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CONTINUING EDUCATION

SOFT TISSUE SURGERY

Surgical Management of Canine Liver Masses

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Primary malignant hepatic tumors are uncommon in dogs; based on necropsy studies, approximately 0.9% of dogs are affected.[1,2] Primary hepatic tumors can generally be subdivided into hepatocellular tumors, cholangiocellular tumors, and neuroendocrine carcinomas, although other, less common, primary tumors occur, such as sarcomas.[1,3] Hepatic metastasis is also reported for a variety of neoplasias.[4]

Depending on the type of neoplasia present, surgical removal is considered the primary treatment of choice.[5] For example, liver lobectomy for massive hepatocellular carcinoma has been associated with a significantly longer median survival time than management without surgical intervention.[2] Specific surgical approaches depend on multiple variables, including surgeon preference as well as tumor characteristics.[6] Described techniques include blunt dissection of the liver parenchyma followed by vessel ligation, as well as use of stapling, vessel sealant, ultrasonic scalpel, and encircling suture devices.[6,7]

LIVER ANATOMY

The liver consists of 6 lobes. From anatomic left to right, they are called the left lateral, left medial, quadrate, right medial, right lateral, and caudate lobes, with the caudate lobe having caudate and papillary processes. The liver has also been described in terms of *division*s, with the left, central, and right divisions consisting of the left lateral and left medial, quadrate and right medial, and right lateral and caudate lobes, respectively (**FIGURE 1**).[8] Ligamentous attachments to the liver include the left and right triangular, falciform, gastrohepatic, and hepatoduodenal ligaments.[9] The gallbladder lies within the gallbladder fossa between the quadrate and right medial lobes.[8,9] On a microanatomic scale, hepatocytes and cholangiocytes are the hepatic cells most commonly implicated in primary liver tumors.[3]

The hepatic artery and portal vein supply blood to the liver. Venous drainage is via the hepatic vein, and biliary collection is via 3 or 4 major divisional ducts emptying into the common bile duct. While the number of branches that

CALL FOR REMOVAL
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originate from the hepatic arterial arch ranges from 1 to 5, most dogs (64%) have 3 hepatic arterial branches, with each branch corresponding to the previously described liver divisions.[9] Each liver lobe, with the caudate lobe being divided into its processes, has been reported to have the following structures generally consistently located anatomically: a single lobar hepatic artery providing arterial blood supply, a single lobar biliary duct for biliary drainage, 1 lobar portal vein for portal blood supply (though up to 3 have been noted), and 1 hepatic vein for drainage (though up to 3 have been reported).[8]

LIVER TUMORS

Hepatocellular Tumors

Hepatocellular tumors arise from hepatocytes and include hepatocellular adenomas (benign) and carcinomas (malignant).[3,10] While the pathogenesis of hepatocellular tumors remains to be fully elucidated, genetic dysregulation, with aberrant microRNA expression being implicated, has been demonstrated in hepatocellular carcinoma.[11] Hepatocellular tumors are the most common primary hepatic tumors, with hepatocellular adenomas accounting for 27% to 52% of hepatocellular tumors.[3,6,10] Hepatocellular carcinoma has been further subdivided into massive, nodular, and diffuse morphologic distributions; massive tumors most commonly affect the left lateral liver lobe (**FIGURE 2**).[1]

Hepatocellular tumors generally arise from grossly normal appearing liver.[3] The reported rate of metastasis is variable, with a metastatic rate in dogs undergoing surgery for massive hepatocellular carcinoma recently reported as 4.8%; commonly reported sites of metastasis include lymph nodes, lungs, and peritoneum.[1,2]

