Insulinoma in Dogs: A Review

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ABSTRACT

Insulinomas are rare malignant functional pancreatic tumors of the β cells that retain the ability to produce and secrete insulin. Insulinomas are the most common pancreatic neuroendocrine tumor in dogs that can induce a variety of clinical signs that result from hypoglycemia and secondary neuroglycopenic and adrenergic effects. Diagnosis and treatment is considered challenging, and the prognosis can be extremely variable depending on the therapeutic choices. This review aims to summarize and update classic knowledge with current trends in the diagnosis, treatment, and prognosis of insulinomas. (*J Am Anim Hosp Assoc* 2012; 48:151–163. DOI 10.5326/JAAHA-MS-5745)

Introduction

Tumors of both the exocrine and endocrine pancreas have been reported in various species, including humans, dogs, cats, and ferrets.[1–6] Exocrine pancreatic neoplasia mainly includes adenocarcinoma of ductular or acinar origin.[7,8] Pancreatic endocrine tumors arise from endocrine tissue of the islets of Langerhans, and such tumors may secrete functional hormones that contribute to clinical signs. Pancreatic endocrine tumors are usually malignant in dogs, which is in contrast to humans where they tend to be benign in nature.[1–6]

Specifically, insulinomas (also referred to as β cell insulin secreting tumors or β cell carcinomas) are functional insulin-secreting tumors arising from pancreatic β cells.[3] Insulinomas are the most common endocrine pancreatic tumors described in companion animals. These malignant tumors commonly metastasize to the lymph nodes and liver.[3,7,9] Although considered rare, their exact incidence is unknown in dogs.[3] Clinical signs result from insulin-induced neuroglycopenia and increased concentrations of insulin antagonistic counterregulatory hormones.[1,7,9–11] Provisional diagnosis and staging of insulinoma relies on laboratory data, serum insulin concentrations, and imaging exams. A definitive diagnosis typically requires surgical exploration and histopathologic evaluation.[3] The purpose of this article is to review the diagnostic and therapeutic recommendations reported in the veterinary literature and current information on prognosis.

Normal Glucose Homeostasis

The normal pancreas is composed of exocrine cells arranged in acini that secrete digestive enzymes into the duodenum (i.e., trypsin, chymotrypsin, carbopolypeptidase) and endocrine cells comprising the Islets of Langerhans that contain α, β, δ, and pancreatic polypeptide-producing cells (PP cells). The α cells comprise about 25% of the total islet cells and secrete glucagon, which has a profound hyperglycemic effect. The δ cells make up about 10% of the total islet cells and secrete somatostatin, a polypeptide hormone with multiple functions, including depression of insulin and glucagon production, as well as decreasing the motility of the stomach, gallbladder, and duodenum. The PP cells are usually present in low numbers within the islets, and these cells secrete pancreatic polypeptide, a hormone of uncertain function at this time.[7,9]

The β cells account for 60–75% of all islet cells and mainly lie in the middle of each islet. β cells secrete insulin, the dominant glucose-lowering hormone, and amylin.[7,9] Importantly, glucose influx within β cells is proportional to the blood glucose concentration and is not influenced by the blood insulin level. As a result, intracellular β cell and plasma glucose concentrations are constantly the same, making the β cells keenly sensitive to changes in plasma glucose levels and key regulators of insulin secretion.[1,2] Physiologic effects of insulin are complex, consisting of rapid, intermediate, and delayed effects on carbohydrate, fat, and protein metabolism. Insulin promotes rapid uptake, storage,

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CNS *central nervous system;* CT *computed tomography;* CTA *CT angiography;* EUS *endoscopic ultrasonography;* PP *pancreatic polypeptide;* SPECT *single-photon emission computed tomography;* SRS *somatostatin receptor scintigraphy*

and use of glucose by various tissues such as the liver, muscle, and adipose tissue. In the liver, insulin secretion results in decreased glucose production because of reduced gluconeogenesis and increased glycogen synthesis. In muscle, insulin facilitates glucose entry into cells where it is either used as energy or stored in the form of muscle glycogen. In adipose tissue, glucose is a substrate for producing the glycerol portion of fat molecules.[1,2,7,9]

Normally, glucose concentration is closely maintained within a narrow physiologic range between 70 mg/dL and 110 mg/dL (3.9–6.1 mmol/L). When the blood glucose concentration rises over a threshold of approximately 100–110 mg/dL, β cells respond by rapidly increasing the rate of insulin secretion. In contrast, when the blood glucose concentration falls below 60 mg/dL, insulin synthesis and secretion cease, resulting in an increase in the blood glucose concentration.[1] These feedback mechanisms keep the glucose concentration within the relatively narrow physiologic range.

Glucose homeostasis is concurrently impacted by the effects of insulin-antagonistic counterregulatory hormones (e.g., glucagon, catecholamines, adrenocorticotropic hormone, cortisol, growth hormone).[1,2] In response to decreasing plasma glucose levels, glucagon is secreted from the α cells into the hepatic portal circulation. Glucagon stimulates hepatic glycogenolysis and gluconeogenesis, transiently increasing hepatic glucose production. Epinephrine also has a hyperglycemic effect, both directly (by causing glycogenolysis of the liver) and indirectly (by its lipolytic effect on adipose cells). These direct and indirect effects are mediated through both α- and β-adrenergic receptors. Elevations of growth hormone and cortisol also limit glucose utilization and stimulate glucose production in response to prolonged hypoglycemia over a period of hours to days.[9,11]

Clinical Features

Signalment

In previous studies of canine insulinoma, the mean age at time of presentation was between 8.5 yr and 10 yr of age.[1,2,12–17] No sex predilection has been identified.[1,2,4,13–15,17,18] Medium- to large-breed dogs were overrepresented, with a mean body weight consistently >25 kg.[1,2,4,13,14,17] The most commonly reported breeds are golden retrievers, Labrador retrievers, boxers, German shepherd dogs, Irish setters, poodles, and mixed-breed dogs, but these results may be influenced by the popularity of several of these breeds.[1,2,4,13,14,17]

History

Clinical signs reported in cases of canine insulinoma are consistent with hypoglycemia and/or high circulating catecholamine hormone

concentrations (**Table 1**).[1,2,13] Most patients show numerous intermittent clinical signs over a few months that are often precipitated by exercise, excitement, and fasting.[2,12,18]

