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Outcomes in 40 cats with discrete intermediate- or large-cell gastrointestinal lymphoma masses treated with surgical mass resection (2005-2015)

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Abstract

Objective: To report outcomes in cats with discrete intermediate- and large-cell gastrointestinal (GI) lymphoma masses after surgical resection.

Study design: Retrospective clinical case series.

Animals: Forty client-owned cats in which intermediate- or large-cell GI lymphoma was diagnosed.

Methods: Records of 40 cats in which discrete intermediate- or large-cell GI lymphoma masses were diagnosed between 2005 and 2015 were reviewed. Cats were included if they survived curative intent surgery and had a known outcome for at least two weeks. Postoperative death was permitted. Data collected included anatomic site, surgical margins, lymphoma subtype, chemotherapy use, and postoperative and long-term outcome (beyond two weeks).

Results: Affected sites consisted of small intestines (n = 23), large intestines (n = 9), and stomach (n = 8). Thirty-six of 40 cats survived to discharge, and 31 cats were alive at suture removal. Median long-term follow-up of 22 cats was 111 days (range, 16-1407). Cats that survived to suture removal had a median survival time (MST) of 185 days (95% confidence interval: 72-465). Cats with large intestinal masses lived longer than those with small intestinal or gastric masses whether all cats (MST, 675, 64, 96 days, respectively; $P = .03$) or only those surviving to suture removal were considered. Complete surgical resection (n = 20) was positively associated with survival (370 vs 83 days, $P = .016$).

Conclusion: Most cats in this population survived the perioperative period, with MST similar to those reported historically with medical management.

Clinical significance: Surgical resection may be a reasonable consideration in cats with solitary lymphoma, particularly those with large intestinal masses.

1 | INTRODUCTION

Lymphoma (LSA) is the most commonly diagnosed hematopoietic tumor in cats. The alimentary tract is now the most

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frequently diagnosed primary site for LSA. The incidence of LSA in other sites, which are more commonly affected by feline leukemia virus-related cancer, is decreasing.[1-3] Feline gastrointestinal (GI) LSA is histologically subtyped according to the World Health Organization (WHO) classification system. The most common form of GI LSA in cats is enteropathy associated T-cell LSA (EATCL) type II,[4] which arises from the mucosal associated lymphoid tissue and is characterized by mucosal infiltration of small to intermediate-sized T cells. Enteropathy associated T-cell LSA type I is composed of large T cells and typically presents as a discrete transmural mass.[3] Large granular lymphocyte LSA (LGL) is an aggressive LSA composed of cytotoxic T cells or natural killer cells.[4] Finally, the most common subtype of B-cell LSA in the feline GI tract is diffuse large B-cell LSA (DLBCL), which presents as transmural mass-like lesions within the stomach, jejunum, or ileocecocolic junction.[5]

Current standard-of-care treatment for cats affected by intermediate- or large-cell GI LSA is use of systemic chemotherapy. Most often, this treatment consists of COP (cyclophosphamide, vincristine, prednisolone) or CHOP (plus doxorubicin)-based protocols. Unlike in dogs, in which multicentric LSA predominates and is overwhelmingly responsive to chemotherapy, the response to multiagent chemotherapy in cats with feline GI large-cell LSA is less predictable, with overall response rates ranging from 30% to 75%.[4-11] Response durability also tends to be less favorable, with reported median survival times (MST) of 3 to 6 months.[1,4-12] However, MST tends to be closely linked to response to chemotherapy. Survival time is short in cats that experience either partial or no response to medical treatment, while survival times exceeding one year are documented in cats that undergo a complete response.[13] The use of surgical intervention in management of feline large-cell LSA is poorly understood. Surgical excision of discrete masses within the GI tract has historically been reserved for cases of obstruction, perforation with subsequent peritonitis, or when noninvasive diagnostics such as fine needle aspirate are unrewarding. Twenty cats treated with surgical resection of discrete GI masses followed by systemic CHOP chemotherapy in a recent study by Gouldin et al[12] had overall MST of 417 days. Although these findings provide evidence supporting the potential benefit of surgery to manage GI LSA, inclusion was restricted to cats with discrete GI masses, no evidence of disease in other anatomic locations, surgery performed at referral practices only, and CHOP chemotherapy administered to all cats after surgical intervention. Because of these strict criteria, many cats in which GI LSA has been newly diagnosed cannot be easily compared with this study population because extra-GI disease at diagnosis is common, and specialty-level medicine is not attainable for some owners. In addition, all cats in the Gouldin et al[12] study were required to survive the surgical procedure, precluding conclusions regarding the incidence of mortality attributed to the surgical procedures. Obtaining information regarding postoperative outcomes in cats that do not meet this narrow inclusion criteria is of interest in guiding treatment decisions in the rest of the GI LSA cat population.

Recommendation for surgical resection of discrete GI LSA masses should consider not only the long-term outcome but also the short-term morbidity and survivability of the procedure. The objective of this retrospective study was to determine the postoperative and long-term outcomes of cats with intermediate- and large-cell GI LSA treated with resection of their primary masses. We specifically intended to evaluate the occurrence of postoperative death and the effect of anatomic location, surgical margins, and treatment with adjunctive chemotherapy on clinical outcome. We hypothesized that incomplete surgical margins would result in a higher incidence of postoperative death and that complete surgical margins, absence of extra-GI disease, and use of systemic chemotherapy would be correlated with longer survival times.

