JAVMA

AVMA

Blood glucose monitoring during surgery in dogs to assess completeness of surgical resection of insulinoma: 11 cases

Núria Comas Collgros, DVM*, and Jonathan Peter Bray, MVSc, PhD, ECVS

Fitzpatrick Referrals Oncology and Soft Tissue, Guildford, UK

*Corresponding author: Dr. Comas Collgros (ncomas@fitzpatrickreferrals.co.uk)

doi.org/10.2460/javma.22.07.0282

OBJECTIVE
To evaluate whether intraoperative detection of rising levels of blood glucose could improve the completeness of resection of insulin-secreting tumor tissue and whether this improves long-term outcomes.

ANIMALS
11 client-owned dogs diagnosed with insulinoma.

PROCEDURES
Retrospective review of medical records of dogs undergoing partial pancreatectomy as treatment for insulinoma. A blood glucose reading was obtained at induction, following removal of the pancreatic mass and/or after each suspected metastatic lesion until blood glucose had normalized. Disease-free interval and survival time were measures of outcome.

RESULTS
A positive increase in blood glucose was detected in all cases, with a mean rise of 6.35 ± 4.5 mmol/L. Mean follow-up was 611 days, mean disease-free interval was 382 days, and median survival time was 762 days. Tumor stage was not associated with outcome. Three cases underwent a second surgery (metastasectomy), achieving further prolongation of disease-free survival.

CLINICAL RELEVANCE
A sustained increase in intraoperative blood glucose provided the surgeon with confidence of more complete resection of insulinoma tissue and resulted in improved outcomes in all cases included in this study. Subsequent metastasectomy of recurrent insulinoma lesions also provided good outcomes. Intraoperative monitoring of blood glucose during surgical treatment of insulinoma resulted in the surgeon continuing to explore and resect abnormal tissue until an increase of glycemia was observed. This was shown to provide the surgeon with more confidence of resection of all active insulinoma tissue and improved clinical outcomes.

Insulinomas are functional tumors of the β-cells and are the most common cancer of the endocrine pancreas. The tumor leads to persistently elevated levels of insulin that are independent of blood glucose (BG) levels. The patient becomes progressively hypoglycemic due to compromise of normal regulatory systems.[1–5] Islet cell carcinomas or adenomas with malignant behavior are the most common histological types of insulinoma.[2,4,6] Local lymph nodes and liver are the main metastatic locations, followed by the lungs, spleen, mesentery, gastrointestinal tract, kidney, spinal cord, and bone.[5,7] Metastasis is suspected in 100% of the cases at the time of diagnosis,[8] although postoperative histopathologic confirmation of metastasis may be reached in only 45% to 50% of cases.[9–11] Relapse of hypoglycemia following insulinoma resection has been reported in approximately 40% to 53% of cases in several studies and is considered to be due to progression of metastatic disease.[7,12] For most patients, the treatment of insulinoma is considered to be rarely curative.[5]

Surgical resection by means of partial pancreatectomy and metastasectomy is the treatment of choice for insulinoma, with median survival times (MST) of between 372 and 785 days and euglycemic periods of between 348 and 424 days reported.[4,5,7,12] Medical management is an option for stabilization prior to surgery for candidates unsuited to surgery due to comorbidities or if surgical treatment is declined. The strategy for medical management consists of correcting hypoglycemia by means of pharmacologic therapies (prednisolone, diazoxide, toceranib phosphate, octreotide, and/or streptozocin), exercise modification, and diet.[1,4,5,7,13] The survival

time for patients treated with medical management is reported to be between 74 and 196 days, which is shorter than that reported for surgical treatment.[4,5,7]

Previously described prognostic factors include age, tumor size, surgical treatment, pathological stage, postoperative pancreatitis, postoperative hyperglycemia, or hypoglycemia.[12] Not all studies agree on the significance of these factors.[7,12] Importantly, persistent hypoglycemia following surgical exploration has been reported in 20% to 23% of cases.[7,12] Postoperative persistent hypoglycemia has been associated with a higher pathological stage, which suggests incomplete excision of the tumors or the presence of undetected and therefore nonresected metastasis.[7] Because residual tumoral tissue is suspected to be the cause of the persistent hypoglycemia in these dogs, a disease-free interval (DFI) has not been previously analyzed or reported for a specific subset of dogs with residual disease. In 1 study, the median duration of remission of all dogs undergoing partial pancreatectomy (postoperatively euglycemic and hypoglycemic) was lower (496 days) compared to the subset of dogs in which normal glycemic control (525 days) was obtained.[1] In another study,[12] patients that remained hypoglycemic following surgery had a lower MST (114 days) compared to those that were euglycemic or hyperglycemic following surgery (746 days). Two studies have calculated that the daily hazard of death for dogs that remain persistently hypoglycemic to be 4.96 or 7.3.[7,12] This evidence suggests that more complete identification of tumor tissue at the time of surgery should translate to improved outcomes for patients.