Insulinomas typically are associated with repetitive, intermittent, and potentially life-threatening periods of hypoglycemia, which are responsible for a large proportion of the clinical signs reported.[1,4] Although β neoplastic cells can retain some responsiveness to physiologic stimuli, these responses are not normal. Neoplastic β cells are able to synthesize and secrete insulin independent of the normal suppressive effects of hypoglycemia. Essentially, insulin and glucose control is unhinged from the normal feedback loops. Hyperinsulinemia results in hypoglycemia through suppression of glucose release and production rather than via increased glucose utilization.[10]

The central nervous system (CNS) derives most of its energy from glucose metabolism, and glucose entry into the CNS is not dependent on insulin.[9] Insulin-induced hypoglycemia creates a general state of neuroglycopenia. As a result, a large variety of clinical signs can be observed, including weakness, nervousness, behavior changes, seizures, coma, and death.[1,9–11] The onset of clinical signs depends on both the degree of hypoglycemia and the rate of the blood glucose fall. Despite extremely low blood glucose values, some dogs with insulinomas will not show any clinical signs because they have adapted to these low concentrations over a period of time.[1,4,12,18] In addition, hyperinsulinemia may suppress neuronal adenosine triphosphate concentrations, damaging CNS cells by sensitizing neuronal activity and increasing excitability. Some clinical signs can also be linked to the release of noninsulin counterregulatory hormones in response to hyperinsulinemia and hypoglycemia. For example, stimulation of the sympathoadrenal system by the release of

TABLE 1

Most Common Clinical Signs Associated with Insulinomas in 204 Dogs[1,2]

Clinical signs	Number of dogs	Total percent
Seizures	128	63
Weakness	80	39
Collapse	65	32
Posterior weakness	52	25
Ataxia	38	19
Muscle fasciculations	36	18
Depression, lethargy	36	18
Bizarre behavior	28	14
Polyphagia	18	9
Polyuria and polydipsia	14	7
Weight gain	13	6

catecholamines will induce muscle fasciculations, behavioral changes, and tremors.[1,7,9]

Physical Examination

Except for clinical signs of hypoglycemia previously mentioned, general physical examination usually shows no evidence of clinically significant findings in dogs with insulinomas. However, jaundice has been reported when a biliary obstruction or hepatic dysfunction due to the primary neoplasia or metastases occurs.[19]

Moreover, changes due to paraneoplastic syndromes associated with insulinomas may also be observed.[1,2,12,18] For example, a peripheral polyneuropathy may be seen in dogs with insulinomas.[20–23] The clinical features of this polyneuropathy are variable but have been reported to include absent to severely depressed spinal reflexes (especially in the thoracic limbs), para/tetraparesis, and facial nerve paralysis.[20–23] Muscle atrophy is commonly seen in association with the previously cited signs. Less often, autonomic dysfunction, such as reduced esophageal motility and decreased anal tone, is present.[20–23] The underlying mechanism of this peripheral neuropathy is still unknown, but several theories have been suggested. For example, glucose-mediated metabolic disturbances in the neurons are often a suspected cause, but there is no distinct correlation between duration/severity of hypoglycemia and occurrence/severity of the polyneuropathy.[22] Clinical signs of neuropathy have been reported to improve or even resolve when euglycemia was restored. Unfortunately some dogs remain clinically abnormal even after restoring euglycemia.[20–24] Alternatively, an immunologically mediated destructive process of the neurons related to the insulinoma antigens had been suggested to explain the polyneuropathy.[22]

Diagnosis

A presumptive diagnosis of insulinoma is based on recognition of clinical signs, laboratory evidence, and imaging. Definitive diagnosis requires histopathologic analysis of samples obtained from the primary tumor and/or metastatic lesions.[1,2,12,13,18]

Historically, the diagnosis of insulinoma depended on demonstrating the features of the Whipple's triad as described in 1935.[25] This consisted of (1) demonstrating subnormal blood glucose levels, (2) recognizing clinical signs of hypoglycemia, and (3) documenting reversibility of signs after resolution of hypoglycemia.[1,2,4] This classic route to insulinoma diagnosis is still helpful but has been supplanted by the availability of advanced imaging and the capacity to measure serum insulin levels.

Differential diagnoses for insulinoma include other causes of hypoglycemia that can be broadly classified into four groups.[1,13,18] The first group of differentials include diseases associated with excess secretion of insulin or insulin-like factors, including extra pancreatic paraneoplastic syndromes (e.g., hepatoma, leiomyoma, lymphoma) and islet cell hyperplasia.[1,13,18] The second group of differentials include diseases with decreased production or increased consumption of glucose, including hypoadrenocorticism, hepatic insufficiency, glycogen storage diseases, and sepsis.[1,13,18] The third group of differentials include iatrogenic insulin overdose and toxic causes of insulin release (e.g., sulfonylurea drugs, xylitol, high dose of aspirin, β-blockers).[1,13,18,26–28] Fourth and finally, spurious laboratory causes of hypoglycemia should be considered prior to initiating a work-up of suspected insulinoma.[13,18,26]

Remember that inappropriately mild clinical signs associated with relatively severe hypoglycemia can be indicative of a chronic process, including an insulinoma. Alternatively, suspicion of acute hypoglycemia might lead a clinician to consider other differentials. Sulfonylurea drugs, such as glipizide, are used to treat diabetes due to their glucose-lowering effects associated with their action on insulin secretion and insulin receptors. In contrast, xylitol is a sugar alcohol used as an artificial sweetener and sugar substitute in many candies and cooking mixes. In companion animals, xylitol stimulates a massive release of insulin, causing hypoglycemia and (sometimes) hepatotoxicity.[26,27] Rarely, high doses of aspirin may trigger hyperinsulinemia by inhibiting IκB kinase-β activity.[28] β-blockers also induce hypoglycemia by modifying the metabolism of carbohydrates and lipids, as well as inhibiting glycogenolysis and the glucose mobilization that usually occurs in response to hypoglycemia.[9,29]

Laboratory Data

In cases of canine insulinoma, complete blood cell count, serum biochemistry, and urinalysis are usually unremarkable with the exception of blood glucose levels.[1,2,18] Mild hypokalemia has been reported in association with insulinomas.[12,14,16] The proposed mechanism of the hypokalemia involves the ability of insulin to stimulate increased potassium uptake into cells.[9] Increased alkaline phosphatase or alanine aminotransferase activities have also been documented.[1,12,14,16] Although this could occur secondary to insulinoma metastasis, these enzyme markers are considered nonspecific as no correlation to an insulinoma has been clearly established by previous authors.[1,12,14,16]

The most consistent laboratory finding in dogs with insulinoma is hypoglycemia (<70 mg/dL or 3.9 mmol/L), but glucose levels may vary erratically and require repeated measurements to document an abnormal value. In addition to fluctuating insulin

concentrations, catecholamines may be increased during hospitalization, which can explain the normal blood glucose values sometimes obtained in these patients.[30,31]

Fructosamine concentration can be used as an indicator of chronic hypoglycemia as this parameter reflects the blood glucose concentrations over the previous 1–2 wk.[30–32] Initially used to evaluate chronic hyperglycemia in dogs with diabetes mellitus, several studies have reported that dogs with insulinomas do have significantly lower fructosamine concentrations than normal.[30–32] The turnaround time of this test varies between laboratories, but may take up to several days.

