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CLINICAL RESEARCH

Retrospective study of 20 cats surgically treated for insulinoma

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Abstract

Objective: To report the clinical signs, histopathology results, and prognostic factors for outcomes following excision for feline insulinoma (INS).

Study design: Retrospective study.

Sample population: Twenty client-owned cats.

Methods: Medical records from 2006 to 2020 were reviewed by Veterinary Society of Surgical Oncology members for cats with hypoglycemia resulting from INS, with surgical excision and follow up. Clinical signs and histopathology results were summarized. Factors potentially related to disease-free interval (DFI), disease-related death (DRD), and overall survival time (OST) were analyzed with a Cox proportional hazards regression analysis.

Results: All cats were hypoglycemic on presentation with neurologic signs in 18 out of 20 and inappropriate insulin levels in 12/13. Excision of insulinomas resulted in immediate euglycemia or hyperglycemia in 18 cats. Eighteen cats survived to hospital discharge. The median time to death or last postoperative

follow up was 664 days (range: 2-1205 days). Prognostic factors included age at presentation (for DFI); time to postoperative euglycemia (for DRD); preoperative and postoperative serum blood glucose concentrations; metastasis at the time of surgery (DFI and DRD), and histopathologic tumor invasion (for OST). The median OST for all cats was 863 days. The 1-, 2- and 3-year survival rates were 75%, 51%, and 10%, respectively.

Conclusion: Excision of insulinoma resulted in euglycemia or hyperglycemia in most cats. Negative prognostic factors included young age, low serum glucose concentrations, metastasis at time of surgery, tumor invasion, and shorter time to euglycemia.

Clinical significance: Surgical excision resulted in survival times comparable to those of canine INS.

1 | INTRODUCTION

Insulin-secreting tumors, or insulinomas (INS), occur uncommonly in dogs and are extremely rare in cats.[1] There remains a paucity of information in the veterinary literature regarding feline INS, with 8 cats reported from 1985 to 2020.[2–9] Of these 8 cases, ages ranged from 12 to 17 years, 6 were castrated males and 2 spayed females, 4 domestic shorthairs, 3 Siamese, and 1 Maine coon.

Clinical signs of feline INS are similar to those in canines and include weakness, collapse, ataxia, and seizures.[10] Presumptive diagnosis is based on demonstration of hypoglycemia with concomitant inappropriately normal to high insulin serum concentrations and diagnostic imaging findings. A presumptive diagnosis can also be made by fulfilling the criteria of Whipple's triad, which includes the presence of clinical signs, serum blood glucose concentrations less than 60 mg/dl, and relief of clinical signs after feeding or glucose administration.[1] Differential diagnoses for pancreatic and extrapancreatic masses causing hypoglycemia in cats include INS, hepatoma,[11] acquired nisidioblastosis,[12] and hepatocellular carcinoma.[13]

Surgical guidelines for the treatment of stage I INS (confined to the pancreas), stage II (lymph node metastasis) or stage III (distant metastasis) disease have not been established for cats and dogs. Nonsurgical perioperative management options include the use of dietary modifications, glucocorticoid administration, diazoxide, streptozocin, or octreotide in dogs.[14] The use of the latter 3 treatment options and comparison of medical versus surgical treatment for INS in cats has not been investigated.

For the previous 8 case reports of INS,[2–9] survival times ranged from 3 days to more than 35 months. One cat was euthanized 18 months after surgical removal of the tumor and postmortem examination performed identified metastasis to the pancreatic lymph nodes and liver.[3] It has been postulated that the long-term prognosis for INS is poor because of the high likelihood of metastasis.[2,4,6] The purpose of this study was to report the clinical signs, histopathology results, and prognostic factors for the outcomes following surgical therapy for feline INS.