2 | MATERIALS AND METHODS

2.1 | Animals and data collection

Medical records from the University of Pennsylvania School of Veterinary Medicine's Department of Pathobiology Diagnostic Laboratory (2005 to 2015) were reviewed for cats in which a histologic diagnosis of intermediate- or large-cell GI LSA had been made. The biopsy submissions were from both internal patients of the University of Pennsylvania Matthew J. Ryan Small Animal Hospital and external patients of specialty and primary care practices. Medical records were obtained from the case hospital. Cases were included if the cat had discrete GI origin mass or masses that were surgically resected and diagnosed as intermediate- or large-cell LSA via biopsy. The presence of LSA disease burden confirmed via histopathology in other organs was permitted. Cats that were euthanized intraoperatively or for which the status was unknown at the recommended time of suture removal were excluded. Cases in which only incisional biopsies of masses were completed and/or definitive or curative intent mass removal was not the surgical goal were excluded. Complete preoperative bloodwork and imaging were not required for inclusion.

Information collected from the medical records consisted of patient signalment (age, breed, sex, body condition, weight), clinical signs prior to surgery, physical examination findings, preoperative bloodwork and imaging results, date of surgery and suture removal, anatomic location of disease, postoperative complications including death, use of postoperative adjunct chemotherapy, date of suspected or confirmed relapse, and date and cause of death. For study

inclusion, cats were required to have a known status (alive or dead) two weeks after surgery was performed. Any additional information regarding treatment and outcome beyond this two-week period was categorized as long-term follow-up. This information was obtained from the veterinary records available for the cat and from telephone conversations with the primary veterinarian of the case if additional information beyond that contained in the records was required. Cats were classified as lost to follow-up when long-term follow-up information was unavailable in the medical records.

Routine hematoxylin and eosin-stained slides were reviewed by a single board-certified anatomic pathologist. Paraffin blocks were available for 37 of 40 cats, and immunohistochemical (IHC) stains for T cells (CD3) and B cells (CD20 and pax5) were performed. Data collected included confirmation of diagnosis, surgical margin assessment, grade, immunophenotype, and WHO classification of subtype. Margins were considered incomplete when neoplastic cells were visualized at the inked surgical edge of the sample.

2.2 | Statistical analysis

Statistical analysis was performed in STATA 13.1 (StataCorp, College Station, Texas). Descriptive statistics were calculated. Categorical data are expressed as frequencies and, because of nonnormality of the data, continuous data are expressed as median and range. Fisher's exact test was used to evaluate the association of completeness of surgical margins with anatomic location of LSA. Anatomic location, completeness of margins, adjunct care with systemic chemotherapy, LSA grade and subtype, and other organ involvement were evaluated for association with all-cause overall survival time (defined as period from date of surgery to date of death). Median survival times with 95% confidence intervals were determined by using the Kaplan-Meier product limit method, and log-rank analysis was used to compare survival curves among groups. Right censoring was applied to cats that were lost to follow-up, with the survival time at the last known contact documented. $P < .05$ was considered statistically significant for all tests performed.

3 | RESULTS

3.1 | Demographics

Seventy-six cats with intermediate- or large-cell GI LSA were initially identified. Medical records were unavailable for 21 cats, 13 cats were lost to follow-up before suture removal, and two cats were euthanized intraoperatively. In total, 40 cats were eligible for inclusion in the study (Table 1), of which 21 were from referral care hospitals, and 19 were from primary care hospitals.

All cats included in the study were initially presented to the examining veterinarian for abnormal clinical signs, and none were presented as healthy cats with subsequent incidental discovery of LSA. The most common presenting complaints in all cats were vomiting (25), weight loss (24), inappetence or anorexia (22), lethargy (20), and diarrhea (5). At initial examination, medical records indicated palpation of an abdominal mass in 30 cats. Complete blood counts were available for 34 cats, and the most commonly noted abnormalities were neutrophilia (11), anemia (11), leukocytosis (10), and monocytosis (4). Blood chemistry results were available for 29 cats, and the most commonly noted abnormalities were hyperglycemia (5), hypoalbuminemia (5), hyperglobulinemia (4), hypocalcemia (4), and low blood urea nitrogen (4).

All cases had at least one form of abdominal imaging. Preoperative radiographs of the thoracic and/or abdominal cavities were completed in 32 cats. Among these cats, 12 were reported to have a midabdominal mass, four had a caudal abdominal mass, four had loss of detail and/or free gas (changes concerning for perforation of the GI tract and secondary septic peritonitis), two had obstructive patterns within the GI tract, and one had mild pleural effusion. One cat had a series of contrast radiographs, and delayed barium emptying of the stomach was reported. Eight of the radiographs were reportedly unremarkable. Preoperative abdominal ultrasound was performed in 25 cats. Gastrointestinal masses were visualized in 23 cats (nine unspecified intestinal, four gastric, one duodenal, four jejunal, two ileal, and three colonic), and peritonitis or mass rupture was suspected in six cats. In the two cats without ultrasonographic evidence of a GI mass, other reported findings included ileocolic intussusception and jejunum thickening with regional peritonitis.