Clinically, it is important to link the presence of hypoglycemia with elevated insulin levels and the presence of β cell neoplasia. Commonly, a diagnosis of insulinoma is supported by documenting hypoglycemia in the presence of inappropriate serum insulin concentrations. Although fasting may assist with documenting hypoglycemia, this provocative step can be dangerous to dogs with insulinomas. If a dog is consistently hypoglycemic, fasting may not be necessary and should be avoided. If an insulinoma is suspected and fasting is required, the dog should be monitored intensively to minimize the risk of unobserved hypoglycemic crisis or seizure. Specifically, glucose should be checked q 1 hr until hypoglycemia is present. When the glucose concentration is <60 mg/dL, a simultaneous blood sample should be obtained to measure insulin levels.[1]

It is important to simultaneously measure insulin at a time when hypoglycemia is documented. A diagnosis of insulinoma can be established by demonstrating inappropriately high levels of insulin associated with hypoglycemia.[1] In some cases, insulin concentrations may be within a normal range but are considered inappropriate in the presence of hypoglycemia. This situation should still raise the suspicion of insulinoma and prompt additional scrutiny for the disease. Recall that in normal patients, pancreatic secretion of insulin ceases and serum insulin levels should be low or even nondetectable when the blood glucose is <60 mg/dL.[1,2,7,9]

Alternatively, random samples can be submitted to establish a blood insulin:glucose ratio, but this technique is not commonly used due to a lack of both sensitivity and specificity. Historically, the amended insulin:glucose ratio (AIGR) can be determined by the following formula: [serum insulin (μU/mL)×10]/[blood glucose (mg/dL)−30]. Most authors have suggested that a ratio >30 is diagnostic of insulinoma.[1,13,14] Unfortunately, the specificity of the amended insulin:glucose ratio is poor because dogs with other causes of hypoglycemia can have abnormal ratios as well.[1,13,14] One study suggests that performing the test on at least four samples from a fasting dog can improve the sensitivity of the test.[33] These results should be taken into consideration with caution as most clinicians consider these ratios poorly specific in general.

Other tests for insulinoma that have been suggested include the glucagon tolerance test and oral glucose tolerance test. These tests are potentially hazardous and often fail to support the diagnosis.[1,32,34] For example, in one study, 25% of dogs with insulinomas that underwent a glucagon tolerance testing experienced rebound hypoglycemia with seizure activity within 5 hr of the test.[34] Thus, these tests are not routinely recommended and should be used with caution.[1,32]

Imaging
Various imaging techniques have been described to allow the visualization of proliferative soft-tissue masses in the pancreas. Enlarged lymph nodes and/or the presence of metastasis in other organs, mainly the liver, have been commonly documented.[3,18,35–38] Other sites of metastasis that have been reported include the duodenum, mesentery, omentum, spleen, spinal cord, kidney, and bones.[3,18,35–38]

Radiographs
Abdominal radiographs are usually unremarkable in dogs with insulinomas due to the small size of most β cell tumors. Lung metastases are rarely found in dogs with insulinomas, and osseous metastases have been reported in only two cases.[13,16,17] Although the diagnostic value of plain film radiography is considered limited for insulinoma, such films may reveal abnormal findings in patients with paraneoplastic hypoglycemia due to other tumor types (e.g., leiomyosarcomas). Therefore, thoracic radiography (to detect pulmonary metastasis) should be considered as part of the diagnostic approach to patients with hypoglycemia.

Abdominal Ultrasound
Abdominal ultrasound can be used to visualize mass(es) in the pancreas in many cases (**Figure 1**). Insulinomas are usually either spherical or lobular and hypoechoic compared with the surroundings tissues. Ultrasound may also be useful to detect metastatic lesions in different organs and lymph nodes. Ultrasonography is known to be operator-dependent, and various factors such as body conformation, abdominal fat, and patient cooperation can interfere with ultrasound interpretation. Depending on the study cited, the sensitivity of abdominal ultrasound in detecting insulinoma varies from 28% to 75%.[5,6,16,17,23]

Endoscopic ultrasonography (EUS) is more sensitive and specific than transabdominal ultrasound in humans, reaching 100% sensitivity and 95% specificity when performed by experienced

FIGURE 1 *Ultrasonographic identification of a nodule (demarcated by the cross symbols) in the right pancreatic lobe of a dog suspected to have an insulinoma.*

operators.[39] This technique has been described in dogs, and one report describes diagnosing a 4 mm insulinoma of the left pancreatic limb.[40] Disadvantages of EUS include the steep learning curve, the need for general anesthesia, and the overall lack of EUS availability in most veterinary settings.[40]

Contrast-enhanced ultrasonography is now widely use in human medicine for the detection of pancreatic neoplasms. In fact, extrapolated from human oncology, some authors suggest that contrast-enhanced ultrasound exams may better detect mass lesion than helical computed tomography (CT).[41,42] Ultrasonographic contrast agents are tiny, gas-filled microspheres stabilized by an outer shell. These microbubbles are smaller than erythrocytes and do not have the risk of capillary air embolism. The use of such contrast improves the detection of perfusion and vascularity of organs. Use of contrast-enhanced ultrasound techniques have been reported recently in dogs with normal pancreases, pancreatitis, pancreatic carcinomas, and insulinomas.[41–43] Some specific contrast agents such as hexafluoride microbubbles may have limited availability in some practice settings. To date, no large studies have been published in veterinary medicine establishing the specificity and sensitivity of contrast-enhanced ultrasound to diagnose insulinomas in dogs.[41,44]