2 | MATERIALS AND METHODS

This was a multi-institutional retrospective study of cats treated between January 2006 to March 2020 at academic ($n = 13$) and private practice ($n = 7$) institutions. Medical records of cats were searched for cytological or histopathologic diagnosis of pancreatic islet cell or neuroendocrine neoplasia. Cats were included if they presented for hypoglycemia or with clinical signs consistent with hypoglycemia, had surgical excision of the pancreatic mass(es) and histopathologic confirmation of pancreatic islet cell or neuroendocrine neoplasia, or immunohistochemical positivity for insulin. Cats were excluded if they had an exocrine pancreatic mass, did not undergo surgery, or if the final diagnosis was not consistent with islet cell or neuroendocrine neoplasia.

Data were collected through an electronic survey (Supplemental Online Form) of members from the Veterinary Society of Surgical Oncology and from medical records including signalment, weight, clinical signs, bloodwork (complete blood count, chemistry, other ancillary blood tests, blood glucose levels, insulin levels, and paired insulin-to-glucose ratio when available), imaging findings, tumor size and localization, presence of locoregional or distant metastasis, excision performed (partial pancreatectomy or nodulectomy/enucleation), method of resection (sutures, sharp, cautery or vessel sealing devices), presence of additional

gross lesions, lymph node or liver histopathology when performed, histopathological assessment (mitotic indices, completeness of excision, evidence of capsular or extracapsular tumor invasion and definitive diagnosis), and immunohistochemistry (IHC) when available.

The short-term outcomes that were evaluated were immediate postoperative blood glucose levels, time to euglycemia or hyperglycemia, adjuvant therapies used, and postoperative complications. Long-term outcomes included disease-free interval (DFI), time to disease-related death (DRD), and overall survival time (OST). Disease-free interval was defined as the time in days between resection and recurrence of hypoglycemia, clinical signs related to hypoglycemia or metastasis. For the DFI calculation, cats were censored if they were lost to follow up, died due to causes unrelated to INS, or had not relapsed or developed metastasis at the time of the last follow up. Death was determined to be disease related if it occurred due to postoperative complications, if humane euthanasia was performed due to persistent hypoglycemia and associated clinical signs, or due to metastasis. Overall survival time was defined as the interval in days between excision and time of death. For time to disease-related death, cats were censored if they were still alive, were lost to follow up, died of an unrelated cause, or had an unknown cause of death. For overall survival, cats were only censored if they were still alive or were lost to follow up. A minimum follow up was not required for study inclusion.

Due to the small sample size, data were reported as median and range. Aalen-Johansen survival analysis was used to determine median DFI, median time to DRD, OST, and 1-year, 2-year, and 3-year survival rates. Aalen-Johansen curves were used because reporting of competing events required a specific order. Cox proportional hazards regression analysis was used to evaluate the effects of various variables on the outcomes of survival time and DFI. Independent variables assessed in the models included age, breed, sex, neuter status, bodyweight, duration of clinical signs, number of body systems affected, blood glucose, and serum insulin concentrations at presentation, lesion localization and tumor size, type of excision performed, postoperative serum glucose concentrations, time to postoperative euglycemia, completeness of excision, histopathological evidence of tumor lymphovascular or capsular invasion, presence of metastasis, and mitotic index. For each outcome, univariate models were assessed initially. Due to the small number of events, multivariable modeling to identify confounding variables was not performed. The level of significance selected was $P < .05$. All analyses were carried out with R version 4.0.2 (R Core Team, Vienna, Austria).[15]

3 | RESULTS

Thirty-eight cats with hypoglycemia and a pancreatic mass with cytological diagnosis consistent with islet-cell or neuroendocrine neoplasia were included from 7 countries. Of these, 20 had surgery, excluding the remaining 18. The median age at presentation was 13.2 years (range: 5.0-17.3). Ten cats were female (3 entire, 7 spayed) and 10 cats were male (2 entire, 8 neutered). The most common breeds were domestic shorthair (7 cats) and domestic longhair (4 cats). There were 2 each of Bengal, Main coon and Persian, and 1 each of domestic medium hair, mixed Japanese and Siamese cats. The median bodyweight at presentation was 4.3 kg (range: 2.6-7.6). The median duration of clinical signs prior to presentation was 12 days (range: 0-200). Common signs on presentation were neurologic in 18/20 (90%), gastrointestinal in 7/20 (35%), behavioral in 6/20 (30%), and respiratory in 1/20 (5%) cats. One cat was asymptomatic but hypoglycemic on presentation for a yearly examination. Clinical signs were weakness or collapse in 8/20 (40%), proprioceptive ataxia in 8/20 (40%), seizures in 7/20 (35%), depression in 4/20 (20%), and tremors in 4/20 (20%) cats.