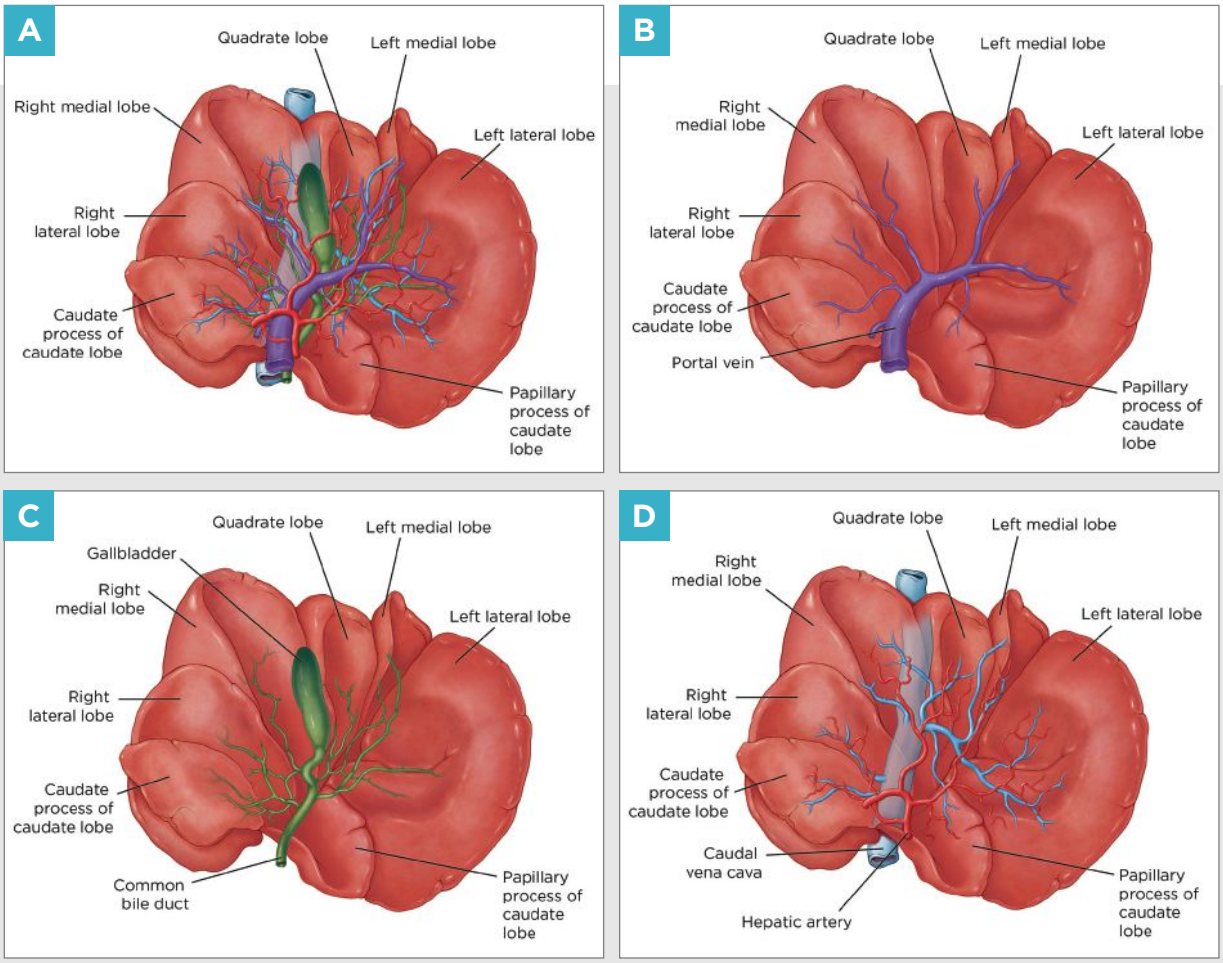

FIGURE 1. Anatomy of the liver, including **(A)** portal blood supply and **(B)** biliary system, as well as **(C)** arterial blood supply and **(D)** venous drainage.

Cholangiocellular Tumors

Cholangiocellular tumors arise from cholangiocytes and include cholangiocellular adenomas and carcinomas. Cholangiocytes and hepatocytes have a shared hepatic progenitor cell; therefore, some neoplastic processes can have characteristics that overlap between hepatocytes and cholangiocytes, such as cholangiocarcinomas.[3] Cholangiocellular tumors are reported less frequently than hepatocellular carcinoma, with cholangiocellular carcinomas more common than cholangiocellular adenomas.[3,10]

Similar to hepatocellular carcinoma, cholangiocellular carcinoma has been divided into massive, nodular, and diffuse morphologic descriptions, with the left lateral lobe most commonly affected in the massive group of tumors; this contributes to the difficulty in differentiating cholangiocellular tumors from hepatocellular tumors grossly and makes histologic examination critical for a definitive diagnosis.[1,12] The metastatic rate for intrahepatic bile duct carcinomas is 86%, with the most common sites including lymph nodes, lungs, and peritoneum, making this disease process overall more malignant than hepatocellular carcinoma.[12]