CT

CT should be considered as an additional tool for the diagnosis and preoperative evaluation of insulinomas in dogs. Three studies report using CT for the detection, localization, and staging of insulinomas in dogs.[5,45,46] In the first of these studies, CT showed a better sensitivity in the detection of insulinoma masses than either abdominal ultrasound or single-photon emission CT

(SPECT) in a case series of insulinomas in 14 dogs.[5] The two latest veterinary studies were performed with dual-phase CT angiography (CTA) on one and three dogs with insulinomas.[45,46] CTA is based on the delineation of vessels by the radiographic contrast medium. In the case of pancreatic lesions, contrast within the splenic and portal veins may help in locating pancreatic lesions.[47] Due to the highly vascular nature of insulinomas, the mass usually appears highly hyperattenuating during the arterial phase, with small amounts of enhancement seen during the venous phase.[45,46,48] Reports using CTA to detect insulinomas are highly promising. Indeed, in both of the published studies cited herein, CT findings regarding mass and metastasis size/location were similar to surgical findings.[45,46] In humans, dual phase CT is superior to abdominal ultrasound for detecting and staging insulinomas, and CTA is superior to traditional CT.[48,49] Nonetheless, further studies are needed to better evaluate the sensitivity of CTA.

Somatostatin Receptor Scintigraphy (SRS) and SPECT

SRS is used in humans to detect insulinomas and reportedly has a sensitivity of 60–70%. Detection of human insulinomas can be affected by diversity in the number of somatostatin receptors expressed by human tumors. In contrast, studies in dogs demonstrate that canine insulinomas are likely to express only one type of somatostatin receptor with a high frequency, potentially leading to better results with the use of SRS with ^{111}In-pentetreotide.[50,51] The use of SRS in a few dogs has been reported, but it is still unclear if this diagnostic tool could be valuable in a clinical setting.[6,50,51] A specific form of SRS called SPECT is under investigation and has a similar sensitivity compared with ultrasound and CT in a series of 14 dogs with insulinomas.[5,6,51] However, caution is needed as scintigraphy does not seem to allow appropriate localization of the tumor.[5,6] For example, Garden *et al.* (2005) report that the anatomic location of the tumor was established in only one of four dogs diagnosed with insulinoma with scintigraphy.[6]
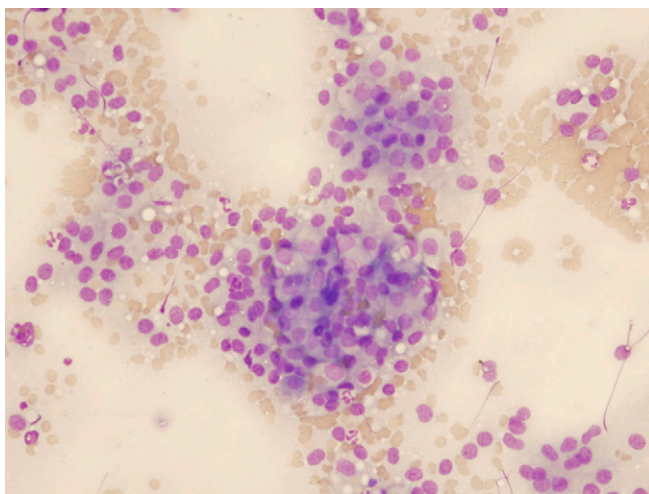
Scintigraphy is a promising imaging technique for the detection of insulinomas and liver and lymph node metastases. Nonetheless, scintigraphy remains limited by its very restricted availability in veterinary specialty hospitals, its apparent inability to localize lesions, and its relatively expensive cost.[5,6]

One recent study showed that the preoperative localization of insulinomas remains challenging in people regardless of the imaging modality used. When imaging modalities were used alone, the authors reported a diagnostic and localization accuracy of 64% with CT, 75% with MRI, 50% with radiolabeled octreotide (a somatostatin analog) scanning, and 63% with EUS.[52] A combination of modalities (e.g., CTA and MRI or CTA and EUS)

is thought to predict tumor existence and localization with a much higher accuracy.[52,53] However, similar data (including the use of MRI in canine insulinomas) is not available in the veterinary literature.

Cytology and Histopathology

Ultrasound-guided fine-needle aspirate cytology may be used as a relatively noninvasive tool to support a diagnosis of insulinoma.[5,54,55] Aspirates should be obtained by back and forth needle movements or rotary drilling motions with continuous suction during the advancement of the needle. Complications associated with aspirations of the pancreas are unusual. In humans, inadvertent penetration of the stomach or small intestines does not increase the risk of complications, but severe acute pancreatitis can develop.[55,56] In dogs, cytologic evaluation of aspirates from β cell tumors reveals clusters of cells typical of neuroendocrine tissue, which has the appearance of free nuclei embedded in cytoplasm without visible cell borders (**Figure 2**).[54] β cell tumors can be easily differentiated from pancreatic exocrine cells because of the pink zymogen granules observed in the cytoplasm of pancreatic exocrine cells.[54] Anaplastic features are often mild or inconsistent, despite the fact that most β cell tumors in dogs are malignant. The lack of anaplastic features should not be used to predict the biologic behavior of the tumor, and the likelihood of malignancy must be considered.[54] Thus, the cytologic appearance of insulinomas differs significantly from other neoplasms such as pancreatic adenocarcinoma (i.e., epithelial cell neoplasm) and may be helpful as an adjunctive diagnostic test.[54]
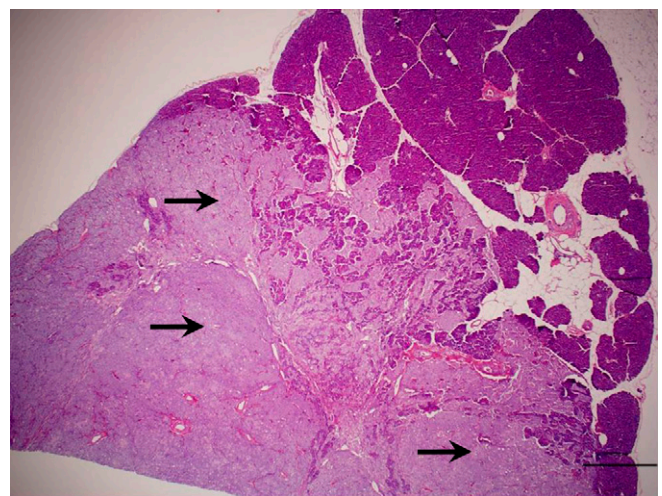
Tissue samples are usually fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (**Figures 3**, **4**).[57] The functionality is then demonstrated by insulin immunohistochemistry (**Figure 5**).[57]

Treatment

Surgical resection of gross pancreatic disease and amenable metastases should be strongly considered even if the goal of the procedure is palliative, not curative. Prior to surgery, medical management is always necessary to control the clinical signs and improve anesthetic stability. In cases where an insulinoma is highly suspected but the tumor has not been confirmed with preoperative imaging techniques, medical treatment followed by surgical exploration is recommended. If surgical treatment is declined or if the patient is not a surgical candidate (e.g., unresectable tumor and/or overwhelming metastasis) then chronic medical management can be applied. The remainder of this review will discuss the different aspects of both surgical and medical management, as well as the prognoses associated with the different types of treatments.