Eighteen cats were reported as hypoglycemic on presentation with a median serum blood glucose concentration of 37.0 mg/dl (range: 14.0-72.0). Two additional cats were hypoglycemic on in-house readings below their reference ranges, but values were not provided. Thirteen of 20 cats had serum insulin concentrations provided with 12/13 inappropriately normal or high. The median serum insulin concentration was 19.0 μIU/ml (range: 1.0-51.0; Table S1). Two cats had paired insulin-to-glucose levels above 30 (63.8 and 78), a value previously noted as suggestive of canine INS.[14] Other lab work abnormalities included leukopenia, anemia, azotemia, hypoproteinemia, hyperproteinemia, liver enzyme elevations, electrolyte disturbances, hyposthenuria, hypocortisolemia, and hyperthyroidism.

Imaging modalities included radiography, abdominal ultrasonography, computed tomography (CT), cephalic magnetic resonance imaging (cMRI), and echocardiography. Of the 20 cats, 16 had a pancreatic mass identified – 12/18 on abdominal ultrasound and 5/6 on abdominal CT scan – with 1 cat having a mass identified on both modalities. Three cats had unremarkable cMRI results.

Twenty-two pancreatic lesions were identified during exploratory celiotomy: 16 in the left limb, 5 in the right limb, and 1 midbody (Figure 1A). Two cats had 2 lesions. Intraoperative measurements were provided for 15 lesions, with median dimensions of 10 mm^3 (range: 3.0-38.3). Partial pancreatectomy (Figure 1B) was performed in 11 cats, nodulectomy in 10 cats and enucleation in 1 cat. The method of resection was reported for

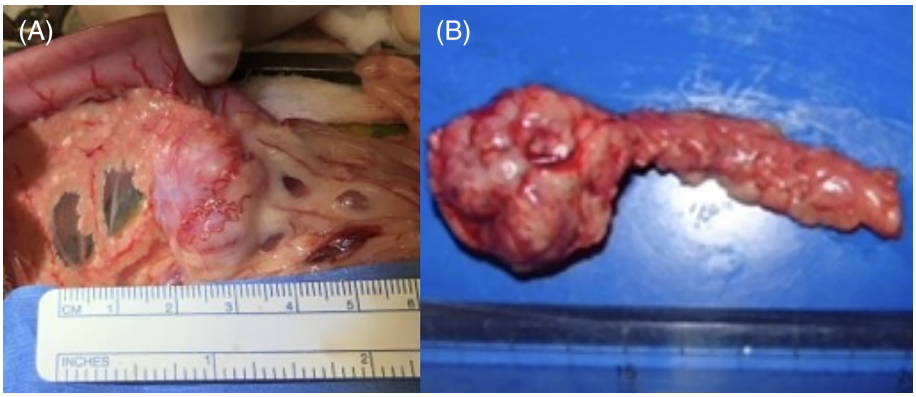

FIGURE 1 (A) intraoperative midbody pancreatic insulinoma lesions from cat 19; (B) partial pancreatectomy from cat 4 (image courtesy of Dr. Satoshi Takagi)

9 cats: suture (guillotine or suture fracture) (in 6 cats), monopolar electrocautery or harmonic shearing device (2 cats), and sharp excision (1 cat).