Abdominal ultrasound is commonly used for investigation of insulinoma, but its sensitivity to detect pancreatic masses or metastatic lesions has been reported to vary from 23% to 75%.[1,4,14–18] Compared to the low specificity of abdominal ultrasound, CT has been reported to correlate with surgical findings in 75% to 100% of cases when considering the presence and size of the primary tumor.[14,19–22] However, CT is less reliable for determining the correct location of the tumor, with a correlation of between 52% and 89% in veterinary studies.[22,23] Coss et al[23] reported the postarterial phase to have a 94% sensitivity for detection of a primary pancreatic mass. However, in that study, suspected metastatic lesions were not always biopsied. Furthermore, the presence of lymph nodes confirmed to be metastatic histopathologically but not detected on CT imaging suggested a low sensitivity for detection of metastatic disease with this modality.[23]

Because of the insufficient sensitivity of imaging diagnostic tests to detect pancreatic tumors and metastatic lesions,[1,4,13–22] we hypothesized that measuring intraoperative BG levels would assist the surgeon to know when insulin-secreting tissue was still present prior to finishing the surgery, with persistent low glycemia being consistent with remaining actively secreting tumor and increase of BG being consistent with complete excision of actively secreting tumor. Further, we hypothesized that more complete removal of insulin-secreting tissue would provide good outcomes in patients, compared to previously published data.

The goal of this study was to evaluate whether detecting rising levels of BG intraoperatively could be used as surrogate evidence to determine when complete resection of active tumor has been achieved, and whether this would translate to improved long-term outcomes.

Materials and Methods

Study design and eligibility criteria

Medical records of dogs treated surgically for insulinoma between July 2017 and March 2021 were searched from the hospital database at a single referral hospital (Fitzpatrick Referrals Oncology and Soft Tissue).

Inclusion criteria consisted of canine patients that underwent partial pancreatectomy and, if appropriate, metastasectomy as treatment of recently diagnosed insulinoma; assessment of BG performed immediately prior to surgery, intraoperatively, and following surgery; histopathological confirmation of the diagnosis; and survival to discharge from hospital and a minimum follow-up of 6 months. Dogs treated medically, administered medical treatments to increase glycemia within 24 hours prior to or during surgery, and with a histopathologic diagnosis of other types of pancreatic tumors were excluded from the analysis.

Data collection

Data collected from the medical records included signalment, clinical signs, diagnostic tests performed for each patient and their results or reports, histopathology results, and the development of any complications in the postoperative period. If any follow-up consultations were performed after the original surgery, the reasons for this follow-up were recorded, including results of any diagnostic tests or imaging. If recurrence of the insulinoma was confirmed, the outcome of any new treatment was obtained.

All patients were staged using the WHO staging system on the basis of diagnostic imaging and histopathologic results.[1] Briefly, dogs were classified as stage 1 if disease was confined to the pancreas, stage 2 if the local lymph nodes were affected, and stage 3 if distant metastasis was observed. BG values that were obtained during the patients' treatment were recorded; hypoglycemia was defined as BG measurement lower than 3.3 mmol/L (60 mg/dL) and hyperglycemia as above 6.2 mmol/L (111 mg/dL). The occurrence of commonly described postoperative complications of surgical treatment for insulinoma, including hyperglycemia, hypoglycemia, or pancreatitis, was recorded.

All follow-up data were obtained by contacting the referring primary care veterinarian to obtain the most recent clinical history of the patient. If the dog had died, the cause and date of death were noted for survival analysis. If the dog was still alive, the pres-

ence of any clinical signs or treatment related with hypoglycemia was recorded. Dogs that remained alive at the close of the study period were censored for survival analysis. The intraoperative increase in BG, DFI, and MST were measures of outcome.

Perioperative BG monitoring

The standard surgical protocol in the hospital is for BG levels to be recorded in all patients throughout the perioperative period. The BG values recorded at various time points were obtained from the clinical and anesthetic records and included the following: the lowest BG level recorded prior to surgery, the preinduction BG level, all BG results obtained intraoperatively, and the highest and lowest BG recorded during the period of postoperative hospitalization. The difference between the BG (△BG) recorded at the end of the surgery and just prior to intubation was calculated.

Surgical procedure

Glycemia was measured preinduction by a handheld machine (AlphaTRAK blood glucose monitoring system; Zoetis) from a peripheral vessel. Dogs were anesthetized at the discretion of the anesthetist or surgeon in charge of the case. The goal of the anesthesia protocol in all cases was for patients to be hypoglycemic at induction. No glucose supplementation or pharmacologic manipulation was used to artificially elevate the BG prior to, or during, the anesthesia. Abdominal aseptic preparation included thorough clipping and scrubbing with an alcohol-chlorhexidine–based scrub (Hibiscrub). Perioperative antimicrobial therapy consisted of IV administration of cephazolin (22 mg/kg; Zinacef) at induction and every 90 minutes thereafter.