3.2 | Surgery and perioperative data

During surgery, eight of the masses were found to be gastric, 23 were small intestinal (two duodenum, 16 jejunum, two ilea, three not specified), and nine were large intestinal. There was full thickness mass rupture and accompanying peritonitis in six cats (all small intestinal). Complete GI obstruction was observed in eight cats (four small intestinal, four large intestinal). The goal of all surgeries was complete mass removal, with partial gastrectomies performed in cats with gastric LSA, resection and anastomoses performed in cats with small intestinal LSA, and subtotal colectomies performed in cats with large intestinal LSA. In addition to the primary surgical goal of GI mass removal, 20 cats had additional secondary surgical procedures including 12 abdominal lymph node biopsies, six liver biopsies, two abdominal lymph node extirpations, two cystotomies (struvite stone removal), two closures of mesenteric rents, one partial omentectomy, and one urinary bladder biopsy. There were

TABLE 1 Demographics of cats enrolled in this study

Variables	All cats, N = 40	Gastric LSA, n = 8	Small intestinal LSA, n = 23	Large intestinal LSA, n = 9
Age, median (range), y	10.2 (4.5-16.7)	10.8 (9.3-13.5)	10.0 (5-15)	10.9 (4.9-16.7)
Breed, n (%)				
DSH	33 (82.5)	7 (87.5)	18 (78.2)	8 (88.9)
DLH	3 (7.5)	1 (12.5)	2 (8.7)	0 (0)
DMH	1 (2.5)	0 (0)	1 (4.3)	0 (0)
Maine coon	1 (2.5)	0 (0)	1 (4.3)	0 (0)
Persian	1 (2.5)	0 (0)	0 (0)	1 (11.1)
Siamese	1 (2.5)	0 (0)	1 (4.3)	0 (0)
Sex, n (%)				
FI	2 (5)	1 (12.5)	1 (4.3)	0 (0)
FS	11 (27.5)	2 (25)	7 (30.4)	2 (22.2)
MI	0 (0)	0 (0)	0 (0)	0 (0)
MC	27 (67.5)	5 (62.5)	15 (65.2)	7 (77.8)
Body condition, n (%)				
Thin	20 (50)	4 (50)	13 (56.5)	3 (33.3)
Normal	15 (37.5)	3 (37.5)	7 (30.4)	5 (55.6)
Overweight	5 (12.5)	1 (12.5)	3 (13)	1 (11.1)
Presenting signs, n (%)				
Vomiting	25 (62.5)	7 (87.5)	17 (74)	1 (11.1)
Weight loss	24 (60)	5 (62.5)	16 (69.6)	3 (33.3)
Inappetence	22 (55)	6 (75	13 (56.5)	3 (33.3)
Lethargy	20 (50)	2 (25)	13 (56.6)	5 (55.6)
Diarrhea	5 (12.5)	1 (12.5)	2 (8.7)	3 (33.3)

Abbreviations: DLH, domestic long hair; DMH, domestic medium hair; DSH, domestic short hair; FI, female intact; FS, female spayed; LSA, lymphoma; MC, male castrated; MI, male intact.

no significant intraoperative complications noted for any of the cats based on the available surgical report notes.

Involvement of other organs was suspected intraoperatively and confirmed by histopathology in 14 cats: one null cell/double-negative (small intestinal), two LGL (1 gastric, one large intestinal), seven DLBCL (1 gastric, four small intestinal, two large intestinal), four EATCL type 1 (3 small intestinal, one large intestinal). Among these, LSA was confirmed in abdominal lymph nodes of all cats; in addition, one cat had LSA in the liver, and another cat had LSA in the urinary bladder. Two of these 14 cats had disease debulking procedures via abdominal lymph node extirpation, and the remaining 12 cats had simple biopsy procedures.

An additional five cats had possible involvement of LSA in abdominal lymph nodes, based on intraoperative gross appearance. However, these lymph nodes were not biopsied and, thus, were not included in the group of cats with other organ involvement of their disease. These five cats were censored from subsequent survival data in the comparison between cats with and without extra-GI LSA burden. We elected to include only those cats with biopsy-confirmed involvement of other organs in the extra-GI disease group because four other cats had samples collected from other organs (four lymph nodes, one liver) that were grossly suspected of containing LSA but were uninvolved after pathologist review. These lymph nodes were interpreted as either reactive nodes or drainage reactions with no evidence of neoplasia seen, and the liver was interpreted as vacuolar hepatic change. Because suspicious gross appearance alone was not indicative of true involvement of LSA, this was not sufficient for extra-GI disease group inclusion, and histopathological confirmation was required.

The median duration of the postoperative hospital stay was 2 days (range, 1-5), and 36 (90%) cats survived to hospital discharge. One cat died of suspected dehiscence (gastric, EATCL type 1) in the hospital two days after surgery. One cat (small intestinal, DLBCL) died of suspected dehiscence in the hospital one day after surgery; two additional cats (small intestinal, EATCL type 1) were euthanized

before discharge, one with confirmed peritonitis and suspected dehiscence and one for continued inappetence and lack of clinical improvement postoperatively. Two of these four cats had been treated by primary care hospitals, and two had been treated by referral level hospitals.

The median duration of time until suture removal was 14 days (range, 10-17), and 31 (78%) cats survived to suture removal. All five of the cats (three DLBCL, two EATCL type 1) that did not survive from hospital discharge to suture removal had small intestinal LSA. Three of these cats were euthanized because of suspected disease recurrence and/or lack of resolution of clinical signs, and two cats were reported to have died at home, with additional details unavailable in the medical records. Three of these five cats had been treated by primary care hospitals and two had been treated by referral level hospitals. Thirty (97%) of the cats that survived to suture removal were reported to have improvement in their clinical signs, and only one cat continued to experience inappetence.

3.3 | Postoperative survival

Among all 40 cats, one cat was alive at the completion of data collection, and 10 cats were lost to follow-up after suture removal (median follow-up time 15 days). Overall MST for all cats was 96 days (95% confidence interval [CI]: 51-23; Figure 1). Median survival time for the 31 cats surviving to suture removal was 185 days (95% CI: 72-465; Figure 2). For the nine cats censored from survival analysis because of death before suture removal, median time to death was 2 days (95% CI: 1-51). There was no difference in survival for cats treated at referral hospitals (MST 213 days [95% CI: 20-721]) compared with primary care hospitals (MST 76 days [95% CI: 16-185], $P = .096$; Figure 3).