Eighteen out of 20 cats had a histopathologic diagnosis of INS or neuroendocrine carcinoma (Table S2). Cat 7 presented with neurologic signs, hypoglycemia, low serum insulin, and a left limb mass that was diagnosed as a beta cell adenoma; this cat remained part of the final population as IHC was insulin positive. Cat 12 presented with hypoglycemia, seizures, and a right pancreatic mass. This cat had previous excision of a different right pancreatic mass 2 months prior; however, histopathology was not provided and it was treated postoperatively with prednisolone 0.5 mg/kg orally every 12 hours due to persistent hypoglycemia. The second excision confirmed a lymphoplasmacytic neutrophilic pancreatitis; however, this cat remained intermittently hypoglycemic despite glucocorticoid administration. Seven months later, a left-sided pancreatic nodule was identified on a CT scan, and was aspirated as a neuroendocrine tumor. A third surgery (partial pancreatectomy) for a 6 mm raised mass was performed and confirmed INS with IHC positivity for insulin; the cat remained euglycemic thereafter. The total number of INS or neuroendocrine carcinomas was therefore 19. Cat 7 was diagnosed with a beta cell adenoma with IHC positivity for insulin and was thereby included.

Mitotic indices (MIs) were reported for 12 lesions, with 1 reported as 30/10 high power fields (HPF); the other 11 MIs were reported as rare, low, or less than or equal to 9/10 HPFs. Margins were reported for 15 of the submissions and lesions were completely excised in 8 cats and incompletely excised in 7 cats. There was neoplastic infiltration in 6 cats, either into the tumor capsule (3 cats) or the surrounding parenchyma (3 cats).

Concurrent lymph node and liver biopsies were obtained in 6 and 12 cats, respectively. Locoregional metastasis was not identified in any of the lymph nodes and distant metastasis was identified in 2 of the liver biopsies (16.7%); thus confirming 18 cats with stage I disease and 2 cats with stage III disease. Immunohistochemistry was performed for 2 pancreatic masses initially, with 1 of them histopathologically confirmed INS negative for insulin and the other as positive for insulin (Cat 7). Cat 12 had a third surgery confirming INS with IHC insulin positivity.

Eighteen out of 20 cats (90%) were reported as immediately euglycemic or hyperglycemic postoperatively, with 1 remaining hypoglycemic and 1 unreported (Tables 1 and S3). Immediate postoperative blood glucose concentrations recorded for 8 cases had a median of 216 mg/dl (range: 110-370). Time to postoperative euglycemia recorded for 19 cats was less than or equal to 4 h in 10/19. For the remaining 9 cats, the median time to euglycemia was 336 h (range: >4-1272).

Postoperative management included analgesics (opioid and nonsteroidal anti-inflammatory drugs), antibiotics, antiemetics, gastroprotectants and appetite stimulants. A single dose of Humulin R was administered to 1 cat for immediate transient postoperative hyperglycemia. Anticonvulsant therapy with phenobarbital was weaned in 1 cat and started in another cat, which died 2 days later from ongoing seizures. A third cat had postoperative therapy with levetiracetam for seizures transitioned to phenobarbital 2 months later, and continued until data collection, despite being asymptomatic.

Six cats (30%) had adjunctive treatments. One cat was treated with octreotide at 6 μg/kg subcutaneously every 8 hours postoperatively for an unspecified length of time, and was euthanized 248 days later for locoregional lymph node metastasis. Five cats (25%) were treated with glucocorticoid (prednisone or prednisolone) therapy at a dosing range of 0.3-0.5 mg/kg every 12 hours, 2 of these doses being administered preoperatively. Of these 5 cats, only Cat 12 was hypoglycemic postoperatively and had persistent intermittent hypoglycemic episodes. This cat had a previous surgery 5 weeks earlier for suspected INS at a different institution. A subsequent third surgery was performed 7 months later, which identified INS. The cat remained euglycemic. Two of the treated cats did not survive to discharge.