A midline laparotomy and thorough exploration of the entire abdomen was performed in each case, followed by a more focused examination of the pancreatic parenchyma, liver, mesentery, and locoregional lymph nodes around the pylorus, liver, and spleen. Partial pancreatectomy was planned and performed on the basis of the location of the mass using a blunt dissection technique and ligation or vessel sealing devices as previously described.[24] Enlarged lymph nodes were removed, and any abnormality observed in the liver was biopsied or removed if deemed suspicious of metastasis.

A BG reading was obtained at the start of the laparotomy with blood obtained from a central line and measured with the same handheld machine used preinduction. Blood glucose was measured again immediately after the main pancreatic mass was removed and repeated after removal of any suspected metastatic lesion. Surgery was considered complete only when the BG level had returned to normal and, ideally, observed to be consistently rising with serial sampling.

Following recovery from surgery and anesthesia, BG was monitored every 2 hours on the first day. If sustained hyperglycemia or normoglycemia was achieved, BG readings were spaced to every 6 to 12 hours on the subsequent days. Standard protocols were established in case transitory hyperglycemia or hypoglycemia occurred. If BG increased to over 20 mmol/L (360 mg/dL), neutral insulin (0.25 U/kg, SC, q 12 h) was given with the goal of maintaining BG within a range of 10 to 20 mmol/L (180 to 360 mg/dL). If BG was 2.5 mmol/L (45 mg/dL) or lower, a glucose bolus (0.5 ml of 50% dextrose/kg diluted 1:4 and administered IV over 5 minutes) was administered, followed by a continuous infusion of dextrose 2.5%.

For the purposes of writing and comprehending this article, the statement "completeness of resection" was used for "a thorough excision of macroscopic and actively insulin-secreting tumoral tissue."

Data analysis

Descriptive statistics were analyzed for all variables with GraphPad Prism (GraphPad Software). The Shapiro-Wilk test was used to analyze normality of distribution of continuous variables, and normally distributed data were reported as mean (SD). Univariate logistic regression analysis was performed to assess the association between continuous and binomial variables such as body weight, age, BG measurements, △BG, mitotic index, stage, MST, and DFI with development of any complications, pancreatitis, or hyperglycemia. A value of $P < .05$ was considered significant. The sample size was considered too small for multivariate analysis.

Survival analysis was performed with R (version 2.8.1; R Foundation for Statistical Computing). Deaths from tumor and recurrence of hypoglycemia were defined end points for the study, defined as survival time and DFI, respectively. The Kaplan-Meier method was used to calculate survival times and DFI, and univariate Cox regression analysis was used to determine the influence of body weight, age, and △BG on either survival or DFI. A value of $P < .05$ was considered significant.

Results

Demographics and diagnoses

Eleven dogs underwent partial pancreatectomy as treatment for insulinoma and were included in the study population **(Supplementary Table S1)**. These included 2 Boxers, 1 Jack Russell Terrier, 1 West Highland White Terrier, 1 Golden Retriever, 1 Flat Coat Retriever, 1 Labrador Retriever, 1 Shetland Sheepdog, 1 English Springer Spaniel, and 2 cross breeds. The mean age at surgery was 8.5 years old (range, 4.1 to 12.2 years old) and mean body weight was 22.7 kg (range, 10 to 31.7 kg). Nine dogs were neutered females, and 2 dogs were neutered males.

Blood analysis revealed elevated insulin levels with concurrent hypoglycemia in 7/11 dogs and paradoxically high-normal insulin levels with concurrent hypoglycemia in 4/11 dogs. A contrast CT scan was performed in 9/11 cases. From these scans, a solitary pancreatic mass was identified in 6/11 dogs, abdominal lymphadenopathy in 7/11 dogs, and liver abnormalities suspicious of metastasis in 3/11 dogs.

BG measurements

All but 1 (10/11) dog had BG measurements obtained prior to induction and at regular intervals during the surgery. One case did not have BG recordings at the first surgery; this patient was included in the study because BG measurements were obtained during a second surgery.

The mean preinduction BG of all patients was 3.3 ± 1.1 mmol/L (59.4 ± 19.8 mg/dL), and the mean BG at the end of surgery was 9.7 ± 4.4 mmol/L (174.6 ± 79.2 mg/dL) with a mean difference from the end to the beginning of the surgery of 6.35 ± 4.5 mmol/L (114.3 ± 81 mg/dL) and with a positive increase in BG in all cases. The mean minimum and maximum postoperative BG were 9.43 ± 11.29 mmol/L (169.74 ± 203.22 mg/dL) and 20.15 ± 11.29 mmol/L (362.7 ± 203.22 mg/dL). A slight to moderate rise in BG was observed in most of the cases (No. 1, 2, 3, 4, 5, 7 [recurrence], 8 [recurrence], 9, 10, and 11) after removing the primary pancreatic mass. In some cases (No. 1, 5, 7 [recurrence], 9, 10, and 11), this was followed by a continuous, slowly progressive increase of BG. This observation was more likely when no other abnormal tissue could be identified during exploratory surgery of the abdomen. In some other cases (No. 2, 3, 4, and 8 [recurrence]), the first rise was followed by a BG drop after removal of the primary pancreatic mass and subsequently followed by a late increase when more tumoral tissue was excised. In the remaining cases (No. 5 [recurrence], 6, and 7), the BG remained low after removal of the primary pancreatic mass but had a late increase after further tumoral tissue was excised. For the cases in which the BG remained low or decreased after a first rise, the surgeon continued exploring for further grossly abnormal tissues. Once subsequent grossly abnormal tissue was resected, another BG reading was obtained. In some cases, several grossly abnormal lesions were removed until an increase of BG was finally observed.