Surgical Treatment

Based on the outcome of most dogs with insulinomas after surgical removal, it is suspected that almost 100% of canine cases have metastases at the time of diagnosis.[1] However, at the time of surgery, metastases may be confirmed in only 45–55% of cases,

FIGURE 2 *Photomicrograph of an impression smear from a patient with a metastatic insulinoma. The nucleated cells are arranged in clusters with indistinct cell borders, typical of neuroendocrine neoplasms. They display mild anisocytosis and anisokaryosis. The nuclei of these cells have coarsely stippled chromatin without prominent nucleoli. Wright-Giemsa, ×50 objective.*

FIGURE 3 *Multifocal well-demarcated nodules of pale pink neoplastic cells (arrows) replace and efface approximately 60–70% of the normal pancreatic architecture. Hematoxylin and eosin stain, original magnification: ×2 Bar=1 mm.*
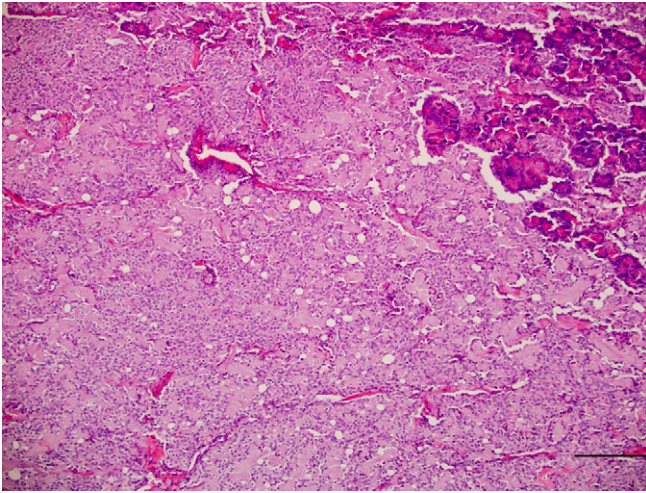
FIGURE 4 *Neoplastic cells are arranged in small nests and packets, separated by moderate amounts of fibrous connective tissue. There are multifocal aggregates of amorphous, homogenous, eosinophilic material (*amyloid*) throughout the neoplasm. ×10 Bar=200 µm.*

thus emphasizing the importance of careful staging to establish a proper treatment plan and provide an accurate prognosis to the owners.[2,13–15] Although surgery is not likely to be curative, debulking the neoplastic tissues improves both the efficacy of medical treatments and survival times.[4,13–18] Surgical visualization and palpation of the pancreas, although invasive, is still considered to be one of the best tools for diagnosing and staging insulinomas in dogs (**Figure 6**).[1,2] A major advantage of surgical exploration remains the possibility to obtain a definitive diagnosis
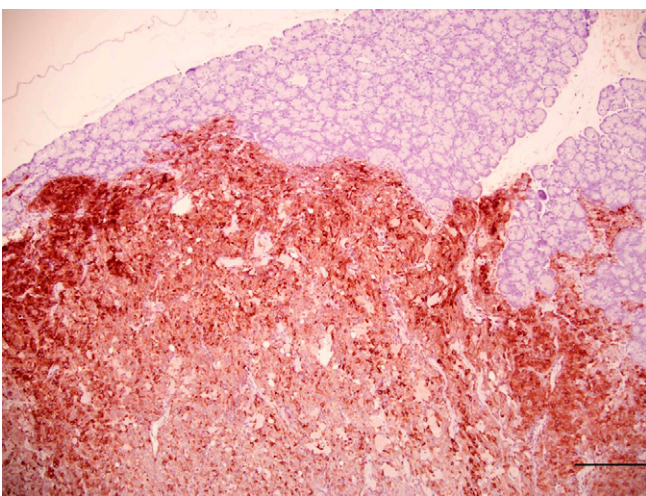
FIGURE 5 *Immunohistochemistry staining for insulin. Strong positive labeling of the population of neoplastic polygonal cells is noted. Immunoperoxidase with 3,3'-diaminobenzidine with Mayer'sn hematoxylin counterstain, original magnification ×10 Bar=200 µm.*
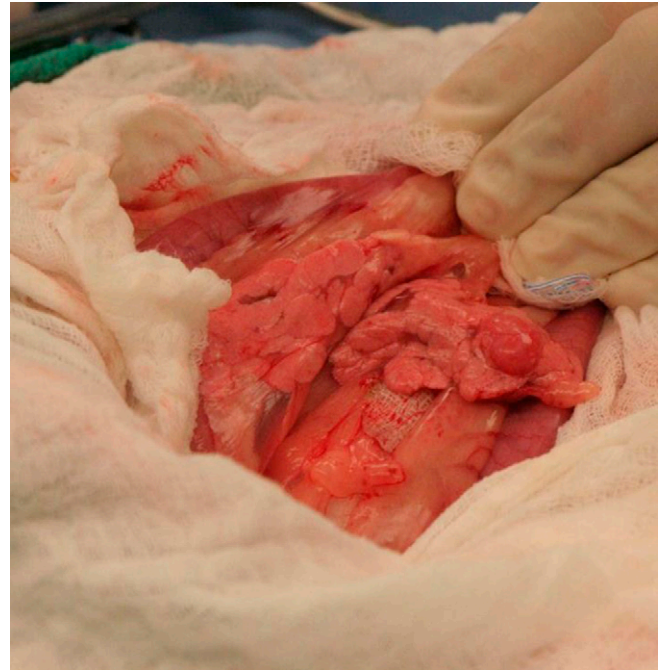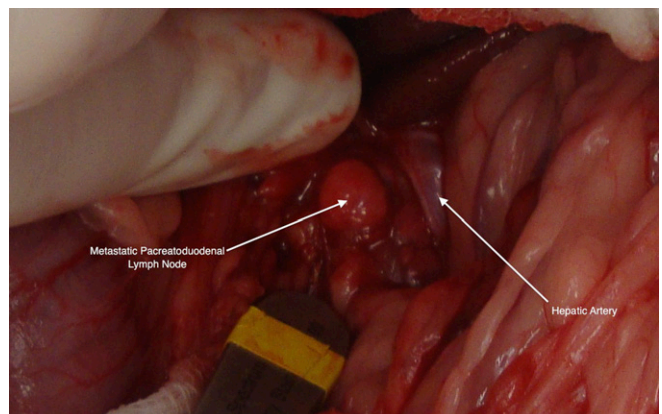