Eighteen out of 20 cats (90%) survived to discharge with 5/20 (25%) having immediate postoperative

TABLE 1 Outcome of 20 cats following surgical resection of pancreatic endocrine tumors

Case #	Postoperative glycemic status	Glucocorticoid administration	Postoperative complications	DFI (days)	Site of postoperative metastasis	Survival time (days)	Status at data collection (cause of death)
1	↑	-	-	1052	-	1052	[a](INS)
2	↑	-	-	399	-	399	[a](CKD)
3	↑	-	-	62[b]	-	132	[a](INS)
4	↑	-	-	687	-	687	[a](CKD)
5	↑	-	Hepatic lipidosis	624	-	710	[a](INS)
6	↑	POST	Anemia, seizures	0	-	2	[a](Seizures)
7	N/A	-	-	1083	-	1083	[a](Unknown)
8	=	PRE	-	93	Liver and pancreas	413	[a](INS)
9	↑	-	-	1205	-	1205	[a](Unknown)
10	=	-	-	878	-	878	[a](Unknown)
11	=	-	-	119	Liver	863	[a](INS)
12	↓	POST	-	214	Pancreas	789	Alive
13	↑	PRE	-	738	-	738	Alive
14	↑	-	-	181	-	181	[a](Oral mass)
15	↑	-	-	680	-	680	Alive
16	↑	-	-	648	-	648	Alive
17	↑	-	-	226	Lymph node	248	[a](INS)
18	=	PRE	Pancreatitis	0	-	5	[a](DIC)
19	↑	-	NCE, pneumonia, pancreatitis	417	-	417	Alive
20	↑	-	Seizures	277	-	277	Alive

Note: = Euglycemia, ↑Hyperglycemia, ↓Hypoglycemia.

Abbreviations: CKD, chronic kidney disease; DFI, disease-free interval; DIC, disseminated intravascular coagulation; INS, insulinoma; N/A, not available; NCE, noncardiogenic edema; PRE, preoperative; POST, postoperative.

[a]Euthanized.

[b]Collapsing episodes and hypoglycemia at time of recurrence.

complications. Cat 6 was markedly anemic (PCV 16%) with persistent seizures, despite being hyperglycemic. This cat was euthanized 48 h postoperatively. Cat 18 was diagnosed with disseminated intravascular coagulopathy (DIC) secondary to pancreatitis 5 days postoperatively and was also euthanized. Cat 5 developed anorexia and lethargy secondary to hepatic lipidosis 4 days postoperatively, which resolved with the placement of an esophagostomy tube and medical management. Cat 19 developed aspiration pneumonia and noncardiogenic pulmonary edema secondary to pancreatitis. It was treated with a nasogastric tube and medical management, before being discharged 6 days postoperatively. Cat 20 had 2 postoperative seizures despite euglycemia and was treated with levetiracetam with 2 ×150 mg doses every 8 hours before transitioning to phenobarbital.

For all cats, the median time to death or last postoperative follow up was 664 days (range: 2-1205). No cats were lost to follow up; 6 were still alive at the time of analysis, 8 died from disease-related causes, and 6 died from causes unrelated to INS or for unknown causes. Seven out of 18 cats (38.9%) surviving to discharge had recurrent clinical signs related to hypoglycemia with a median recurrence time of 214 days (range: 62-1052). Five of these 7 had no further treatment, with 2 initiating or continuing glucocorticoid administration (Cat 5 and Cat 12). At the time of data collection, 4/9 cats had reported postoperative metastatic disease and 5/9 without. In those 4 cases the location of postoperative metastasis included locoregional lymph nodes (1 cat), liver (1 cat), pancreas (1 cat), or both the liver and pancreas (1 cat), with no reported thoracic metastasis. Of the 14 cats that were dead at the time of data collection, 12/14 survived to discharge. Of these, 3 were euthanized for reasons unrelated to INS, 2 were euthanized due to end-stage renal disease,