In total, 22 cats had long-term follow-up data available for review, meaning they survived the two-week perioperative period and had additional medical records available beyond this time. The median long-term follow-up time in this group of cats was 111 days (range, 16-1407). According to medical records, owners reported via telephone conversations that three cats died at home. Eighteen cats had dates of death noted in the medical records after euthanasia was performed by the reporting veterinarian. One cat was reported to be alive at the completion of data collection 1407 days after surgery.

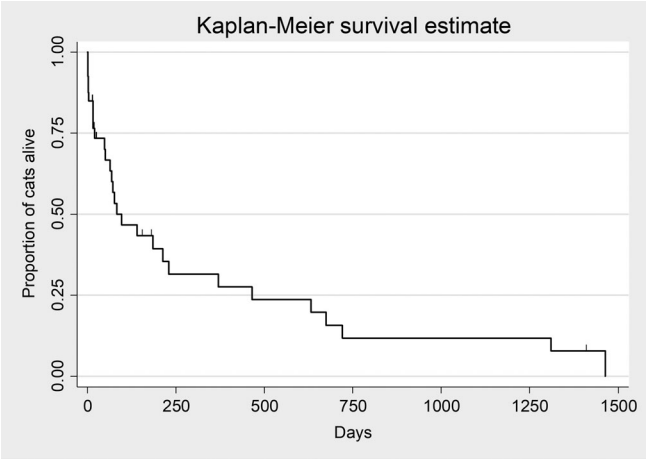

FIGURE 1 Kaplan–Meier survival curve of all 40 cats (MST 96 days [95% CI: 51-230]). MST, median survival time

3.4 | Anatomic location of lymphoma

When all cats were evaluated, MST of cats with large intestinal LSA (9) was longer compared with cats with gastric

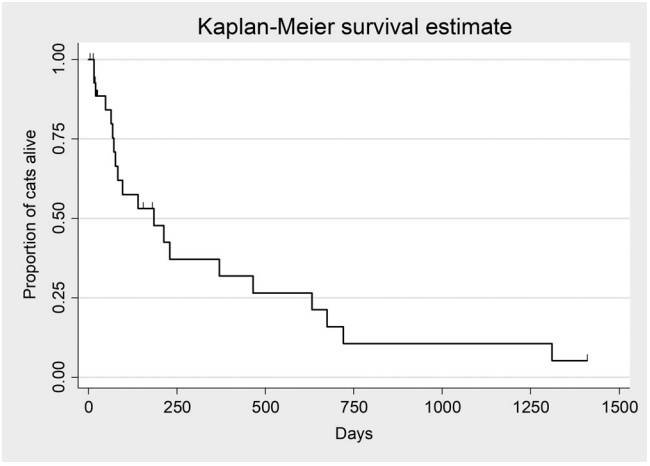

FIGURE 2 Kaplan–Meier survival curve of the 31 cats (MST 185 days [95% CI: 72-465]) that survived to suture removal. MST, median survival time

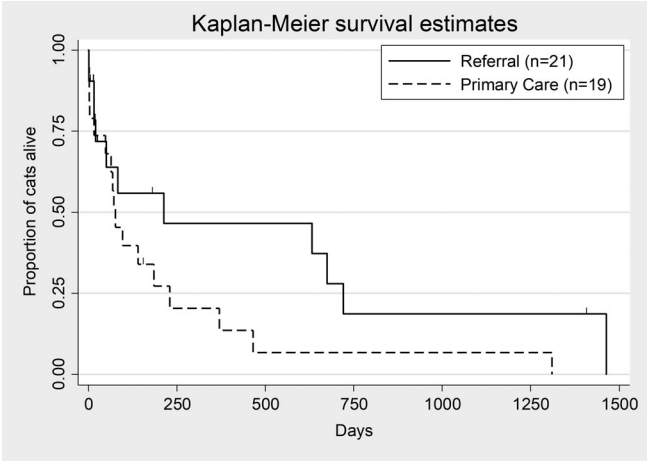

FIGURE 3 Kaplan–Meier survival curve for cats treated at referral hospitals (MST 213 days [95% CI: 20-721]) compared with primary care hospitals (MST 76 days [95% CI: 16-185]). MST, median survival time

(8) or small intestinal (23) LSA (675 days [95% CI: 76-not reached] vs 96 days [95% CI: 2-not reached] and 64 days [95% CI: 16-213], respectively, $P = .03$; Figure 4). Compared with small intestinal LSA, the hazard ratio (HR) for gastric LSA was 1.08, and the HR for large intestinal LSA was 0.30 ($P = .031$) in all cats. When cats that did not survive to suture removal were excluded, the MST of cats with large intestinal LSA was longer compared with cats with gastric or small intestinal LSA (675 days [95% CI: 76-not reached] vs 96 days [95% CI: 16-not reached] and 140 days [95% CI: 20-230], respectively, $P = .03$). Compared with small intestinal LSA, the HR for gastric LSA was 1.29 and the HR for large intestinal LSA was 0.17 ($P = .04$) in this censored group of cats. There was no difference in MST for cats with GI perforation/peritonitis compared with those without this finding (51 days [95% CI: 1-not reached] vs 140 [95% CI: 68-370], respectively, $P = .795$).

