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Feline primary nonhematopoietic malignant liver tumours: A multicenter retrospective study (2000–2021)

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Abstract

There is scant literature on primary nonhematopoietic malignant liver tumours (PMLT) in cats. In this retrospective study, medical data of 40 cats diagnosed with PMLT were reviewed over a period of 22 years (2000–2021). The most frequent epithelial tumours were hepatocellular (42.5%) and bile duct carcinomas (32.5%), only six (15%) cats had mesenchymal tumours. The median age was 13 years and clinical signs commonly included ano-/hyporexia (62.5%), apathy/lethargy (52.5%), weight loss (42.5%) and vomiting (35%). At initial diagnosis, metastases were confirmed in 1 (2.5%) and suspected in three (7.5%) cats. Massive was the most frequent morphology (75%). Most intrahepatic tumours were left-sided (54.2%) with the left medial lobe being primarily affected (25%). Extrahepatic tumours were rare (5%). In 34 (85%) cats, liver lobectomy was performed (surgery group), four (10%) were treated palliatively (non-surgery group), and two (5%) received no treatment. Intraoperative complications occurred in 11.8% with four (15.4%) postoperative deaths. Recurrence was detected in 28.6% at a median of 151 days (range, 79–684 days), while postoperative metastases were suspected in 21.4% at a median of 186 days (range, 79–479 days). The median survival time (MST) was significantly longer in cats of the surgery group (375 days) than in the non-surgery group (16 days) ($p = .002$). MST was 868 days for hepatocellular compared to 270 days for bile duct carcinomas ($p = .06$). In summary, liver lobectomy is associated with prolonged survival times and good prognosis in cats with hepatocellular, and an acceptable prognosis in cats with bile duct carcinoma.

KEYWORDS
bile duct carcinoma, cats, hepatocellular, liver neoplasia, prognosis, surgical treatment

1 | INTRODUCTION

Primary nonhematopoietic malignant liver tumours (PMLT) are rarely diagnosed in cats and the existing information on them is based on comparatively small and older studies or single case reports,[1–9] with the largest studies on feline nonhematopoietic neoplasia describing only 12[7] and 14[2] PMLT. According to these limited data, PMLT are most commonly of epithelial origin, and bile duct carcinoma is the most common tumour type. Furthermore, PMLT also include hepatocellular carcinoma, neuroendocrine carcinoma and mesenchymal liver tumours.[2,6,7,10,11] There is scarce data on survival times in cats, but the prognosis after surgery is generally considered poor, as 86% of cats in a study on PMLT[2] and 82.4% of cats with hepatobiliary neuroendocrine carcinomas[9] died or were euthanized before discharge from the hospital. Another study on cats with visceral hemangiosarcoma (which most commonly affected the liver in that study) reported a poor post-surgical MST of 77 days.[12] Survival times for cats with bile duct carcinomas are considered even worse, with all patients dying perioperatively in previous studies.[2,8] However, as in dogs,[13] hepatocellular carcinoma seems to have a more favourable prognosis, and a recent feline study described a median survival of 2.4 years in six surgically treated cats with this tumour type.[14] In recent years, significant progress has been made in preoperative diagnostic imaging, veterinary surgical oncology, and postoperative care, suggesting that much of the existing prognostic information may no longer be accurate. Therefore, we conducted a retrospective, multicenter study to describe clinical and diagnostic findings, frequency distribution of histopathological tumour types and outcome in a larger cohort of cats with PMLT. We hypothesized that the prognosis for cats undergoing treatment for malignant, nonhematopoietic liver neoplasms may not be as dismal as often described.

2 | METHODS

The medical databases of eight veterinary referral institutions from continental Europe, the United Kingdom and the United States were retrospectively reviewed for cats with PMLT that presented between January 1st, 2000 and December 31st, 2021. Cats were included, if PMLT was confirmed by histopathological examination. Benign and haematopoietic liver tumours were excluded as well as tumours diagnosed by cytology only. Cases with multiple liver masses were included, provided that at least one of them was histopathologically diagnosed as PMLT.