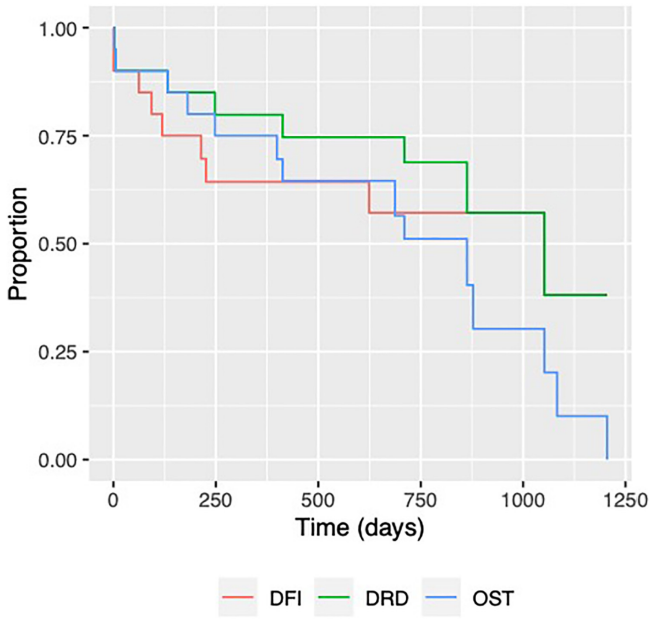

FIGURE 2 Aalen-Johansen curve for disease-free interval, disease-related death, and overall survival time (OST) for all cats

and 1 was euthanized due to the presence of a mandibular tumor of unknown etiology. The remaining 6 cats were euthanized due to recurrence of clinical signs from hypoglycemia in 2 cases, metastatic disease to the liver or pancreas in 3, and suspicion of recurrence in another cat with neurologic signs. Necropsy was performed in Cat 8 with metastasis to the liver and pancreas identified, as well as an incidental finding of a cerebral meningioma (Table 1).

A Cox proportional hazards regression analysis estimating hazard ratios with 95% confidence intervals and *P*-values was reported for all 18 continuous variables tested (Table S4). Nine relationships met the predetermined cutoff of $P < .05$ for DFI, DRD, and OST. For DFI, these relationships included age, presenting serum glucose concentration, postoperative serum glucose concentration, and metastasis at surgery. For DRD, these relationships included presenting serum glucose concentration, postoperative serum glucose concentration, time to postoperative euglycemia, and metastasis at surgery. For OST, this included histopathologic tumor invasion (Table S5).

The median DFIs for cats with metastasis and all cats were 93 and 1052 days, respectively (Figure S1); the times to DRD for cats with metastasis and all cats were 413 and 1052 days, respectively (Figure S2). The OSTs for cats with and without histopathologic invasion were 710 and 1083 days, respectively. The OST for all cats was 863 days (Figure 2). The 1-year, 2-year and 3-year survival rates for all cats were 75%, 51%, and 10%, respectively. Multivariable analysis was not appropriate due to an insufficient number of observed events.[16] All outcomes are reported in Table S6.

4 | DISCUSSION

A mortality rate of 10% and a median OST for cats with surgically treated INS of 863 days was identified in the present study. The 1-year, 2-year, and 3-year survival rates were 75%, 51%, and 10%, respectively. Cats with histopathologic tumor invasion were more likely to have a reduced survival time.

Feline insulinoma is a rarely reported neoplastic condition and data collected on hypoglycemic cats with a pancreatic mass consistent with INS was presented in this study. Prior to 1966, feline islet-cell carcinoma (FICT) was documented by Lombard in 1935, in a nonfunctional pancreatic tail mass with liver metastasis in a 3 year old male cat, and by Smith and Jones in 1961, in a nonmetastasizing mass in a 10 year old, female Persian in a photomicrograph.[17] In 1974, 2 more cases of primary FICT were identified using the Veterinary Medical Database (VMD).[18] Since then, there have been 8 published case reports of INS,[2–9] and 2 online institutional case submissions.[19,20] The 20 cats reported in this study include 1 of these case reports[7] and online case submissions.[20]