3.5 | Role of adjuvant chemotherapy

Medical records detailed the use of adjuvant systemic chemotherapy in 10 of the 31 cats that survived to suture removal. All initially were treated with a COP- or CHOP-based protocol. An additional 11 cats had records describing either no additional medical therapy (7) or the use of prednisolone (4), while 10 cats were lost to long-term follow-up without documentation of continued medical care. Median survival time was not different between these treatments, with cats receiving adjuvant chemotherapy having an MST of 51 days (95% CI: 1-not reached) vs an MST of 72 days for cats receiving prednisolone alone (95% CI: 4-not reached) and an MST of 140 days with no additional treatment (95% CI: 2-not reached, $P = .71$). The HR of no continued medical care compared with continued care was 1.03.

3.6 | Histopathologic findings and WHO Classification

Among the 40 total cats, 35 were large-cell type and five were intermediate-cell type. Standard grading indicated that 27 were high grade, 12 were intermediate grade, and one was low grade. For all cats, there was no difference in overall survival time in relation to grade ($P = .349$). Median survival time of cats with high-grade LSA was 96 days (95% CI: 20-230) compared with MST of 83 days (95% CI: 1-1310) for cats with intermediate-grade LSA. The single cat with low-grade LSA had a survival time of 48 days. The HR of high-grade LSA compared with intermediate-grade LSA was 0.70.

In total, 37 of 40 cats had formalin-fixed paraffin-embedded biopsy samples available for IHC staining. The remaining three cats were characterized according to their histopathological appearance alone. Two of these three cats were characterized as LGL, and one cat was characterized as anaplastic large-cell LSA. There was no difference in survival for any of the WHO subtype groups among the 16 cats with EATCL type-1 LSA having an MST of 76 days (95% CI: 16-230), the four cats with LGL having an MST of 370 days (95% CI: 16-not reached), the 18 cats with DLBCL LSA having an MST of 185 days (95% CI: 20-675), and the two "other" cats (one null cell and one anaplastic LSA) living for 1 day postsurgery and until suture removal (lost to follow-up), respectively ($P = .676$). Compared with cats with DLBCL, the HR for EATCL type-1 was 1.28, and the HR for LGL was 1.01.

Complete margins were documented in 20 of 40 cats. Two of the eight (25%) gastric LSA, 12 of the 23 (52%) small intestine LSA, and six of the nine (67%) large intestine LSA cases were found to have complete margins. Completeness of surgical margins was not associated with anatomic location of LSA. Median survival time of cats with complete margins was longer compared with cats with incomplete margins (213 days [95% CI: 16-675] vs 72 days [95% CI: 20-140], respectively, $P = .016$; Figure 5). For all cats, the HR in cats with incomplete margins compared with complete margins was 2.00. The difference in survival was also significant when only cats that survived to suture removal were assessed (370 days [95% CI: 48-721] vs 83 days [95% CI: 64-not reached], $P = .016$]. Within this group of cats, the HR in cats with incomplete margins compared with complete margins was 3.64 ($P = .022$).

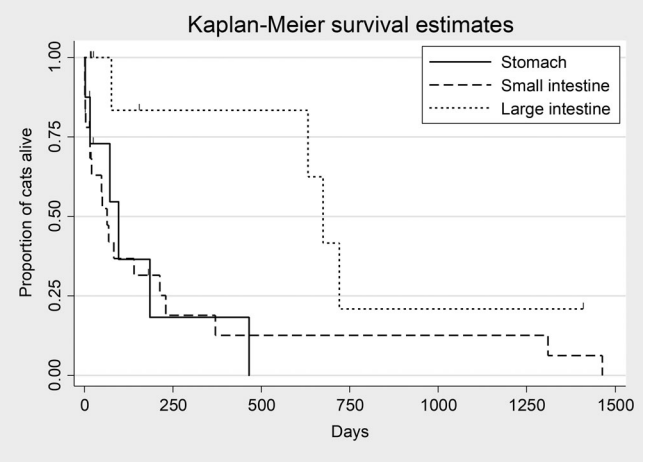

FIGURE 4 Kaplan–Meier overall survival curve of cats based on anatomic location of the primary gastrointestinal mass. Mean survival time: gastric (n = 8) 96 days (95% CI: 2-not reached), small intestine (n = 23) 64 days (95% CI: 16-213), large intestine (n = 9) 675 days (95% CI: 76-not reached); $P = .03$

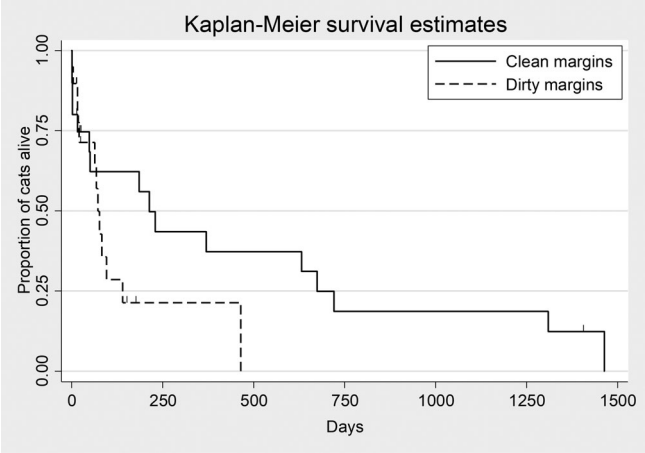

FIGURE 5 Kaplan Meier overall survival curve for cats with complete surgical margins (n = 20) 213 days (95% CI: 16-675) compared with those with incomplete surgical margins (n = 20) 72 days (95% CI: 20-140); $P = .016$

Eight cats with incomplete margins (3 gastric, five small intestinal) and seven cats with complete margins (one gastric, six small intestinal) died of suspected local GI LSA recurrence. In addition, no difference was noted in MST between cats with biopsy-confirmed LSA in other organs (14) compared with those without (21; 83 days [95% CI: 20-465] vs 140 days [95% CI: 16-370], respectively, $P = .43$]. The HR for cats without confirmed extra-GI LSA compared with those with confirmed involvement was 0.73. The use of systemic chemotherapy was not found to be more common in cats with incomplete surgical margins or diffuse LSA. Five of the 10 cats that received chemotherapy had incomplete surgical margins, and five cats had evidence of LSA in other abdominal organs.