Medical data were reviewed for signalment (age, bodyweight, sex, neuter status, and breed), clinical signs, presurgical laboratory findings (blood results, liver mass fine-needle aspiration cytology and bacterial culture), pre- and postsurgical imaging results (thoracic and abdominal imaging), presence of metastatic disease at time of first presentation (staging), treatment type, surgical procedure, gross morphology (morphologic classification, liver lobe distribution, liver side, maximum tumour diameter in centimetres at the time of diagnosis), histopathology, surgical outcome, follow-up information, time to recurrence or metastasis and survival time (ST). Selected preoperative blood count (CBC) and clinical biochemistry (BC) data included: haematocrit (HCT), white blood cell (WBC) count, platelet (PLT) count, total protein (TP) content, albumin (Alb), serum glucose (Glu), serum alkaline phosphatase (ALP), serum alanine aminotransferase (ALT), blood urea nitrogen (BUN), serum creatinine (CREA), and total bilirubin (T-bil) concentration in SI-units. Date of first presentation, surgery/biopsy sampling, recurrence or metastatic disease and date of death, euthanasia or last follow-up were recorded. Follow-up information was defined as diagnostic procedures performed between surgery date and death, euthanasia, or date of last follow-up. The outcome of the cats was determined from medical follow-up data (if available) and from telephone calls with referring veterinarians and pet owners. Tumours originating in the hepatic ducts, the cystic duct, or the common bile duct (ductus choledochus) were defined as extrahepatic. Intrahepatic tumours were either classified as massive (single mass in one liver lobe), multifocal nodular (multiple nodules of varying size in more than one liver lobe), or diffuse (diffuse infiltration of all liver lobes).[6,11,15,16] The location of massive and nodular intrahepatic hepatobiliary tumours was recorded according to Liptak et al. as either left, central, or right.[13] Left-sided tumours involved the left lateral and medial lobe, or the papillary process of the caudate lobe. Central tumours affected either the right medial or quadrate liver lobes. Right-sided tumours originated either from the right lateral lobe or the caudate process of the caudate lobe.[13] The maximum tumour dimension at the time of diagnosis was determined from the surgery report or from abdominal imaging (CT, ultrasonography) and given as the maximum diameter in centimetres (cm). Intraoperative complications were classified as grade I-IV (CLASSIC system[17]) ranging from no deviation of the ideal operative course to patient death. Postoperative complications were classified as mild, moderate, severe, and those leading to postoperative death (level 4) according to the Accordion classification reported by Follette et al.[17]

2.1 | Statistical analysis

All statistical data were analysed under supervision of a biostatistician using a commercially available statistical software program (IBM SPSS Statistics Version 28.0.0.0) and Microsoft Excel. Descriptive statistics and frequency tables were used to summarize the potential variables of interest. Normal distribution of continuous variables was assessed visually and using the Shapiro-Wilks test for normality. Normally distributed values were described with mean ± standard deviation, variables which did not meet the assumption of normal distribution by median and the range from minimum to maximum value. Categorical variables were described as the proportion of the study population and percentage. The Mann–Whitney *U* test (for continuous variables) and the Pearson Chi-Square test (χ^2) (for categorical variables) were used to determine if there were any significant differences between the most representative histopathological groups (hepatocellular carcinoma, bile duct carcinoma) for age, bodyweight, clinical symptoms, blood results, morphologic classification, liver side, tumour diameter

TABLE 1 Frequency distribution of histopathological tumour types in 40 cats with PMLT

Diagnosis	Number (*n*)	Percentage of the study population (%)
Hepatocellular carcinoma	17	42.5
Bile duct carcinoma	13	
Intrahepatic	12	30
Extrahepatic	1	2.5
Undefined carcinoma	2	
Intrahepatic	1	2.5
Extrahepatic	1	2.5
Neuroendocrine carcinoma	2	5
Primary mesenchymal tumours	6	
Hemangiosarcoma	4	10
Fibrosarcoma	1	2.5
Undefined sarcoma	1	2.5
Total	40	100

Abbreviation: PMLT, primary nonhematopoietic malignant liver tumours.

and complete excision. The Pearson χ^2 test was further used to determine the correlation between tumour diameter and inoperability as well as complete excision and between complete excision and local recurrence. To compare outcome and survival data, cats were further allocated into a (curative-intent) surgery and a non-surgery (conservative treatment) group. The time to recurrence or metastasis was defined as the number of days from the date of definitive diagnosis (liver lobectomy or biopsy sampling) to the day of recurrence or metastatic disease (based on imaging findings and cytological examination). The survival time (ST) was defined as the interval from the date of definitive diagnosis until death or euthanasia. The Kaplan–Meier analysis with log rank was used to compare the survival time between different treatment and histopathological groups and between completely versus incompletely excised tumours. Cats without treatment ($n = 2$) and animals euthanized intraoperatively ($n = 8$), were excluded from these analyses. Cats that were still alive at the closing date of data collection or lost to follow-up were censored for survival analyses at the last known date alive. For all statistical analyses, a p value of ≤.05 was considered significant.

3 | RESULTS

3.1 | Type and frequency distribution of tumours

Forty cats across eight institutions were included in the study. Thirty-four of 40 (85%) PMLT were histopathologically diagnosed after surgical excision of the masses (liver lobectomy). In a minority of cases (6/40; 15%) diagnosis was made by collecting incisional biopsy samples via laparotomic incisional liver biopsies (4/40; 10%) or TruCut biopsies (2/40; 5%). On histopathology, 34/40 (85%) tumours were of epithelial origin and 6/40 (15%) were mesenchymal. The most frequent epithelial tumours were 17/40 (42.5%) hepatocellular carcinomas and 13/40 (32.5%) bile duct carcinomas (see Table 1).