FIGURE 6 *Perioperative photograph of a pancreatic nodule before pancreatectomy in a dog diagnosed with an insulinoma.*

by visualizing the tumor and obtaining tissues for histopathologic evaluation.

Anesthesia and Perioperative Management
Nearly 50% of human insulinoma patients will develop fasting hypoglycemia within 12 hours (with 67 and 95% of patients respectively developing documented hypoglycemia at 24 and 48 hours).[58] Consequently, in contrast to other surgical patients, preoperative fasting is not recommended in patients with insulinoma. Instead, a small meal should be fed 2–3 hr prior to surgery.[59]

FIGURE 7 *Perioperative photograph demonstrating lymph node metastasis (*pancreaticoduodenal lymph nodes near the hepatic artery*) in a dog diagnosed with an insulinoma.*

A 5% dextrose solution should be administered before, during, and after surgery until the patient is stable. Because the signs of hypoglycemia (e.g., tachycardia, palpitations, tremulousness, seizures) may be obscured by general anesthesia, in addition to basic preoperative management, blood glucose should be monitored q 15–30 min intraoperatively so that hypoglycemia can be either avoided or managed.[59,60] Remember that insulinomas are a reactive, functional, hormone-producing tumors, and high dextrose infusions or boluses may precipitate insulin release leading to "rebound hypoglycemia." Relying on dextrose boluses or using high concentration dextrose infusions may overstimulate insulinoma cells to release insulin, resulting in dangerous, unpredictable, and potentially fatal fluctuations in both insulin and glucose concentrations.[18,59,61]

Anesthetic protocols should take into account the general needs of major abdominal surgery and the specific challenges of the hypoglycemic patient. IV fluids should be given at an adequate rate (generally during the procedure and 1–2 days postoperatively).[18,59,61] Pain and stress will lead to a stimulation of the sympathetic nervous system, causing an increase in circulating catecholamines, which will lead to hyperglycemia. Therefore, it is prudent to use locoregional analgesia in combination with opioids to control pain and surgical stress.[62] Commonly, opioids are administered preoperatively with acepromazine or benzodiazepines. Induction may preferentially be performed with propofol, thiopental, or etomidate, as all of those drugs provide cerebral protection during periods of hypoglycemia. Isoflurane or sevoflurane should be used for maintenance rather than halothane because they are better able to reduce the cerebral metabolic rate.[59] α_2-adrenergic agonists should be avoided because they may suppress the release of insulin, leading to hyperglycemia.[59]

Surgical Exploration and Pancreatectomy
During surgery, the cranial abdominal cavity is explored for evidence of neoplasia. The entire pancreas is examined, both visually and by palpation, evaluating each anatomic area.[61] A partial pancreatectomy is usually performed, as well as resection of grossly visible metastases. Excised tissues are submitted for histopathologic examination.[13–17]

β cell tumors are usually single, small (0.5–4 cm), yellow to dark spherical nodules on the surface of the pancreas. In 3–4% of dogs, a discrete pancreatic nodule cannot be located at the time of surgery.[1,59] Pancreatic nodules are more commonly found in either the right or left lobe of the pancreas, rather than in the pancreatic body. Of 155 dogs with insulinomas, 71 dogs had a tumor in the left lobe (44%), 56 dogs in the right lobe (35%), and 23 dogs in the body (14%).[3]

When intraoperative visualization and palpation are unsuccessful, intraoperative ultrasound can be used, although this promising technique is not yet performed routinely.[2] Intraoperative IV infusion of methylene blue has also been described in dogs to improve localization and tumor staging at the time of surgery.[63,64] Methylene blue stains normal pancreatic endocrine tissue a dusky slate blue, whereas hyperfunctioning tissue, such as adenomatous or carcinomatous areas, will stain more intensely in a reddish blue.[1] Despite its utility, methylene blue is rarely used because of its side effects, which include induction of Heinz body hemolytic anemia and acute renal failure. Additionally, methylene blue staining usually requires up to 30 min before the color changes are obvious. Therefore, IV methylene blue administration is not routine practice.[63,64]

Surgical removal of metastatic lesions should be weighed carefully. Metastectomy not only has the potential to improve the prognosis but also increases the risk of morbidity.[17] The removal of either the peripancreatic or hepatic lymph nodes may increase the risk of interfering with the blood supply of adjacent organs (**Figure 7**). Some authors think that surgical management may be inappropriate when extrapancreatic disease is detected preoperatively.[17] Clinical assessment of metastatic disease should be interpreted cautiously as both imaging modalities and gross observation during surgery may overestimate the presence of metastases.[5,16]

Postoperative Complications
Postoperative monitoring of blood glucose and pain should be managed according to published protocols for abdominal surgery and/or pancreatitis.[59] In many cases, euglycemia will be documented early in the postoperative period. Persistent hypoglycemia in the postoperative period warrants a potentially guarded prognosis and usually indicates the presence of unrecognized tumors, metastases, and/or incompletely resected masses.[1,13,18] Hyperglycemia can develop, but is usually transient until the remaining healthy β cells regain their function. Indeed, suppression of normal β cell activity by either insulin released by the tumor or repetitive hypoglycemia can result in either glucose intolerance or transient diabetes after removing or debulking insulinomas. Typically, β cells will regain their normal secretory capabilities over time, with transient diabetes lasting from a few days to a few months.[1,9] Some dogs require long-term treatment with exogenous insulin because of persistent diabetes mellitus. Unless the majority of the pancreas has been removed, permanent diabetes is uncommon and implies additional abnormalities of the β cells (e.g., loss from pancreatitis, etc.).[9]