Histopathological and IHC data are presented in Table 2. Case summaries are presented in Table 3.

TABLE 2 Histopathologic findings and WHO classification

Variables	All cats, N = 40	Gastric LSA, n = 8	Small intestinal LSA, n = 23	Large intestinal LSA, n = 9
Margins, n (%)				
Complete	20 (50)	2 (25)	12 (52.2)	6 (66.7)
Incomplete	20 (50)	6 (75)	11 (47.8)	3 (33.3)
Lymphocyte size, n (%)				
Intermediate	5 (12.5)	0 (0)	4 (17.4)	1 (11.1)
Large	35 (87.5)	8 (100)	19 (82.6)	8 (88.9)
Grade, n (%)				
Low	1 (2.5)	0 (0)	1 (4.3)	0 (0)
Mid	12 (30)	0 (0)	6 (26.1)	6 (66.7)
High	27 (67.5)	08 (100)	16 (69.6)	3 (33.3)
Immunophenotype, n (%)				
T cell	19 (47.5)	0 (0)	16 (69.6)	3 (33.3)
B cell	17 (42.5)	6 (75)	6 (26.1)	5 (55.6)
Not assessed	3 (7.5)	2 (25)	0 (0)	1 (11.1)
Double negative	1 (2.5)	0 (0)	1 (4.3)	0 (0)
WHO classification, n (%)				
DLBCL	18 (42.5)	0 (0)	14 (60.9)	2 (22.2)
EATCL type I	16 (40)	6 (75)	7 (30.4)	5 (56.5)
LGL	4 (10)	2 (25)	1 (4.3)	1 (11.1)
Null cell	1 (2.5)	0 (0)	1 (4.3)	0 (0)
Anaplastic LSA	1 (2.5)	0 (0)	0 (0)	1 (11.1)

Abbreviations: DLBCL, diffuse large B-cell LSA; EATCL type I, enteropathy associated T-cell LSA type I; LGL, large granular LSA; LSA, lymphoma; WHO, World Health Organization.

TABLE 3 Case summaries

Case No.	Tumor location	Length of follow-up	Continued care	Outcome	Cause of death
1	Small intestine	1	N/A	Dead	Postop death, suspected dehiscence
2	Jejunum	140	None documented	Dead	Unknown, died at home
3	Stomach	198	Prednisolone	Dead	LSA
4	Jejunum	1	N/A	Dead	Postop euthanasia, peritonitis and suspected dehiscence
5	Jejunum	1310	Prednisolone	Dead	Suspected recurrence
6	Jejunum	16	N/A	Dead	Postop euthanasia, suspected recurrence
7	Large intestine	721	None documented	Dead	LSA
8	Jejunum	230	None documented	Dead	LSA
9	Jejunum	14	COP	Dead	Postop euthanasia, continued inappetence
10	Jejunum	370	None documented	Dead	LSA
11	Stomach	30	COP	Dead	LSA
12	Ileum	84	None documented	Dead	LSA
13	Stomach	957	CHOP	Dead	Suspected recurrence
14	Jejunum	4	N/A	Dead	Postop death, died at home
15	Large intestine	15	N/A	Lost to follow-up	N/A
16	Large intestine	676	COP	Dead	LSA
17	Stomach	22	N/A	Lost to follow-up	N/A
18	Duodenum	20	N/A	Lost to follow-up	N/A
19	Stomach	2	N/A	Dead	Postop death, suspected dehiscence
20	Large intestine	24	N/A	Lost to follow-up	N/A
21	Small intestine	1	N/A	Dead	Postop euthanasia, peritonitis
22	Stomach	12	N/A	Lost to follow-up	N/A
23	Jejunum	11	N/A	Lost to follow-up	N/A
24	Large intestine	77	COP	Dead	LSA
25	Jejunum	21	COP	Dead	LSA
26	Duodenum	15	N/A	Lost to follow-up	N/A
27	Jejunum	3	N/A	Dead	Postop euthanasia, continued inappetence
28	Small intestine	49	None documented	Dead	Suspected recurrence
29	Jejunum	69	Prednisolone	Dead	Suspected recurrence
30	Large intestine	1408	CHOP	Alive	N/A
31	Ileum	6	N/A	Dead	Postop death, died at home
32	Jejunum	157	N/A	Lost to follow-up	N/A
33	Stomach	80	Prednisolone	Dead	Suspected recurrence
34	Stomach	97	None documented	Dead	LSA
35	Large intestine	633	COP	Dead	LSA
36	Jejunum	52	N/A	Dead	LSA
37	Jejunum	87	COP	Dead	LSA
38	Large intestine	36	N/A	Lost to follow-up	N/A
39	Large intestine	153	N/A	Lost to follow-up	N/A
40	Jejunum	221	COP	Dead	LSA

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; COP cyclophosphamide, vincristine, prednisolone; LSA, lymphoma; N/A, not applicable; Postop, postoperative.