Postoperative findings

Hypoglycemia, hyperglycemia, or pancreatitis was not reported in 6/11 dogs (No. 1, 4, 5, 6, 10, and 11). Three dogs (No. 7, 8, and 9) experienced sustained postoperative hyperglycemia during the hospitalization time and were treated with insulin as previously described. One case (No. 8) developed signs of pancreatitis and was treated with supportive care until recovery to discharge. One case (No. 2) remained hypoglycemic immediately after surgery. This dog had an indistinct, contrast-enhancing lesion on the cranial aspect of the right medial liver lobe, which was not readily accessed at surgery, and the owner declined hilar resection of this lobe. Due to the persistent hypoglycemia, incomplete insulinoma resection was suspected. Treatment with toceranib phosphate (1.6 mg/kg, q 48 to 72 h) and prednisolone (0.25 mg/kg, once daily) was started; this medication helped maintained a euglycemic state. This dog remained stable until hypoglycemia was detected 303 days after surgery. At this time, the dose of toceranib phosphate was increased to 2.6 mg/kg, PO, once a week, with prednisolone continued at previous levels. The dog was eventually euthanized 418 days after surgery. Late complications occurred in 1 case (No. 3), revealing signs of hyperglycemia and pancreatitis 3 months after surgery.

Histopathology

Histopathology confirmed the diagnosis of neuroendocrine carcinoma in all cases. The mean mitotic count was 7.7 mitoses/10 hpf (mitotic count range, 0 to 30). At the time of the first surgery, metastatic lymph nodes were found in 5/11 dogs. The pancreatic lymph node was affected in 2 cases (No. 4 and 10), a mesenteric lymph node in 1 case (No. 6), and the exact lymph node was not recorded in 2 cases (No. 2 and 11). Liver metastasis was encountered in 2/11 cases (No. 2 and 9).

Disease-free interval

Mean follow-up was 611 days (range, 186 to 1,375 days). Eight of 11 dogs suffered recurrence of the insulinoma at a mean of 390 days (range, 3 to 816 days). The median DFI was 382 days **(Figure 1)**.

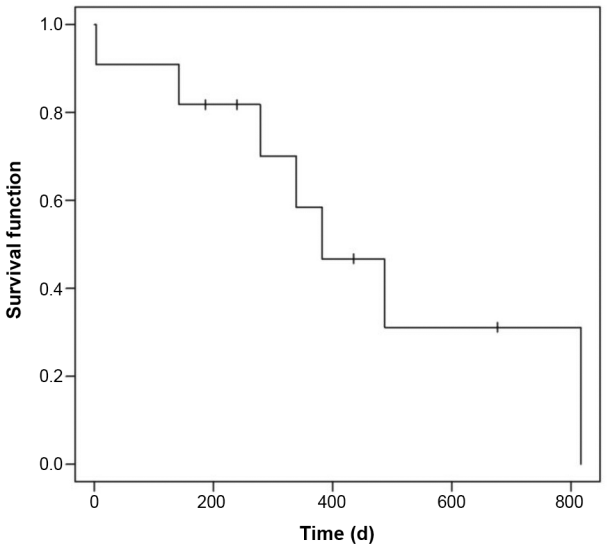

Figure 1—Kaplan-Meier curve depicting the disease-free interval of the 8 dogs that suffered recurrence during the study period. The median disease-free interval was 382 days (range, 3 to 816 days).

If the only case suffering persistence of hypoglycemia immediately postsurgery due to suspected incomplete tumor resection were censored, the mean time of recurrence would be 487 days.

Survival times

The MST of all dogs was 762 days **(Figure 2)**. Four of 11 dogs were still alive at the time of data collection with an MST of 452 days (range, 186 to 951 days). Case No. 8 (recurrence) was still alive 224 days after the second surgery. All deceased dogs had insulinoma recurrence, and at least 5 of them were suspected to have been euthanized due to clinical signs relating to this disease.