Other Tumors

Primary hepatic neuroendocrine carcinomas are rare and likely arise from existing neuroendocrine cells in the biliary epithelium.[3] Primary hepatic neuroendocrine carcinomas cause nodular or diffuse lesions throughout the liver, with lymph node metastasis, peritoneal carcinomatosis, and intrahepatic metastasis occurring in most cases.[3,12,13] Other primary malignant tumors of the liver include several types of sarcoma (e.g., fibrosarcoma, hemangiosarcoma, histiocytic sarcoma), lymphoma, and malignant peripheral nerve sheath tumor.[1,10]

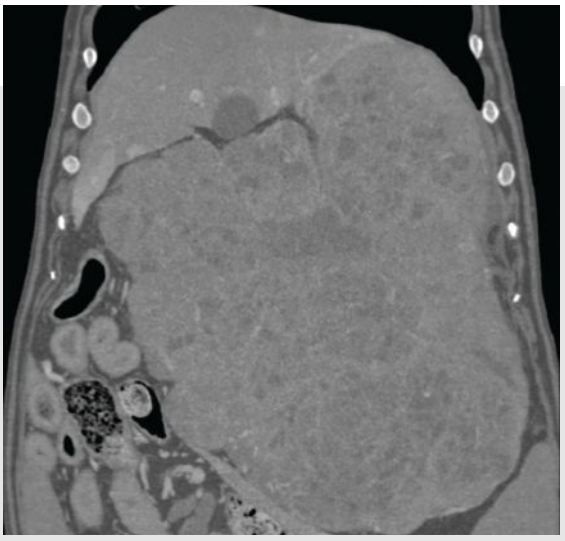

FIGURE 2. Computed tomography image of left divisional massive hepatocellular carcinoma.

INDICATIONS FOR SURGERY

Surgical intervention is indicated as the treatment of choice for massive, solitary liver tumors.[5] Nodular and diffuse disease processes are intrinsically considered to be nonresectable tumors, as multiple liver lobes are commonly involved.[14,15] While further diagnostics, as discussed below, are indicated before surgical intervention, it has been proposed that exploratory surgery should also be performed when a large intra-abdominal mass is present, even without a definitive diagnosis, for further staging purposes as well as to further determine the ability to resect the mass.[2]

The left division is more mobile than the other divisions and has a deep fissure from the remaining liver, making left-division liver lobectomies generally less technically challenging than right- or central-division lobectomies.[16] Hilar tumors generally need extensive resection, increasing the surgical difficulty compared with more peripheral lesions; for example, complete resection of hilar tumors using surgical stapling devices alone is often challenging.[8,16]

Compared with hepatocellular carcinomas, hepatocellular adenomas are presumed to have a better prognosis, while biliary carcinomas, sarcomas, and neuroendocrine carcinomas are suspected to have a worse prognosis; however, there is little to no primary literature to support these assumptions.[6] The prognosis is regarded as poor for dogs with nodular and diffuse forms of hepatocellular carcinoma, as surgery is not feasible in most of these cases.[15] In dogs undergoing surgery for massive hepatocellular carcinoma, negative prognostic factors include high serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, increased alkaline phosphatase (ALP):AST and ALT:AST ratios, and the presence of right-sided tumors, although this last indicator was suspected to be secondary to a high intraoperative mortality rate associated with right-sided tumors.[2] Additionally, nontachypneic dogs and dogs with a history of lethargy have been associated with a higher risk of death during liver lobectomy to address a liver tumor than dogs without these characteristics.[6]

CLINICAL PRESENTATION

The reported mean age at presentation for hepatocellular carcinoma is 11 to 13 years.[1,10] In one study, dogs with bile duct carcinomas, sarcomas, and neuroendocrine carcinomas had a mean age at presentation of 10, 11, and 8 years, respectively; it is important to note that the bile duct carcinoma group consisted of 22 intrahepatic cholangiocellular carcinomas and 2 extrahepatic masses.[1] Males, Shih Tzus, and Yorkshire terriers have been reported to be overrepresented in cases of hepatocellular carcinoma; however, these reports vary between studies.[1,10]