No predilection for age, sex, breed, or body weight was statistically significant in our population. The majority were older domestic cats presenting with neurologic signs (all hypoglycemic and 92.3% had inappropriate serum insulin concentrations), consistent with prior INS case reports[2–9] and canine INS publications.[10,21,22] Metastasis was noted as an important factor influencing DFI and DRD. Two previous cases of stage III feline INS have been documented; however, 1 cat had no follow up[17] and the other was euthanized on presentation with final diagnosis made on postmortem examination.[19] All of the previous case reports were cats with stage I disease.[2–9] Similar findings were noted in 2 larger canine studies in which pathologic stage was a predictor of survival time.[10,22] The authors of a recent report on the outcome of 48 dogs surgically treated for INS concluded that stage I disease MST was 652 days (range: 2-1680) and stage II/III disease MST was 320 days (range: 1-1260). The authors did not recommend surgery for stage III disease.[22] Only 2 cats in our current study had stage III disease, and these may represent the only 2 cats with follow up in the veterinary literature. One cat with metastasis to the liver was euthanized 5 days postoperatively for DIC secondary to pancreatitis. The second cat with metastasis to the liver lived another 413 days postoperatively and was euthanized due to new masses in the liver and pancreas. Due to the limited number of cats with stage III

disease, recommendations for surgery cannot be elucidated at this time.

In accordance with prior publications, abdominal ultrasonography was performed as part of the diagnostic workup and surgical planning, with 66.7% of lesions identified; 83.3% of lesions were identified on contrast-enhancing abdominal CT scan. Comparing the feline and canine pancreatic anatomy, subjectively, the feline pancreas stands out against surrounding fat tissues better; the stomach also tends to contain less gas allowing for easier examination of the pancreatic body as well as the subcostal portions, and the left pancreatic lobe extends further caudally allowing for a more complete ultrasonography exam (personal communication with Valentina Mashnikova (V.M)). These anatomical differences may be why INS was detected more commonly in this study via ultrasound than in the previously reported ultrasound detection of canine INS, which had 28%-75% sensitivity rates.[16,23,24] Triple-phase CT has also been recommended for characterization of canine INS.[23,25] In our study, 3 cats had cMRI performed with no distinguishable central nervous system cause for their neurologic derangements. Magnetic resonance imaging has been used in people for diagnosis of neuroendocrine tumors with a sensitivity of 85%. Magnetic resonance imaging has also been described for canine INS,[26] but guidelines have yet to be established for the diagnosis of INS.

Immunohistochemistry is performed to confirm the presence of insulin-producing beta cells.[27] Canine INS has also been shown to produce glucagon, somatostatin, pancreatic polypeptide, and growth hormone,[9,21] whereas immunohistochemical examination of INS indicated that tumor cells expressed insulin, chromogranin A and somatostatin, but not glucagon or pancreatic polypeptide.[27] Six out of 8 of the previous case reports[2–9] had IHC performed; however, this does not reflect our case population as only 3 cats in the current study had IHC performed.

Surgical complications reported for INS include seizures, pancreatitis, ongoing hypoglycemia, transient hyperglycemia, and death.[2–9] In our study, the complication and mortality rates were 25% and 10%, respectively, with 90% of cats surviving to hospital discharge. Three of the complications were considered grade 4, and 2 of the complications were considered grade 5 according to the Veterinary Cooperative Oncology Group guidelines.[28] Complications encountered included anemia, hepatic lipidosis, noncardiogenic pulmonary edema, pancreatitis, pneumonia, and death. Tumor location has previously been reported as a risk factor for pancreatitis in dogs, with lesions in the body of the pancreas having a higher risk for pancreatitis due to intertwining with the pancreatic ducts, blood vessels, and lymphatics, requiring extensive manipulation and dissection of the pancreas.[29] Cat 18 had a left-sided mass and was euthanized 5 days postoperatively; Cat 19 had a midbody mass and survived to discharge. Other complications reported in canines include diabetes mellitus and endocrine pancreatic insufficiency.[9] Eighteen out of 20 (90%) of cats were euglycemic or hyperglycemic postoperatively. Although none of our cats became diabetic or had insufficiency, 1 was treated with a single dose of insulin for transient hyperglycemia. Of the 2 cats with postoperative seizures, both presented with seizures and were euglycemic postoperatively. Cat 6 was euthanized 2 days later for uncontrollable seizure activity while Cat 20 was alive at data collection, having been treated with antiepileptic therapy. In a previous case report, a 14 year old cat with a surgically excised INS continued to have postoperative neurologic complications (pacing, disorientation, and aggressive behavior) despite euglycemia, and was euthanized 1 month later. The authors hypothesized that chronic states of hypoglycemia caused irreversible neurologic lesions in this cat.[4] This theory could not be excluded for our 2 cats as brain imaging was not performed.