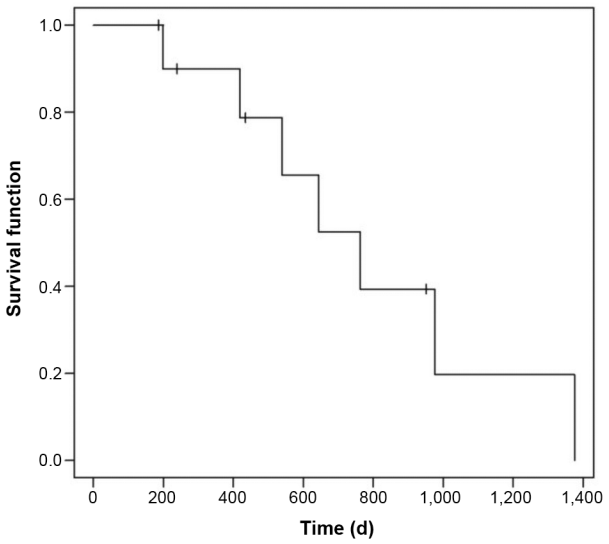

Figure 2—Kaplan-Meier curve depicting survival time of the 7 dogs that died prior to data collection. The median survival time was 762 days (range, 186 to 951 days).

Recurrences

Three cases (No. 5, 7, and 8) were operated a second time after experiencing insulinoma recurrence **(Supplementary Table S2)**. Laboratory analysis revealed normal levels of insulin concurrent with hypoglycemia in all 3 cases. Lymphadenopathy (3/3) and liver nodules (2/3) were revealed on contrast CT scan assessment.

Recurrence of the insulinoma was detected at 816, 382, and 676 days after the first surgery (mean, 625 days), and a second exploratory surgery was performed in these cases 818, 444, and 678 days after the initial surgery (cases No. 5, 7, and 8, respectively). One of the cases (No. 5) had metastatic lymph nodes removed at the first treatment; further lymph nodes were found to be affected during the second treatment. In the other 2 cases, no metastasis had been found at first treatment but metastasis to the lymph nodes (2) and liver (1) were found at the second treatment. Hyperglycemia was detected postoperatively in one of the cases (No. 7).

One of these cases (No. 8) remained alive and euglycemic 224 days after the second surgery, giving an overall survival time (OST) of 902 days. The other 2 cases were euthanized at 318 and 557 days after this second surgery, resulting in an OST of 762 and 1,375 days (cases No. 5 and 7, respectively).

Statistical analysis

Results of univariate analysis are reported **(Tables 1 and 2)**. The development of any complications or postoperative hyperglycemia was associated with both the minimal ($P = .028$; $P < .001$) and maximal ($P < .001$; $P < .001$) postoperative glycemia and the BG reading at the end of surgery ($P = .006$). Development of postoperative hyperglycemia was also associated with the △BG ($P = .012$). Lower weight was associated with development of pancreatitis ($P = .007$). Complications were not found to be associated with any other variables. No associations were found between MST or DFI and signalment data, BG values, disease stage, or mitotic index.

Table 1—Logistic regression (*P* values).

Variables	Complications	Pancreatitis	Hyperglycemia
Age	.443	.717	.922
Weight	.590	<.001[a]	.881
DFI	.091	.137	.545
MST	.064	—	.160
Preinduction BG	.794	.458	.418
End surgery BG	.019[a]	—	<.001[a]
△BG	.063	—	.012[a]
Minimum postoperative BG	.028[a]	.067	<.001[a]
Maximum postoperative BG	<.001[a]	.583	<.001[a]
Mitotic index	.213	.961	.313
Stage	.704	—	.218

BG = Blood glucose. △BG = Difference in blood glucose. DFI = Disease free interval. MI = Mitotic index. MST = Median survival time.
[a]Statistically significant.

Table 2—Univariate Cox regression analysis results.

Variables	MST hazard ratio	*P* value	DFI hazard ratio	*P* value
Stage	0.86	.842	0.87	.826
MI	1.01	.829	0.99	.839
Age	1.37	.364	1.82	.147
△BG	1.02	.501	1.02	.563
Weight	0.98	.669	0.98	.668

△BG = Difference in blood glucose. DFI = Disease-free interval. MI = Mitotic index. MST = Median survival time.

Discussion

The current study is the first to use BG measurement intraoperatively to determine when all active primary or metastatic lesions had been successfully removed during surgical treatment of insulinoma in dogs. Because the half-life of insulin is limited to a few minutes,[25] increases in BG can be observed shortly after removal of any actively secreting tumor tissue. An intraoperative increase in BG is surrogate evidence that all gross deposits of insulin-producing tumoral tissue have been removed, leading to an improved prognosis. The MST of dogs in this study was 762 days, which compared favorably with previously reported MST of 308 to 381 days.[15,26] While 2 studies[1,4] have reported similar MST to the current study (725 to 785 days), case selection in those studies tended to be biased toward the management of stage 1 disease only. In the current study, almost 65% of dogs had metastatic disease at the time of surgery, compared to 55% and 32% metastasis found in these previous studies.[1,4] The findings of this study therefore suggest that intraoperative measurement of BG can guide the surgeon in assessing for a more thorough resection of actively insulin-secreting neoplastic tis-

sue, with persistent hypoglycemia suggested to be associated with remaining tumoral tissue. It also suggests that more complete removal of actively secreting tumor tissue can lead to improved clinical outcomes for patients with insulinoma.