3.2 | Signalment, clinical characteristics

The median age at the time of first presentation was 13 years (range, 2.6–18.2 years) and 75% of the cats were older than 10 years. The median bodyweight was 4.1 kg (range, 1.9–11 kg). No statistically significant differences in age ($p = 0.41$) or bodyweight ($p = .75$) were found among histopathological tumour types. Among the female cats, 3 were intact and 14 were spayed. There were three intact male cats and 20 neutered males. The 11 breeds represented in the total data were 28 domestic short-hair (DSH; 70%), two domestic long-hair (DLH; 5%), 2 Maine Coon (5%), and one each of eight other breeds. Information on presenting clinical signs was available from 38/40 (95%). Clinical symptoms were documented in 36/40 (90%) cats, whereas 2/40 (5%) cats were asymptomatic, and in 2/40 (5%) no information was reported. The most frequent clinical signs were ano- or hyporexia (25/40; 62.5%) and apathy/lethargy (21/40; 52.5%), followed by weight loss (17/40; 42.5%) and vomiting (14/40; 35%). Jaundice was detected in 5/40 (12.5%) cats (3/5 jaundiced cats had a bile duct carcinoma). When comparing the histopathological groups, bile duct carcinomas caused jaundice more often ($p = .02$), whereas hepatocellular carcinomas were more likely to cause vomitus ($p = .04$).

3.3 | Laboratory findings

3.3.1 | Blood results

Selected preoperative blood count (CBC) and clinical biochemistry (BC) data were available in most cats (38/40; 95%). Anaemia was common (15/29; 51.7%), however further characterization of anaemia was not available. Five (33.3%) cats had concurrent thrombocytopenia. One out of 33 (3.0%) cats was leucopenic and in 6/33 (18.2%) cats leucocytosis was found (in 4 cats above 25 G/L). Serum total protein (TP) values were decreased in 5/29 (17.2%) cats and albumin was decreased in 9/31 (29.0%). Serum hyperglycemia was reported in 14/27 cats (51.9%), whereas a minority (3/27; 11.1%) was hypoglycemic. Elevation of at least one liver enzyme (alkaline phosphatase [ALP], alanine aminotransferase [ALT]) was recorded in 16/38 (42.1%) cats. Hyperbilirubinemia was present in 22/26 (84.6%) of patients. Clinical jaundice was only observed in 5/40 (12.5%) cats, three of which had marked elevation of total serum bilirubin (above 150 µmol/L). Blood urea nitrogen (BUN) was decreased in 7/28 (25.0%) and creatinine levels were increased in 8/31 (25.8%) cats. Significantly higher ALT values ($p = .003$) were observed in hepatocellular carcinomas

compared to bile duct carcinomas. No difference between histopathological groups could be recorded in any other CBC or BC parameter.

3.3.2 | Cytology and bacteriology results

Ultrasound-guided fine-needle aspiration (FNA) biopsies were performed in 23/40 (57.5%) cats. Cytology was non-diagnostic in 6/23 (15%) cases. A cytological diagnosis was assigned in 17/23 cats (bile duct carcinoma [$n = 5$], undefined carcinoma [$n = 5$], hepatocellular carcinoma [$n = 2$], hepatocellular adenoma [$n = 1$], biliary cystadenoma [$n = 1$], round cell tumour [$n = 1$], undefined sarcoma [$n = 2$]). However, cytological diagnoses were consistent with the histopathological results in only 6/17 (35.3%) cases, namely three bile duct carcinomas, two hepatocellular carcinomas, and 1 undefined carcinoma. Bacterial hepatic/biliary cultures were performed in 1/40 (2.5%) cats and were negative. Twelve out of 40 (30%) cats had peritoneal effusions (transudate [$n = 1$], exudate [$n = 3$], hemorrhagic [$n = 2$], chylous [$n = 1$], undetermined [$n = 5$]). One exudate was due to septic bile peritonitis.

3.4 | Imaging findings

Thoracic imaging was performed in 31/40 (77.5%) cats including thoracic radiographs in 19/40 (47.5%) cats (two cats had 3-view radiographs) and thoracic computed tomography (CT) in 15/40 (37.5%) cats. Abdominal imaging was available in 38/40 (95%) cats and included radiography in 2/40 (5%) cats, ultrasonography in 33/40 (82.5%) and abdominal CT in 16/40 (40%) patients. In two cases (neuroendocrine carcinoma ($n = 1$), hepatocellular carcinoma ($n = 1$)), mesenteric lymphadenomegaly was suspicious for metastatic disease on abdominal ultrasonography at the time of initial presentation, however no cytological evaluation was recorded.