Pancreatitis is a concern following any pancreatic surgery. One study reported pancreatitis in 10% of the dogs postsurgically.[15]

Prompt medical treatment and management should be able to minimize morbidity and mortality linked to this complication. Other complications that have been described following pancreatectomy or metastectomy for insulinomas are ventricular arrhythmias, bleeding, sepsis, leukopenia, cardiac arrest, and syncope.[2,15,18,61]

Medical Treatment and Management (Table 2)

Acute Management: Emergent Treatment of Hypoglycemic Crisis

Dextrose Bolus. Hypoglycemic crises (i.e., episodes of clinical signs) should be managed initially with the IV administration of 1 mL/kg of 25% dextrose over 10 min. A normal blood glucose value may be difficult to either achieve or maintain due to ongoing insulin release from the tumor. Thus, the goal of the dextrose bolus is to simply raise blood glucose levels above the threshold that results in clinical signs. Stabilization in some dogs can be difficult to manage as the dextrose bolus may induce further insulin release from the tumor, leading to worsening of the hypoglycemia. In such cases, repetitive dextrose boluses are not effective as a single strategy and either alternative or adjunctive therapies should be considered.[4,59] A number of adjunctive therapies are outlined below. The simplest adjunctive therapy is the frequent feeding of small meals. After stabilization, food should be offered and fluids containing 5% dextrose should be maintained IV.[1,4] The use of either 10% or 12% dextrose containing fluids is usually avoided unless a central venous catheter can be used because peripheral veins do not tolerate hypertonic solutions for long periods of time and are susceptible to thrombophlebitis. Moreover, the use of 10% dextrose and rapid dextrose boluses raises the concern of a possible reactive insulin release from the tumor. Indeed, insulinomas retain some sensitivity to plasma glucose concentrations, so large infusions of glucose may stimulate the tumor cells to release even more insulin, resulting in unpredictable and dangerous fluctuations in blood glucose concentrations.[1,7,9]

Steroids. Dexamethasone (0.5 mg/kg administered IV over 6 hr *q* 12–24 hr) is commonly recommended. Other steroids such as prednisone or prednisolone may also be used. These drugs antagonize the effects of insulin, stabilize blood glucose concentrations, and logically are an important part of palliative medical therapy of hypoglycemia caused by hyperinsulinism.[9,18] See additional information below regarding the use of steroids in the chronic management of insulinomas.

Glucagon. The insulin antagonistic hormone glucagon has a profound hyperglycemic effect by encouraging the breakdown of liver glycogen (glycogenolysis) and by increasing hepatic gluconeogenesis from available amino acids substrates.[7,9] A constant rate infusion of glucagon has been used in refractory hypoglycemic crisis to maintain euglycemia despite intractable hyperinsulinism. The initial reported infusion rate is 5 ng/kg/min, which is then adjusted depending on the blood glucose values. Use of glucagon has shown promising results in the management of acute hypoglycemic episodes and, like glucocorticoids, will not stimulate reactive insulin release and rebound hypoglycemia.[65]

Chronic Management

Medical treatment is indicated before surgery and postoperatively, when hyperinsulinemia persists, or in cases in which surgery has not been performed.[2,18]

Diet and Exercise. Dogs with insulinomas should be fed at least *q* 4–8 hr, and food should contain high levels of proteins, fats, and complex carbohydrates. By avoiding simple sugars, an appropriate diet can dramatically reduce the stimulus for tumor insulin release, thereby controlling the clinical signs of hypoglycemia. The only exception is when a patient is actively exhibiting signs of hypoglycemia. In those cases, a rapidly absorbed source of sugar (such as honey, corn syrup, or maple syrup) may be administered

TABLE 2

Acute and Chronic Medical Management of Hypoglycemia

Acute management	
Dextrose	Bolus of 25% dextrose IV over 10 min followed by 5–10% dextrose IV continuously
Dexamethasone	0.5 mg/kg IV over 6 hr then *q* 12–24 hr
Glucagon	Initial rate is 5 ng/kg/min. Rate is adjusted according to the blood glucose values and can be increased to 13 ng/kg/min
Octreotide	20–40 μg/kg subcutaneously *q* 8–12 hr
Chronic management	
Prednisone	0.5 mg/kg/day *per os* (divided in 2–3 doses). Can be increased gradually up to 4 mg/kg/day
Diazoxide	5 mg/kg *per os q* 12 hr. Can be increased gradually up to 40 mg/kg but <60 mg/kg
Octreotide	2–4 μg/kg subcutaneously *q* 8–12 hr

orally at home pending further veterinary consultation. Exercise should be restricted to short leash walks only and excitement avoided as long as the patient is at risk for hypoglycemia. Indeed, exercise can precipitate hypoglycemia by increasing the muscle uptake of glucose and accelerating insulin absorption.[1,4,7] Dietary management is often complemented with additional drug therapy in most cases.

Glucocorticoids. Glucocorticoids are commonly used in conjunction with diet and exercise modifications for the long-term management of insulinoma patients. Glucocorticoids stimulate hepatic gluconeogenesis and glycogenolysis and interfere with the affinity of cellular insulin receptors for glucose. These effects result in an increase in blood glucose levels. At a dose of 0.5 mg/kg/day (divided into 2–3 doses/day), prednisone will help prevent hypoglycemia and clinical signs. Higher steroid doses can be used in refractory cases (up to 4–6 mg/kg/day), but are often met with unacceptable side effects. If intolerable adverse effects of glucocorticoid therapy are noted, alternative therapies should be considered.[1,2,4]

Diazoxide. Diazoxide is a benzothiadiazine diuretic and potassium channel activator that blocks insulin release, promotes glycogenolysis and hepatic gluconeogenesis, inhibits cellular glucose uptake, and stimulates epinephrine secretion. The recommended dose of diazoxide is 5 mg/kg *per os* *q* 12 hr, which can be increased gradually without exceeding 60 mg/kg/day.[1,4,14,16] The hyperglycemic effects of diazoxide are reportedly beneficial for some dogs with insulinomas, with one study reporting control of hypoglycemia in 70% of the cases.[1,4,15,17]

The most common side effects reported with the use of diazoxide are anorexia, diarrhea, and vomiting, which may often be prevented by administering diazoxide with meals. Other signs that occur less frequently include hyperglycemia, bone marrow suppression, and sodium retention.[2,4] Importantly, diazoxide may not be available in many pharmacies and can potentially be prohibitively expensive.