Previously reported overall MST for dogs with insulinoma has been relatively wide, with a tendency of shorter survival times in earlier studies compared to more recent ones. Surgical treatment has consistently been shown to increase survival (34 to 785 days) in comparison to medical treatment (74 to 308 days).[1,4,7,9,12,15,26,27] Ryan et al[27] found that surgically treated dogs are 3-fold more likely to survive, 2 times as likely to survive 1 year, and 6-fold more likely to survive 2 years than medically treated dogs. In the same study, neutering status regardless of sex was a good prognostic factor for survival.[27]

In previous studies, relapse of clinical signs has been reported as soon as at 90 days postsurgery.[15] Tumor stage and postoperative hypoglycemia has been associated with greater odds of relapse.[5,7] Median DFI was reported to be as low as 244 and 275 days[7,10] and as high as 496, 403, or 424 days.[1,9,12] However, the latter studies had fewer cases presenting with metastasis within their study population (32%, 45%, and 55%),[1,9,12] compared to our study (63%). In the current study, tumor stage and mitotic index were not associated with the DFI or MST. We suspected that the long MST and DFI obtained in this study despite the high percentage of metastatic disease displayed at the time of surgical treatment was due to higher likeliness of complete excision of the actively secreting insulinoma and its metastasis, with surgery effectively downstaging all patients to residual microscopic disease only. However, the data of our study cannot be directly compared to previous studies, given the lack of rigorous matching between the included cases. Also, factors such as biases due to the retrospective nature of this study or changes in clinical practices over time might have affected the differences encountered.

Only 1 case remained hypoglycemic immediately after surgery. This dog experienced a lower survival time compared to the MST of the rest of the cases at the end of the study. In previous studies, persistent hypoglycemia immediately following surgery has been reported in 20% to 35% of patients and is suggested to be due to incomplete tumor resection.[1] A survival advantage for being normoglycemic at the close of surgery, with MST of 746 days versus MST of 114 days in hypoglycemic dogs, has been previously reported,[12] with an increased death hazard ratio (4.9 and 7.3) also described for persistently hypoglycemic dogs[7,12]

Metastatic disease at presentation has mostly been associated with poorer prognosis in the past, with mean survival time of 652 to 785 days in stage 1, 574 days in stage 2, 182 to 217 days in stage 3, and 320 days in combined stage 2 and 3.[7,12] As a result, there are controversial views on surgical treatment in dogs with insulinoma at stage 2 and 3. However, Hixon et al[4] did not find any association between stage and survival, and neither mitotic index nor histopathologic stage were associated with MST. Our results were consistent with this, reporting no association between tumor stage and OST or DFI. Given that most of the dogs with insulinoma are considered to suffer metastasis at the time of diagnosis,[8] the authors suggest that the surgical strategy detailed in this paper allows downstaging of the tumor. Results of this study indicated that surgical treatment of cases at stage 2 and 3, with BG levels measured to ensure complete metastasectomy has been achieved, can provide considerably improved outcomes in dogs with insulinoma.

Three of the cases in this study (2 stage 2 and 1 stage 3) underwent a second surgical treatment to resect new insulin-producing metastases following recurrence of hypoglycemia. The mean DFI of these cases after the second surgery was 326 days (range, 182 to 557 days); 2 cases died at 557 and 318 days after the second surgery. The third case was still alive at 224 days after the second surgery. The OST of these 3 cases was 762, 951, and 1,375 days. The long OST of these cases suggests that repeated metastasectomy of insulinoma is a well-tolerated intervention and can provide a further period of disease stability.

The challenges that laboratory and imaging techniques provide for the diagnosis of insulinoma can lead to higher risk of incomplete tumor resection during surgical treatment, which impacts negatively on patient survival. To the authors' knowledge, intraoperative monitoring of BG during insulinoma resection has not been previously described in the canine species. However, in humans, monitoring of glucose levels has been used as a guide to the completeness of insulinoma resection, with increase of glycemia being consistent with complete insulin-producing tissue resected and persistent low glycemia being consistent with additional primary or metastatic neoplastic tissue not identified.[28–30] An increase in BG has been shown in both adult and pediatric patients once the insulin-producing tissue has been completely resected and has assisted with the anesthesia protocol and maintenance of normoglycemia in the younger group.[31–33] However, this technique has been questioned by some,[34] and a delayed rather than immediate response has also been reported.[30] Serum insulin decrease, assessed with 30-minute-long radioimmunoassay, has also been successfully used to assess for complete resection of insulin-producing tissues in humans, with significant differences compared to noninsulinoma laparotomy cases.[32,35] Serum insulin changes are suggested to be more significant compared to changes in BG levels.[32] Selective portal venous sampling for serum insulin analysis has also been described in humans, assisting in the localization of primary insulinomas.[36] Intraoperative insulin assessment in dogs would be challenging given the limited availability to perform this test in-house in most hospitals.