3.5 | Treatment

Thirty-four cats (85%) were managed by curative-intent liver lobectomy ("surgery group"). Four cats (10%) were treated conservatively/palliatively ("non-surgery group"), while two (5%) cats received no treatment at all.

The only surgery-related complication during liver lobectomy was haemorrhage (4/34; 11.8%), considered as mild (grade I[17]) in 2/34 (5.9%) and moderate (grade II[17]) in 2/34 (5.9%). The latter two received a blood transfusion postoperatively. Eight out of 34 (23.5%) cats were euthanized intraoperatively as the liver mass was judged as unresectable (hepatocellular carcinomas ($n = 2$), bile duct carcinoma ($n = 3$), hemangiosarcomas ($n = 1$), undefined carcinoma ($n = 1$) and undefined sarcoma ($n = 1$)). Reasons were reported in 5 out of 8 cats and included multilobar distribution ($n = 2$), major involvement of the bile ducts ($n = 2$) and suspected metastatic disease ($n = 1$) and PMLT was confirmed on post-mortem histopathology. In two cases (hepatocellular carcinomas ($n = 1$), hemangiosarcomas ($n = 1$)), highly invasive growth, involving major vascular structures prevented complete removal of the mass and resulted in partial liver lobectomy or incisional biopsy, respectively. No significant association was found between tumour diameter and inoperability ($p = .56$). Intraoperative deaths related to complications associated with surgery or anaesthesia were not reported. An oesophageal tube was subsequently placed in four cats during surgery due to preoperative anorexia/hyporexia, and two cats received an abdominal drainage owing to preoperative ascites. Short-term postoperative complications (during hospitalization) related to surgery were reported in 14/26 (53.9%) cats. Mild complications (6/26; 23.1%) included anorexia/hyporexia (2/26; 7.7%), apathy/lethargy (1/26; 3.9%), retching and esophagitis (1/26; 3.9%), pancreatitis (1/26; 3.9%), and mild postoperative ascites (1/26; 3.9%). In 15.4% (4/26) cats, moderate complications were reported (blood transfusion ($n = 3$), blood transfusion and nasogastric tube ($n = 1$)). Four (15.4%) cats died within 1 day after liver lobectomy (hypothermia and hypotension ($n = 2$), hypothermia and anaemia ($n = 1$), no details ($n = 1$)).

Adjuvant chemotherapy was initiated in one cat with neuroendocrine carcinoma (carboplatin; 240 mg/m^2, IV two times at an interval of 30 days) 2 months postoperatively. A Tyrosine Kinase receptor inhibitor (toceranib phosphate; dosage and duration not noted) was started 18 months post liver lobectomy in one cat with bile duct carcinoma due to metastatic disease. In one cat of the non-surgery group (hepatocellular carcinoma), metronomic chemotherapy (thalidomide, cyclophosphamide, piroxicam) was started after the biopsy result was obtained.

3.6 | Gross tumour morphology

Information on morphologic classification and liver lobe distribution of massive and nodular PMLT is shown in Tables 2 and 3. Invasion of adjacent lobes was noted in 23.3% (7/30) of the massive lesions. Of those, the left medial and left lateral ipsilateral lobes ($n = 2$), as well as the right medial and quadrate lobes ($n = 2$) were most commonly affected. Two tumours involved the extrahepatic bile ducts (bile duct carcinoma ($n = 1$), undefined carcinoma ($n = 1$)): one originated from the cystic duct, the other from the common bile duct. Maximum tumour diameter was reported for 31/40 (77.5%) cases and varied from 1 to 15 cm (median 5 cm), with 45.2% of them exceeding 5 cm. The entire lobe was affected in two cases. There was no statistically significant difference in tumour diameter among histopathological groups ($p = .83$).

3.7 | Histopathologic findings

Surgical margins were assessed in 30/34 (88.2%) of surgically treated patients. Most tumours 21/30 (70%) were incompletely excised

TABLE 2 Morphologic classification of PMLT in cats

	Number (%)			
Tumour type	**Massive**	**Nodular**	**Diffuse**	**Total**
Hepatocellular carcinoma	13 (76.5)	2 (11.8)	2 (11.8)	17 (100)
Bile duct carcinoma	9 (69.2)	2 (15.4)	2 (15.4)	13 (100)
Neuroendocrine carcinoma	2 (100)	0 (0)	0 (0)	2 (100)
Sarcoma	5 (83.3)	0 (0)	1 (16.7)	6 (100)
Other	1 (50)	0 (0)	1 (50)	2 (100)
Total	30 (75)	4 (15)	6 (15)	40 (100)

Abbreviation: PMLT, primary nonhematopoietic malignant liver tumours.

