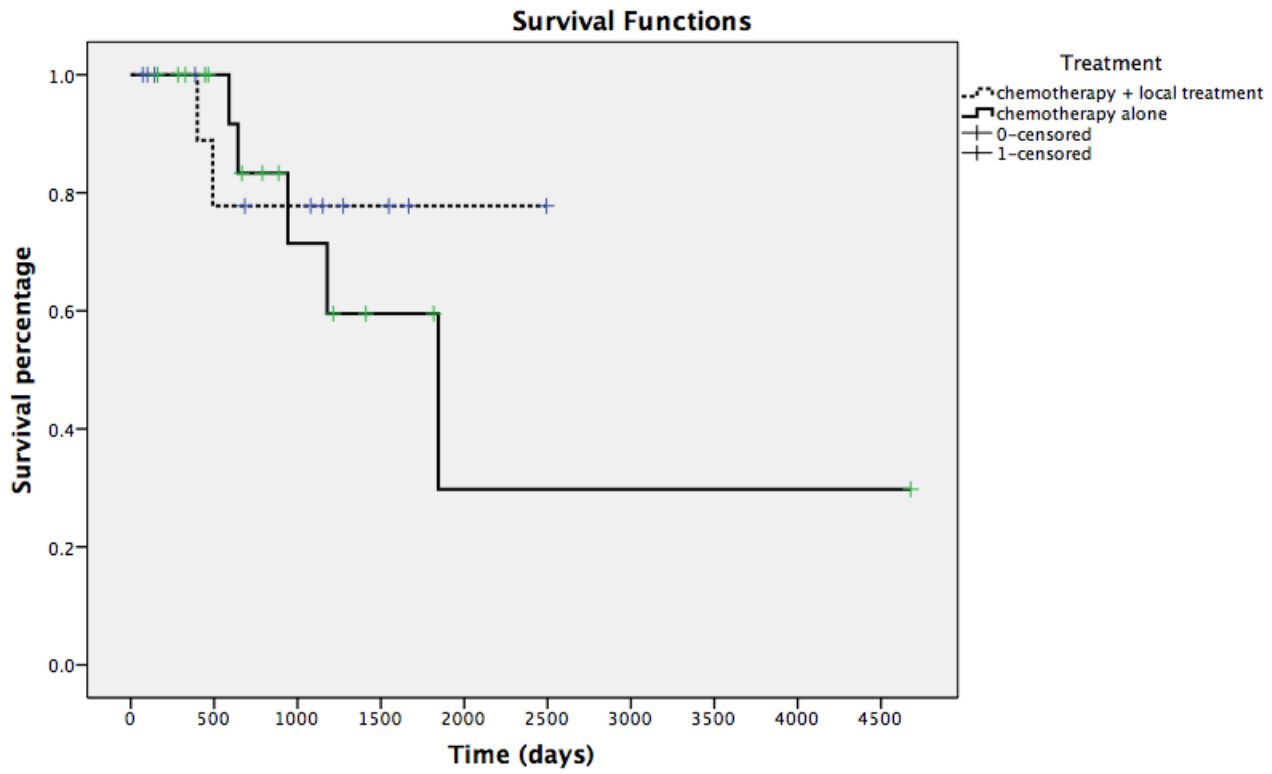
- Dawson's criteria:
- No generalized, superficial, or mediastinal lymphadenopathy
 - No leukemic or lymphomatous abnormalities in the peripheral blood
 - Lesion confined to the bowel, with only regional lymphadenopathy at the time of laparotomy
 - No involvement of the spleen or the liver at the time of diagnosis

620 Figure 2: Kaplan Meier of the estimated survival time with the event being dogs that died from
621 lymphoma. The estimated MST was 1845 days (confidence interval not available).



622
623

624 Figure 3: Kaplan Meier of the estimated survival time for dogs receiving chemotherapy versus dogs
625 receiving chemotherapy plus a local treatment. The addition of a local treatment to chemotherapy did
626 not impact the overall prognosis (p-value = 0.564).



627