4 | DISCUSSION

In this study of cats that underwent curative intent surgical resection of discrete GI LSA masses, 90% (36/40) survived to hospital discharge, and 78% (31/40) survived to suture removal. Ninety-seven percent of cats that survived to suture removal had improvement in their presenting clinical signs, indicating successful palliation of their cancers. The anatomic location of the tumor was associated with clinical outcome; cats with large intestinal lymphoma had the longest MST. Obtaining complete surgical margins was also associated with improved survival. Other factors that were assessed and found not to be associated with survival included immunophenotype, tumor grade, confirmed presence of lymphoma in local lymph nodes or other organs, and the use of postoperative chemotherapy. Although this population of cats varied in terms of patient status and clinical care setting, neither the presence of septic peritonitis at the time of surgery nor the level of care (primary vs specialist) was associated with patient outcome.

The overall survival times in this study are comparable to those reported for cats with GI LSA treated with systemic chemotherapy alone.[1,4-6,10-15] In addition to improving survival time, maintaining quality of life is an important goal in LSA case management because treatment is often palliative in nature. Most cats (97% [30/31]) that survived the perioperative period experienced improvement in their clinical signs, indicating successful palliation of a rarely cured cancer. For cats that experience stress with veterinary visits or have poor tolerance of systemic chemotherapy, consideration of a single palliative surgical procedure rather than weekly treatments may be warranted. There is also a dichotomy in cases of feline LSA, with potentially greater than half of cats lacking significant response to chemotherapy and only a small subset of cats entering a durable clinical remission. Cats that are nonresponsive to chemotherapy have short MST ranging from 27 to 73 days,[6-9,13,14] which is less than or statistically equal to the MST in this study.

The population of cats enrolled in our study was more heterogenous than in the study recently described by Gouldin et al in which cats were enrolled only if care was performed at a referral hospital. Nearly half of the cats in our study were surgically treated at primary care hospitals, which could have introduced bias of less aggressive surgeries, differences in patient monitoring, and decreased ability to care for complications. However, assessing such population is clinically relevant because some cat owners are not geographically or financially positioned to pursue surgery with referral clinics. While no significant difference in survival times or postoperative outcome was found between cases from primary care or specialty care hospitals in this study, the comparison between the group survival times was trending toward significance ($P = .095$). It is possible that with additional time for case data collection, a true difference in outcome between the groups would have been documented, so it is still reasonable to offer referral level surgical care in cats with suspected GI LSA because there may be a true survival benefit to cats, depending on surgeon expertise.

Similarly to previous reports, immunophenotype and/or morphological phenotype was not found to be predictive of survival. Although large granular LSA historically has been noted to have a poor long-term prognosis, with some reported MST less than two months, this group had the longest MST in the study reported here.[8,9] This subtype is often noted to be particularly aggressive, usually with advanced disease at diagnosis, but only 50% of the LGL-type cats in this study had confirmed involvement of their LSA in local lymph nodes. The isolated GI nature of the LSA in the group of cats in this study may have contributed to the observed longer survival compared with what is more commonly reported. In addition, 75% of the LGL cats in our study were noted to have received adjunct systemic chemotherapy. Although chemotherapy did not provide a survival benefit for the broader group, it is possible that it was of benefit in one or more of these specific cats, helping to account for the longer than expected survival within this group. However, given the small number of cats with this particular type of LSA (n = 4), continuing to give these cats a guarded prognosis is warranted until additional data are available.

The anatomic location of the tumor was a significant factor in survival time. Although there was a greater proportion of cats in the large intestinal LSA group with complete margins, there was not a significant correlation between anatomic location of the tumor and completeness of surgical margins. In addition, none of the cats with large intestinal LSA removed with complete margins had confirmed LSA recurrence at the surgery sites. It is possible that the biological behavior of large intestinal LSA is somehow different from that affecting the remaining GI tract. A prospective study with a control group is required to confirm whether this finding is persistent in a larger population of LSA cats. Incomplete surgical margins were a negative prognostic factor in this study and, for many other cancers, incomplete resection is associated with an increased risk of local recurrence. However, in this study, similar numbers of cats were suspected to develop local recurrence regardless of the status of histopathologic margins, which suggests that this may not be a reliable predictor of this outcome. Also, among cats with adequate follow-up, 50% of cats with complete margins and 45% of cats with incomplete margins were treated with adjunct systemic chemotherapy, suggesting that additional care was not a factor in local recurrence compared with margin status. Most cats in this study survived the perioperative period and experienced improvement of their

clinical signs even with incomplete surgical margins being noted. This suggests that, for many cats, use of surgery to debulk through removal of the gross tumor, even without obtaining complete margins, is likely sufficient to palliate their cancer.

No significant difference in survival was noted between cats with LSA confined to the GI tract and those with other organ involvement. We elected to include only cats with biopsy-confirmed extra-GI involvement of their LSA in this group. By excluding cats with abnormal gross organ appearance but no confirmatory biopsy collection from the group, there may have been underestimation of the number of cats affected by extra-GI LSA, and the impact of diffuse disease on survival may have been masked. This gap in our data reflects the importance of biopsy collection from other organs during surgery because it may influence a clinician's recommendations for continued medical care and/or an owner's interest in pursuing additional treatments. Chemotherapy-treated cats (n = 10) seemed to have a shorter MST than cats that received either no adjunctive treatment or prednisolone alone. However, lack of statistical significance and small sample size in each group preclude firm conclusions. In this particular series, cats with more diffuse disease or incomplete margins were not consistently treated more aggressively. There may have been an element of selection bias in determining which owners elected to pursue additional treatment with chemotherapy. Because some cases were from primary care hospitals, lack of availability of oncologists in the area or clinician discomfort with administering chemotherapy may have precluded treatment of some cats.