Adjunctive medical treatment for INS has been poorly described apart from frequent feedings and glucocorticoid administration.[2–9] Glucocorticoids act by antagonizing the effects of insulin as well as increasing hepatic gluconeogenesis and glycogenolysis.[1] Adjunct treatment with prednisolone was provided in 5 cats, 3 of which survived to discharge. Only 1 of the cats remained hypoglycemic postoperatively, and this cat required surgery 7 months later to remove the INS. Following that procedure, the cat remained euglycemic. Octreotide is a somatostatin analogue used to inhibit insulin synthesis by activation of somatostatin receptors.[1] One cat was treated with adjuvant octreotide postoperatively despite euglycemia and survived for 248 days, eventually being euthanized due to locoregional lymph node metastasis. Treatment duration was not specified but, to the best of our knowledge, the use of octreotide for feline INS has not been reported previously.

In our study, hypoglycemic relapse or clinical signs related to hypoglycemia were documented in 7/18 (38.9%) of cats that survived to discharge with a median time to recurrence of 214 days (range: 62-1052). In a previous report of 28 dogs with INS, 19 had partial pancreatectomy performed with MST of 785 days.[30] Nine of these dogs had postsurgical relapse, indicated by the recurrence of clinical signs of hypoglycemia on blood work. These 9 were treated with prednisolone alone or with diazoxide therapy if glycemic control was inadequate on prednisolone. The MST for these 9 dogs was 1316 days (95% CI: 484-2184). Of the 7 cats with relapse in our study, 5 had no further treatment performed and had a DRD time of 70 days (range: 0-744) after relapse. Four of 18 cats

(22.2%) had metastasis at the time of follow up, with Cat 12 still alive at data collection and Cat 8 diagnosed via necropsy. Two other cats with metastasis had survival times of 5 and 413 days. Prolonged survival for cats with relapse and metastasis may be possible in select cases with appropriate management based on this and prior studies.[30]

In the previous 8 case reports of feline INS, survival times ranged from 3 days to 35 months.[2–9] The median OST for all cats that survived to hospital discharge in this study was 863 days. This is comparable to 2 previous studies for canine INS in a group of 48 and 49 dogs treated with surgery with MST reported as 372 and 561 days, respectively.[22,10]

The limitations of our study are those inherent to its multi-institutional retrospective nature and include the lack of standardization for data collection, surgical procedures performed, case management, and follow up, and also the limited sample size. With the large number of variables in this study and the small number of outcomes, there is not enough information to make a clinically relevant conclusion. The small sample size could also have influenced the precision of our estimates of the effects, and confounding variables possibly impacted the ability to report on the multivariable analysis. A second limitation is that the overwhelming majority of cats had stage I disease, possibly causing selection bias for recommendations for surgical excision. Lastly, none of the cases collected had a second opinion or review of histological slides and immunohistochemistry was performed in only 3 cases. The lack of pathological review and IHC could have changed the final diagnosis in some cases and may be the cause of the low metastatic rate.

Long-term survival was possible after surgical management of feline INS with similar complication rates and survival times to its canine counterpart. The future direction for treatment of INS cases could be directed toward laparoscopic partial pancreatectomy as is performed in people to reduce morbidity and was previously reported in 1 dog;[31,32] it could also include glucocorticoid administration at relapse to improve survival time,[30] or metastasectomy.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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