The main limitations of this study were inherent in its retrospective design. Data recording was not standardized prior to the performance of any of the included cases, and the results obtained relied on the accuracy of the clinical records. Long-term follow-up was mostly performed at the referring prac-

tice, and detection of clinical signs, medical management once recurrence was observed, and accuracy of the clinical notes may have had some influence on the results. The small number of included cases may have also induced a type II statistical error, and the lack of a control group prevented our ability to contrast and confirm the results.

The results of this study suggested that intraoperative measurement of BG levels during insulinoma resection and, more specifically, observing rising glycemia levels can be used as a tool for the surgeon to assess for completeness of actively insulin-secreting neoplastic tissue resection. This could subsequently have an impact on good outcomes in terms of mean survival time and DFI. Further prospective investigations with a larger number of cases and a control group not suffering insulinoma would be necessary to assess the accuracy of intraoperative BG monitoring and the completeness of primary and metastatic insulinoma resection and to assess the specificity and sensitivity of this technique.

Acknowledgments

Dr. Comas Collgros contributed to the study design, data collection, analysis and interpretation, manuscript drafting, confection and revision, and approval of the version to be published. Dr. Bray contributed to the study design, data analysis and interpretation, manuscript confection and revision, and approval of the version to be published.

The authors declare that there were no conflicts of interest.

The authors acknowledge Prof. Nick Bacon, Dr. Laurent Findji, and Gerard McLauchlan for contributing sharing data of their clinical cases.

An abstract of this work was presented in the format of short oral communication in the European College of Veterinary Surgeons Congress in July 2022 in Porto, Portugal.