This study has several limitations because of its retrospective nature. The cases were collected from multiple institutions, resulting in nonstandardized care prior to surgery and level of detail in provided medical records. One-quarter of the cats were lost to follow-up or had insufficient medical records available for information regarding long-term survival data beyond the time of suture removal. The care provided both at the time of surgery and postoperatively varied considerably among cats, making direct comparisons between groups difficult. The sample in this study was small, and there were no control cats that received chemotherapy alone without surgical intervention. None of the cats were necropsied, and several cats were reported to have died at home, without a corresponding veterinary examination. These deaths were suspected to have been results of either postoperative complications or residual/relapsed LSA, depending on the date of death in relation to surgery. However, without confirmation via imaging, cytology, and/or necropsy, the incidence of LSA and surgical complications as the cause of death may be overestimated.

In conclusion, this study provides evidence to support surgical resection of GI masses of intermediate- or large-cell LSA in cats. Indeed, most cats survived to suture removal and improved clinically. Palliation is the overall goal when managing feline GI LSA, and this goal was achieved for most cats described here. It is reasonable to consider surgical resection of LSA from the GI tract, especially in cats with large intestinal LSA because surgical survivability and long-term outcome for these cats were especially promising. If surgery is selected, the surgeon's objective should be aggressive resection of discrete GI masses because cats with complete surgical margins survived longer in our population. Future studies should focus on prospective enrollment of a control group treated with chemotherapy alone, comparison of cats treated with surgery alone or with adjunct chemotherapy, influence of staging on surgical candidacy, and inclusion of a consistent management approach at a single veterinary hospital.

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CONFLICT OF INTEREST

None of the authors declare any financial or personal conflicts of interest that could inappropriately influence the content of this article.

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REFERENCES

1. Limmer S, Eberle N, Nerschbach V, Nolte I, Betz D. Treatment of feline lymphoma using a 12-week, maintenance-free combination chemotherapy protocol in 26 cats. *Vet Comp Oncol.* 2016;1:21-31.
2. Schneider R. Comparison of age- and sex-specific incidence rate patterns of the leukemia complex in the cat and the dog. *J Natl Cancer Inst.* 1983;70(5):971-977.
3. Louwerens M, London CA, Pedersen NC, Lyons LA. Feline lymphoma in the postfeline leukemia virus era. *J Vet Intern Med.* 2005;19:329-335.
4. Moore PF, Rodriguez-Bertos A, Kass PH. Feline gastrointestinal lymphoma: mucosal architecture, immunophenotype, and molecular clonality. *Vet Pathol.* 2012;49(4):658-668.
5. Pohlman LM, Higginbotham ML, Welles EG, Johnson CM. Immunophenotypic and histologic classification of 50 cases of feline gastrointestinal lymphoma. *Vet Pathol.* 2009;46:259-268.
6. Collette SA, Allstadt SD, Chon EM, et al. Treatment of feline intermediate- to high-grade lymphoma with a modified university of Wisconsin Madison protocol: 119 cases (2004-2012). *Vet Comp Oncol.* 2016;14(Suppl 1):136-146.

7. Slawienski MJ, Mauldin GE, Mauldin GN, Patnaik AK. Malignant colonic neoplasia in cats: 46 cases (1990-1996). *J Am Vet Med Assoc.* 1997;211(7):878-881.
8. Sapierzynski R, Jankowska U, Jagielski D, Kliczkowska-Klarowicz K. Large granular lymphoma in six cats. *Pol J Vet Sci.* 2015;18(1):163-169.
9. Krick EL, Little L, Patel R, et al. Description of clinical and pathological findings, treatment, and outcome of feline large granular lymphocyte lymphoma (1996-2004). *Vet Comp Oncol.* 2008;6(2):102-110.
10. Gustafson TL, Armando V, Taylor BE, Flory A. A retrospective study of feline gastric lymphoma in 16 chemotherapy-treated cats. *J Am Vet Med Assoc.* 2014;50(1):46-52.
11. Rau SE, Burgess KE. A retrospective evaluation of lomustine (CeeNU) in 32 treatment naïve cats with intermediate to large cell gastrointestinal lymphoma (2006-2013). *Vet Comp Oncol.* 2016;15(3):1019-1028.
12. Gouldin ED, Mullin C, Morges M, et al. Feline discrete high-grade gastrointestinal lymphoma treated with surgical resection and adjuvant CHOP-based chemotherapy: retrospective study of 20 cases. *Vet Comp Oncol.* 2017;15(2):328-335.
13. Waite AH, Jackson K, Gregor TP, Krick EL. Lymphoma in cats treated with a weekly cyclophosphamide-, vincristine-, and prednisone-based protocol: 114 cases (1998-2008). *J Am Vet Med Assoc.* 2013;242(8):1104-1109.
14. Simon D, Eberle N, Laacke-Singer L, Nolte I. Combination chemotherapy in feline lymphoma: treatment, outcome, tolerability, and duration in 23 cats. *J Vet Intern Med.* 2008;22(2):394-400.
15. Krick EL, Cohen RB, Gregor TP, Salah PC, Sorenmo KU. Prospective clinical trial to compare vincristine and vinblastine in a COP-based protocol for lymphoma in cats. *J Vet Intern Med.* 2013;27(1):134-140.

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