TABLE 3 Liver lobe distribution of massive and nodular PMLT in cats

	Number (*n*)										
	Intrahepatic										
Tumour type	**LL**	**LM**	**RL**	**RM**	**C**	**Q**	**Left**	**Central**	**Right**	**NC**	**Extrahepatic**
Hepatocellular carcinoma	5	3	2	6	1	2	7	5	1	4	0
Bile duct carcinoma	3	4	0	3	4	2	4	4	0	5	1
Neuroendocrine carcinoma	1	1	0	0	1	1	0	0	0	2	0
Sarcoma	0	2	1	0	0	0	2	0	1	3	0
Other	0	0	0	0	0	0	0	0	0	2	1
Total	9	10	3	9	6	5	13	9	2	16	2

Abbreviations: C, caudate lobe; LL, left lateral lobe; LM, left medial lobe; NC, not classified; PMLT, primary nonhematopoietic malignant liver tumours; Q, quadrate lobe; RL, right lateral lobe; RM, right medial lobe.

irrespective of histopathological group ($p = .41$) or tumour diameter ($p = .90$). Complete excision was documented in 9/30 (30%) cats. No significant correlation was found between complete excision and local recurrence ($p = .88$). Complete excision was not associated with a longer survival time ($p = .84$). Mesenteric lymph node metastases were histopathologically confirmed in 1 hepatocellular carcinoma (2.5%), while in two other cases (undefined carcinoma ($n = 1$), bile duct carcinoma ($n = 1$)) (5%) intraperitoneal metastases (peritoneum, mesentery, omentum, spleen) were suspected intraoperatively based on their appearance.

3.8 | Follow-up information

Local recurrence was suspected on abdominal ultrasonography in 4/14 (28.6%) cats (bile duct carcinoma [$n = 1$], neuroendocrine carcinoma [$n = 1$], hepatocellular carcinoma [$n = 1$] and fibrosarcoma [$n = 1$]). Ultrasound-guided FNA biopsy was consistent with recurrence in the cat with hepatocellular carcinoma. The median time from surgery to recurrence was 151 days (range, 79–684 days; mean 266 days), while the median time from surgery to metastasis (3/14; 21.4%) was 186 days (range, 79–479 days; mean, 248 days). In all three cases (bile duct carcinoma [$n = 2$], fibrosarcoma [$n = 1$]), the metastases were suspected intraperitoneal (omentum, small intestine, diffuse) on abdominal ultrasonography, with cytological confirmation in only one cat (bile duct carcinoma).

The median follow-up time for censored cases (still alive or lost to follow-up) from the date of definitive diagnosis was 457 days (range, 246–962 days).

3.9 | Survival time

In the surgery group, the median survival time (MST) was 375 days (range, 0–2033 days; mean, 732.9 days) from the date of definitive diagnosis (liver lobectomy). In the non-surgery group, MST was 16 days (range, 0 to 81 days; mean, 33.8 days) from the date of definitive diagnosis (biopsy sampling). Cats in the surgery group had significantly longer survival times from the date of definitive diagnosis ($p = .002$) than cats in the non-surgery group. Cats with hepatocellular carcinomas had an MST of 868 days (range, 1 to 2033; mean, 987.9 days) from the date of definitive diagnosis. In contrast, bile duct carcinomas had an MST of 270 days (range, 0–889; mean, 338.2 days) from the date of definitive diagnosis. However, the difference in MST was not statistically significant ($p = .06$). The survival analysis included one cat with neuroendocrine carcinoma, which had a survival of 246 days from date of definitive diagnosis. Primary mesenchymal tumours had a median survival time of 16 days (range, 1 to 427; mean, 143.3 days) from date of diagnosis.

The Kaplan–Meier survival data of the most representative histopathological and treatment groups are outlined in Figures 1 and 2. At the closing date of data collection, 2 (7.7%) cats of the surgery group