Octreotide. Octreotide, a long-acting synthetic somatostatin analog, has been useful in controlling hormone hypersecretion and clinical signs of insulinomas in humans.[66] It induces hyperglycemia by inhibiting the production of insulin and growth hormone.[7] Canine insulinoma cells have receptors with a high affinity for this drug.[67]

Although octreotide's suppressive effect on plasma insulin concentrations was well documented in one veterinary study, the insulin suppressive effect was transient, lasting no more than 3–4 hr.[67] This could explain the long-term therapeutic failures described in diverse studies.[66,67] Long-term medical treatment with slow release somatostatin analogs, such as lanreotide, needs to be investigated as lanreotide could provide better control over clinical signs.

Chemotherapy

Streptozocin. Streptozocin is a nitrosurea chemotherapeutic agent that is commonly used for unresectable metastatic insulinomas in humans because it is specifically cytotoxic to pancreatic β cells. Its use has been limited by the high nephrotoxicity documented in the first veterinary trials, but recent studies document that streptozocin can be used safely in dogs with aggressive 0.9% saline dieresis, which prevents clinical nephrotoxicity.[24,38,68,69] When streptozocin was administered IV at a dose of 500 mg/m² *q* 3 wk combined with pre- and postdiuresis over 7 hr, no toxicity was observed. However, the drug is very emetogenic; thus, appropriate antiemetic treatment should be used concurrently. Dogs treated with streptozocin can develop an acute transient hypoglycemia resulting from damaged tumor cells releasing their intracellular insulin stores.[24] Additionally, dogs can develop diabetes mellitus resulting from chronic damage to normal pancreatic β cells.[24,38] However, in the largest veterinary study (including 17 dogs), 2 dogs developed diabetes but survived the longest, possibly due to the effectiveness of streptozocin chemotherapy in those select cases. In some dogs a longer duration of normoglycemia and/or reductions in the size of lesions was achieved.[24]

Alloxan. Alloxan, an unstable uric acid derivative, has two distinct effects: (1) cytotoxicity for islet cells and (2) stimulation of hepatic gluconeogenesis. Reported complications include renal tubular necrosis, acute renal failure, and persistent hyperglycemia. Only five cases have been reported in veterinary medicine with the use of this drug. In humans, response to alloxan was disappointing and further studies are needed in dogs to determine its usefulness.[4]

Future Directions: Targeted Therapies

Human studies have recently looked into the overexpression of tyrosine kinase receptors (such as c-kit), epidermal growth factor receptor, vascular endothelial growth factor and its receptor, or insulin-like growth factor receptor in insulinomas.[70,71] These potential molecular targets led to numerous studies looking at the possible role of drugs such as gefitinib, sunitinib malate, sorafenib, toceranib, and masitinib.[70,71] This area of study may hold promise for future veterinary research in canine insulinomas.

Prognosis

Prognosis of dogs diagnosed with insulinomas can be assessed in two different fashions: (1) length of euglycemia, which reflects the control of clinical signs, and (2) overall survival. Despite being rarely curative, surgical therapy undoubtedly offers the greatest chance of both durable control of clinical signs and prolonged survival time in dogs with insulinomas. One study (n=39) reported a median survival time of 381 days for dogs that underwent partial pancreatectomy compared with 74 days for dogs treated with medical therapy alone.[16] That study illustrates the consensus that surgical management is beneficial compared with medical management alone.[13–17] As reported in several studies, the median survival time in dogs that undergo partial pancreatectomy is 12–14 mo.[16,18] One study also states that dogs that undergo surgical resection remain normoglycemic for a mean period of 11.6 mo.[13]

Benefits of surgery depend on the clinical stage of the disease. Dogs presenting with metastases at the time of surgery have a dramatically worse prognosis at 1 yr.[13] Caywood *et al.* (1988) showed that >50% of stage I (i.e., tumor strictly localized to the pancreas) dogs were considered disease-free 14 mo postsurgically compared with <20% for stage II (i.e., tumor spread to local lymph nodes) and stage III (i.e., tumor with distant metastasis with or without local lymph nodes) dogs.[13] Stage III dogs had a significantly shorter survival time than stage I and II dogs. All stage III dogs died by 18 mo postsurgically.[13]

As mentioned previously, postoperative hypoglycemia reportedly has a negative prognostic indicator.[18] However, Tobin *et al.* (1999) did not report any significant difference in mean survival time between dogs that underwent partial pancreatectomy only (381 days) and dogs that were administered prednisone and diazoxide postsurgically for hypoglycemia (349 days).[16] Dunn *et al.* (1993) reported identical results.[12] In two other studies, neither signalment of the animal nor clinical signs and their duration, blood insulin concentrations, or tumor location had a significant influence on prognosis.[12,13]

One recent study reports significantly longer survival times compared with older reports.[17] In the recent study, dogs that underwent partial pancreatectomy showed median duration of remission of 496 days and a median survival time of 785 days. Dogs treated only medically had a median survival time of 196 days, and dogs treated both surgically and medically had a median survival time of 1,316 days.[17] This data should still be considered with caution because of the low case numbers (n=28), but it seems likely that the improved prognosis compared with the previous studies might be explained by an earlier diagnosis, an improved surgical case selection, improvements in surgical technique, and superior postoperative care.[17]

Conclusion

Insulinoma is a malignant endocrine pancreatic tumor of dogs which commonly metastasizes to lymph nodes and liver. The mean age at the time of diagnosis is approximately 10 years of age. Clinical signs are consistent with hypoglycemia and high circulating catecholamine hormone concentrations. Diagnosis of canine insulinoma is based on clinical signs, laboratory evidence and imaging in combination with histopathology of biopsy samples. The most consistent laboratory finding in dogs with insulinoma is hypoglycemia, but glucose levels may vary erratically (sometimes entering the normal range). Abdominal ultrasound is commonly used to visualize lesions in the pancreas. Multiple adjunctive imaging techniques have been described to enhance pre-operative diagnosis. These modalities include endoscopic ultrasonography, computed tomography (CT), and scintigraphy. Surgical resection of gross pancreatic disease and possibly metastases should be strongly considered even if the procedure will be palliative and not curative. Medical therapy generally seeks to limit clinical signs of hypoglycemia. The combination of surgical and medical therapy offers the greatest chance to control clinical signs and prolong survival time. ■

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