References

1. Polton GA, White RN, Brearley MJ, Eastwood JM. Improved survival in a retrospective cohort of 28 dogs with insulinoma. *J Small Anim Pract*. 2007;48(3):151–156.
2. Madarame H, Kayanuma H, Shida T, Tsuchiya R. Retrospective study of canine insulinomas: eight cases (2005–2008). *J Vet Med Sci*. 2009;71(7):905–911.
3. Guedes AG, Rude EP. Effects of pre-operative administration of medetomidine on plasma insulin and glucose concentrations in healthy dogs and dogs with insulinoma. *Vet Anaesth Analg*. 2013;40(5):472–481.
4. Hixon LP, Grimes JA, Wallace ML, Schmiedt CW. Risk factors for gastrointestinal upset and evaluation of outcome following surgical resection of canine pancreatic β-cell tumors. *Can Vet J*. 2019;60(12):1312–1318.
5. Goutal CM, Brugmann BL, Ryan KA. Insulinoma in dogs: a review. *J Am Anim Hosp Assoc*. 2012;48(3):151–163.
6. Bailey DB, Page RL. Tumors of the endocrine system. In: Vail DM, Withrow SJ, eds. Withrow and MacEwen's Small Animal Clinical Oncology. Saunders Elsevier; 2007:583–609.
7. Del Busto I, German AJ, Treggiari E, et al. Incidence of postoperative complications and outcome of 48 dogs undergoing surgical management of insulinoma. *J Vet Intern Med*. 2020;34(3):1135–1143.
8. Feldman ECNR. Beta cell neoplasia: insulinoma. In: Feldman E, Nelson R, eds. *Canine and Feline Endocrinology and Reproduction.* 3rd ed. Saunders Elsevier; 2004:616–644.
9. Leifer CE, Peterson ME, Matus RE. Insulin-secreting tumor: diagnosis and medical and surgical management in 55 dogs. *J Am Vet Med Assoc*. 1986;188(1):60–64.
10. Trifonidou MA, Kirpensteijn J, Robben JH. A retrospective evaluation of 51 dogs with insulinoma. *Vet Q*. 1998;20(suppl 1):S114–S115.
11. Steiner JM, Bruyette DS. Canine insulinoma. *Compend Contin Educ Pract Vet*. 1996;18(1):13–22.
12. Cleland NT, Morton J, Delisser PJ. Outcome after surgical management of canine insulinoma in 49 cases. *Vet Comp Oncol*. 2021;19(3):428–441.
13. Flesner BK, Fletcher JM, Smithee T, Boudreaux B. Long-term survival and glycemic control with toceranib phosphate and prednisone for a metastatic canine insulinoma. *J Am Anim Hosp Assoc*. 2019;55(1):e55105. doi:10.5326/JAAHA-MS-6751
14. Robben JH, Pollak YWEA, Kirpensteijn J, et al. Comparison of ultrasonography, computed tomography, and single-photon emission computed tomography for the detection and localization of canine insulinoma. *J Vet Intern Med*. 2005;19(1):15–22.
15. Tobin RL, Nelson RW, Lucroy MD, Wooldridge JD, Feldman EC. Outcome of surgical versus medical treatment of dogs with beta cell neoplasia: 39 cases (1990–1997). *J Am Vet Med Assoc*. 1999;215(2):226–230.
16. Garden OA, Reubi JC, Dykes NL, Yeager AE, McDonough SP, Simpson KW. Somatostatin receptor imaging in vivo by planar scintigraphy facilitates the diagnosis of canine insulinomas. *J Vet Intern Med*. 2005;19(2):168–176.
17. Harris ME, Weatherton L, Block CP. Glucagon therapy in canines with an insulinoma: a retrospective descriptive study of 11 dogs. *Can Vet J*. 2020;61(7):737–742.
18. Lamb CR, Simpson KW, Boswood A, Matthewman LA. Ultrasonography of pancreatic neoplasia in the dog: a retrospective review of 16 cases. *Vet Rec*. 1995;137(3):65–68.
19. Mai W, Cáceres AV. Dual-phase computed tomographic angiography in three dogs with pancreatic insulinoma. *Vet Radiol Ultrasound*. 2008;49(2):141–148.
20. Iseri T, Yamada K, Chijiwa K, et al. Dynamic computed tomography of the pancreas in normal dogs and in a dog with pancreatic insulinoma. *Vet Radiol Ultrasound*. 2007;48(4):328–331.
21. Fukushima K, Fujiwara R, Yamamoto K, et al. Characterization of triple-phase computed tomography in dogs with pancreatic insulinoma. *J Vet Med Sci*. 2016;77(12):1549–1553.
22. Buishand FO, Vilaplana Grosso FR, Kirpensteijn J, van Nimwegen SA. Utility of contrast-enhanced computed tomography in the evaluation of canine insulinoma location. *Vet Q*. 2018;38(1):53–62.
23. Coss P, Gilman O, Warren-Smith C, Major AC. The appearance of canine insulinoma on dual phase computed tomographic angiography. *J Small Anim Pract*. 2021;62(7):540–546.
24. Johnston S, Tobias K. *Veterinary Surgery Small Animal.* 2nd ed. Elsevier Saunders; 2017.
25. Duckworth WC, Bennett RG, Hamel FG. Insulin degradation: progress and potential. *Endocr Rev*. 1998;19(5):608–624.
26. Northrup NC, Rassnick KM, Gieger TL, Kosarek CE, McFadden CW, Rosenberg MP. Prospective evaluation of biweekly streptozotocin in 19 dogs with insulinoma. *J Vet Intern Med*. 2013;27(3):483–490.
27. Ryan D, Pérez-Accino J, Gonçalves R, et al. Clinical findings, neurological manifestations and survival of dogs with insulinoma: 116 cases (2009–2020). *J Small Anim Pract*. 2021;62(7):531–539.
28. Katz LB, Aufses AH Jr, Rayfield E, Mitty H. Preoperative localization and intraoperative glucose monitoring in the management of patients with pancreatic insulinoma. *Surg Gynecol Obstet*. 1986;163(6):509–512.
29. Deixonne B, Baudin G, Rodier M, et al. Pancreatic insulinoma. Peroperative topographical diagnosis. Article in French. *Presse Med*. 1988;17(32):1625–1628.
30. Tutt GO Jr, Edis AJ, Service FJ, van Heerden JA. Plasma

glucose monitoring during operation for insulinoma: a critical reappraisal. *Surgery*. 1980;88(3):351–356.
31. Manabe M, Morimatsu H, Egi M, et al. Anesthetic management of pediatric patients with insulinoma using continuous glucose monitoring. Article in Japanese. *Masui*. 2009;58(6):757–759.
32. Krentz AJ, Hale PJ, Baddeley RM, Williams AC, Natrass M. Intra-operative blood glucose and serum insulin concentrations in the surgical management of insulinoma. *Postgrad Med J*. 1990;66(771):24–27.
33. Haji S, Nomura H, Yasuda K, Hashimoto N, Ohyanagi H. Combining the selective arterial calcium injection test and intraoperative blood glucose monitoring for multiple insulinomas: report of two cases. *Surg Today*. 2000;30(6):537–540.
34. Harrison TS, Child CG, Fry WJ, Floyd JC Jr, Fajans SS. Current surgical management of functioning islet cell tumors of the pancreas. *Ann Surg*. 1973;178(4):485–495. doi:10.1097/00000658-197310000-00011
35. Asao Y, Matsumoto M, Wake M, et al. Usefulness of rapid detection of plasma insulin levels during resection of insulinoma. Article in Japanese. *Masui*. 1995;44(5):729–731.
36. Doherty GM, Doppman JL, Shawker TH, et al. Results of a prospective strategy to diagnose, localize, and resect insulinomas. *Surgery*. 1991;110(6):989–996.

Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org