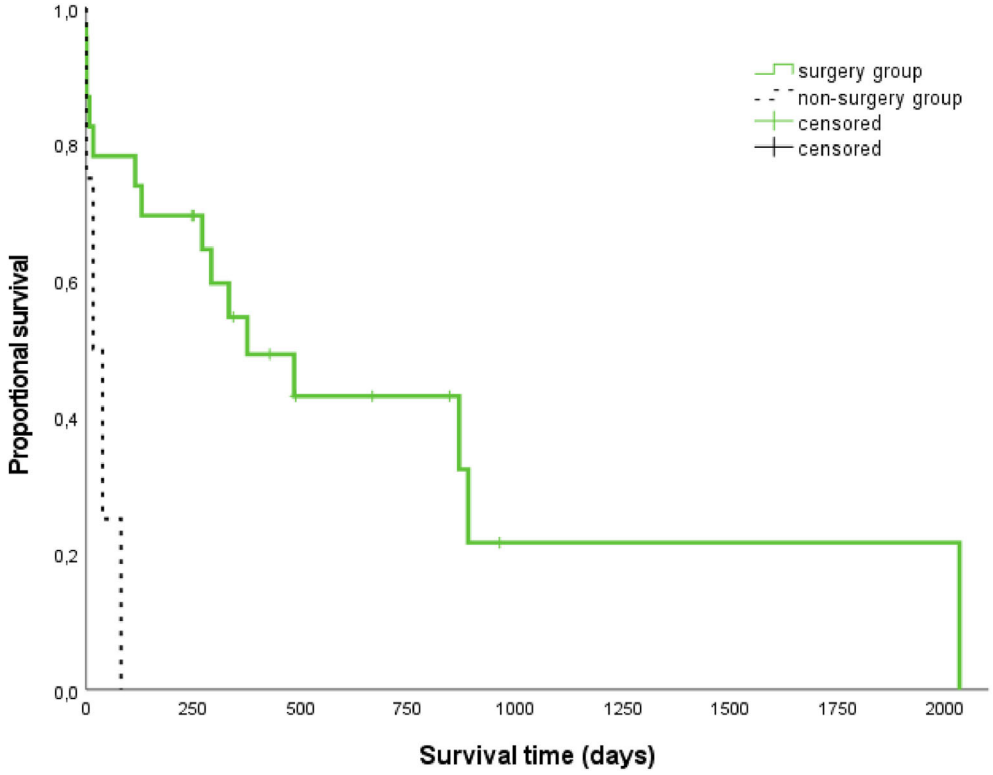

FIGURE 1 Kaplan–Meier curves for survival time from date of definitive diagnosis in cats with primary nonhematopoietic malignant liver tumours, treated with surgery ("surgery group", solid green line; median 375 days; $n = 23$) compared to those treated palliatively ("non-surgery group", dashed black line; median 16 days; $n = 4$). MST was significantly different ($p = .003$)

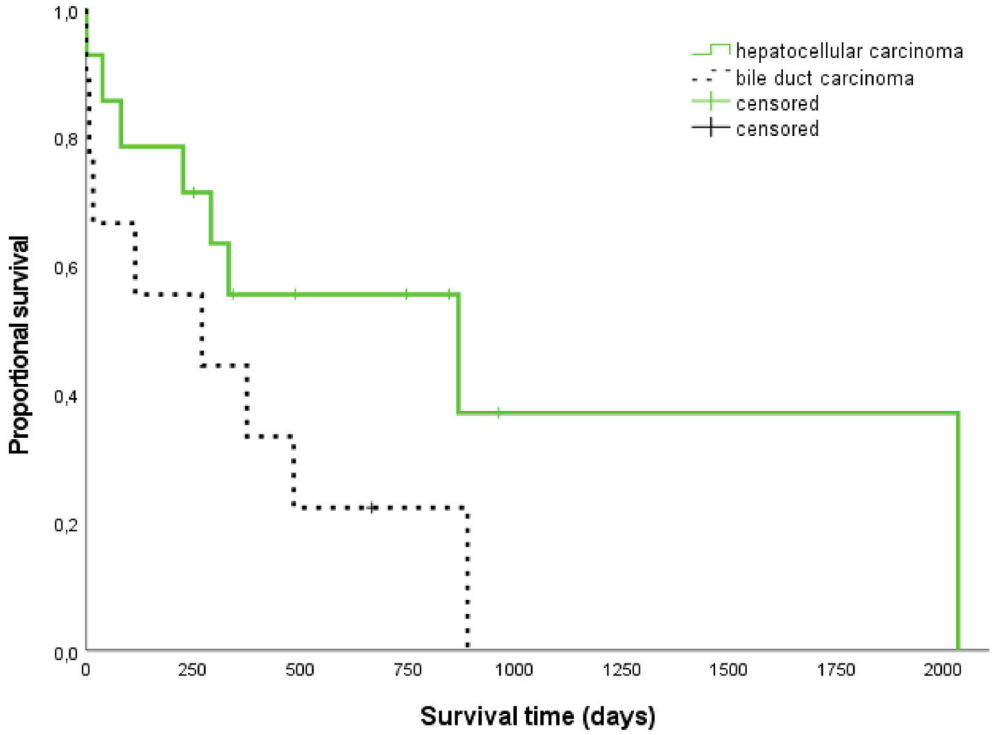

FIGURE 2 Kaplan–Meier curves for survival time from date of definitive diagnosis in hepatocellular carcinomas (solid green line; median 868 days; $n = 14$) compared to bile duct carcinomas (dashed black line; median 270 days; $n = 9$). MST was not significantly different ($p = .06$)

were still alive, whereas 15 (57.7%) cats had died or been euthanized, and nine (34.6%) cats of the surgery group were lost to follow-up. Of all the cats with local recurrence or metastatic disease, none were reported to be alive at the closing date of data collection (dead [$n = 3$], lost to follow-up [$n = 3$]). None of the patients of the non-surgery group was still alive.

4 | DISCUSSION

Primary nonhematopoietic malignant liver tumours (PMLT) are rarely diagnosed in cats. In this retrospective study, 40 cats with PMLT were presented at their respective institutions within a period of 22 years (2000–2021). Our findings suggest that liver lobectomy represents an

effective treatment option for PMLT, with prolonged survival times for cats with hepatocellular carcinoma and bile duct carcinoma.

Signalment, clinical presentation, and laboratory findings of cats with PMLT in the present study were largely consistent with previous reports on feline liver tumours.[2,5,7,11,14,16,18] Further, while haematopoietic tumours (e.g. hepatic lymphoma) can occur at any age and even in (very) young cats, PMLT are expected to predominantly occur in middle-aged to older cats.[2,3,7,9,14,19] Accordingly, in the present study 75% of cats were older than 10 years. Clinical signs and laboratory findings of cats with PMLT in the current study were typically non-specific and notably jaundice (12.5%) and liver enzyme elevation (42.1%) were present in only a minority of patients. While serum bilirubin level was only assessed in 26/40 (65%) cats, it was elevated in 84.6% of them and may be a more sensitive marker for PMLT than liver enzyme elevations. Cytological examination was of limited use for definitive diagnosis of PMLT as it was consistent with the histopathological results in only 6/17 (35.3%) cases. Similar results have been found in previous studies, which reported a rather low accuracy ranging from 33% to 51%.[14,20–22] The high accuracy of 86%, reported by Roth (2001)[23] has been critically discussed in an earlier study, as their not fully specified method of cytological specimen acquisition may have positively biased the results.[20] Thus, cytological evaluation may be useful, but results need to be interpreted with caution.[21] Histopathological examination remains the gold standard, especially in poorly exfoliative tumours and cavitated lesions.[14,18,21,23]

In the current study, hepatocellular carcinoma was most common (42.5%). Primary hepatic sarcomas were less frequently diagnosed in this study (15%) and hemangiosarcoma was the most common mesenchymal tumour type, similar to previous reports.[2,4,6,7] There is no consensus about the most common malignant hepatobiliary tumour in cats. Whereas an older study reported that hepatocellular carcinomas were the most frequent,[4] more recent studies described bile duct carcinomas as the most common PMLT in cats.[2,6,7,10] Massive was the most common morphological manifestation in all histopathological groups. This is in contrast to previous studies in cats which reported a majority of diffuse morphology with most malignant tumours (58.3%).[6] In the present study, 54.2% of the intrahepatic tumours were left-sided. This finding differs from a previous study in cats, in which the right-sided lobes were affected in 46.7%,[14] but is consistent with the results in dogs.[13,15,24,25] Unlike in dogs however,[25] the left medial lobe of the liver was primarily affected in our study population (25%), followed by the left lateral and right medial liver lobes (each 22.5%). Malignant tumours involving the extrahepatic bile ducts were rare in our study (5%), while previous studies reported higher rates (13.3% to 52.9%).[2,4,6,9] However, similarly low rates of 2%[15] and 8.3%[24] have been reported in canine studies.

The metastatic rate and pattern depends on the type and morphology of the tumour.[16,18] In dogs, metastatic rates from 4.8% to 61% have been reported in massive hepatocellular carcinomas,[13,15,25] 88% in bile duct carcinomas,[15,24] 86% in sarcomas[15] and 93% in hepatic carcinoids.[15] The most commonly reported metastatic sites are regional lymph nodes, lungs and peritoneum for epithelial and spleen for mesenchymal tumours.[13,15,24,25] For cats limited information is available on metastatic rates and sites in malignant hepatobiliary tumours. Patnaik (1992) reported extrahepatic metastases in 56% of epithelial neoplasms in cats, with the most common metastatic sites being intraperitoneal (>50% of the cases), lung, lymph nodes and spleen.[6] According to some reports, hepatocellular carcinomas have a lower metastatic rate than biliary neoplasms,[6,14] whereas hemangiosarcomas and hepatobiliary neuroendocrine carcinomas in cats have a high metastatic potential.[1,6,9,12] In the present study, mesenteric lymph node metastases were histopathologically confirmed in 1 (2.5%) cat with hepatocellular carcinoma and suspected on ultrasonography or intraoperatively in another three cases (hepatic lymph nodes [$n = 1$], intraperitoneal [$n = 2$]) (7.5%) at the time of presentation/diagnosis. Therefore, the metastatic rate at time of diagnosis may range between 2.5% and 10%. Three (21.4%) cats developed intraperitoneal metastatic disease after a median of 186 days from surgery (bile duct carcinoma [$n = 2$], fibrosarcoma [$n = 1$]). Metastasis rates are low but may have been underestimated in this study due to inconsistent staging procedures and postoperative follow-up. Screening for pulmonary metastases[1,16,18] by CT was performed in only 37.5% (15/40) cats and by three view radiographs in a minority of 5% (2/40) cats. Abdominal ultrasonography is commonly recommended for the identification and characterization of hepatobiliary neoplasms in small animals[16] and was used in most cases (82.5%). However, ultrasonography has severe limitations for staging and surgical planning.[12,26] Therefore, cross-sectional imaging (MRI, CT) should be considered for more accurate assessment, especially in diffuse or multifocal hepatobiliary diseases.[1,13,16,18,26,27] In our study, a large proportion of cats (23.5%) were euthanized at the time of surgery owing to unresectable neoplasms. Apart from the fact that resectability also depends on the surgeon's experience and expertise, none of these cases had a preoperative CT or MRI scan. We hypothesize that outcomes in some cases may have been different if advanced imaging was done prior to surgery.

For massive hepatic neoplasms, surgical resection is the treatment of choice[1,5,11,16] even though, due to scant literature, the true benefit is still largely undetermined. In the present study, there was a moderate rate (11.8%) of surgical complications but no intraoperative deaths. However, four (15.4%) cats died within 1 day after liver lobectomy. This is less than the 86% of cats with PMLT that died during surgery or hospitalization in an older study.[2] In dogs, surgical complications of 28.6% with an intraoperative mortality rate of 4.8% in hepatocellular carcinomas[13] and 20% in extrahepatic biliary neoplasia[28] have been reported. A previous study in cats with PMLT described a poor MST of 0.1 months (range, <1 day–4 months).[2] We report an MST of 375 days from the date of diagnosis for the surgery group, which was significantly higher, compared to 16 days in the non-surgery group (Figure 1). We found a prolonged MST of 868 days (2.4 years) from the date of diagnosis in the 14 hepatocellular carcinomas of the surgery-group, which is consistent with a recent study by Goussev et al. Interestingly, they described a similar MST of 2.4 (1–6.5) years in six surgically treated cats with histopathological diagnosis of hepatocellular carcinoma.[14] In comparison, an MST of >1460 days (4 years) has been reported for surgically treated dogs

with massive hepatocellular carcinoma.[13] In the present study, bile duct carcinomas had a shorter, albeit statistically not significantly different, MST of 270 days (0.7 years), compared to hepatocellular carcinomas (Figure 2). In comparison, an earlier study reported that all 10 cats with bile duct carcinoma died or were euthanized during surgery or hospitalization.[2] Equally poor survival has been reported for hepatobiliary neuroendocrine carcinomas, with 14/17 cats dying perioperatively.[9] In our study, only one cat with neuroendocrine carcinoma had adequate follow-up after surgery and died 246 days after surgery.

This study has several limitations. Even though it is the largest study on feline PMLT to date, the number of tumours in the different histopathological groups are still comparatively small, which precluded statistical comparisons between all groups. Further, because of its retrospective nature, cats did not receive standardized protocols for staging, treatment, or follow-up, and treatment decisions were influenced by the preferences and habits of individual clinicians. Cats that were euthanized intraoperatively were excluded from survival analysis, which may have biased the results toward inclusion of cats with better prognosis. However, better preoperative planning by cross-sectional imaging may have resulted in a better outcome in some of those euthanized cats.

5 | CONCLUSIONS AND CLINICAL RELEVANCE

This study provides valuable information on a poorly characterized set of malignant neoplasms in cats and may improve therapeutic decision-making. Clinical signs and laboratory findings of cats with PMLT have typically been non-specific and although hyperbilirubinemia and cytological tumour diagnosis may provide some indication, the diagnosis is based on histopathological confirmation. Surgical intervention is associated with a prolonged survival time and good prognosis in cats with hepatocellular carcinoma and acceptable survival times in cats with bile duct carcinoma. Therefore, in general, such treatment should be considered and discussed with the owners. The overall local recurrence and metastatic rates in surgically treated cats with PMLT appear to be low. However, the small case numbers and non-standardized protocols of this retrospective study do not allow definitive conclusions to be drawn. Since preoperative abdominal and thoracic CT scans are nowadays increasingly performed in most hospitals for staging and surgical planning, we encourage further investigations on their effect toward a better patient selection.

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CONFLICT OF INTEREST

The authors of this manuscript declare that they have no competing interests financial or non-financial that might have influenced their interpretation or presentation of the data presented in this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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