Dogs often have clinical signs that could be attributed to a liver mass.[6] In some dogs, however, hepatic masses are found incidentally.[16] Historical findings can include anorexia, hyporexia, lethargy, weakness, vomiting, weight loss, diarrhea, polyuria, and polydipsia.[1,6] Clinical signs can include hepatomegaly, palpable abdominal mass, abdominal distention, abdominal effusion, abdominal pain, icterus, and increased respiratory rate or effort.[1,6,16] Ascites, diarrhea, jaundice, and weight loss may be more common in dogs with neuroendocrine carcinoma, while hepatomegaly is not typically associated with neuroendocrine carcinoma.[1] Neurologic clinical signs are less frequently reported but may include ataxia, seizures, and other signs consistent with a myelopathy; neurologic signs may be caused by hepatoencephalopathy, metastatic disease, or concurrent primary neurologic disease.[1,6]

Dogs with primary hepatic tumors can present with multiple disease processes, highlighting the importance of a thorough physical examination.[2] Hemoabdomen is uncommonly noted at the time of presentation but can be identified in dogs with various types of hepatic tumors.[6]

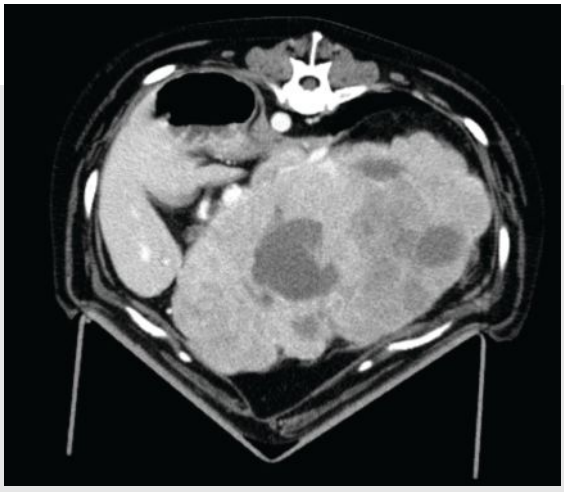

FIGURE 3. Cross-sectional computed tomography image of a right divisional liver mass.

DIAGNOSTIC TESTING

Baseline clinicopathologic diagnostic tests include complete blood count, serum chemistry profile, pre- and post-prandial bile acid assays, coagulation profile, blood typing, and urinalysis.[2,6] Thrombocytosis, anemia, and increased serum liver enzyme activities are frequently noted in dogs with massive hepatocellular carcinoma.[2] Pre- and post-prandial bile acid levels are often increased, which may be suggestive of some liver dysfunction.[2,6] Coagulation profiles are often normal, although prolonged prothrombin time and partial thromboplastin time, as well as hyperfibrinogenemia, can be noted.[6,16] Urinalysis most commonly reveals hypersthenuria and aciduria, though many variations are noted.[6]

Cytologic samples can be obtained via ultrasound-guided liver aspiration.[2] Diagnosis of some neoplasias, such as hepatocellular carcinoma, can be achieved by cytology; however, making a diagnosis can be challenging if cytologic morphology is relatively normal.[17]

Imaging modalities include abdominal radiography, ultrasonography, and computed tomography (CT) (**FIGURE 3**), as well as thoracic radiography to assess for pulmonary metastasis.[2] Both CT and ultrasonography can be used to localize solitary hepatic masses;[5] however, they should not be relied on alone to make a specific diagnosis. Various hepatic diseases can have similar ultrasonographic characteristics,[4] and dual-phase CT does not allow the distinguishing of benign and malignant liver tumors, with hepatic nodular hyperplasia, adenoma, and carcinoma all having similar imaging characteristics.[18] Triple-phase CT may be able to assist in determining if a focal liver lesion is benign or malignant, but definitive diagnosis requires histopathologic interpretation of a biopsy sample.[19] Overall, CT and ultrasonography appear to be useful for surgical planning, with a high specificity for localizing hepatic masses in all 3 divisions and high sensitivity for masses within the left division.[5]

PRESURGICAL CONSIDERATIONS

The liver is a very vascular organ. Intraoperative

hemorrhage has been reported in 25% of patients undergoing liver lobectomy, with major hemorrhage recorded as being secondary to trauma to the caudal vena cava, occurring in over 7% of cases.[2] Before surgery, coagulation profiles, blood type, and crossmatch as appropriate should be evaluated. Surgery should only be performed in facilities with access to blood products. Fortunately, an increased bleeding tendency has not been clinically observed in most dogs with liver masses.

It is important to monitor blood glucose levels during the intraoperative period. Hypoglycemia has been associated with hepatocellular carcinoma,[20] and severe metabolic deficits have been implicated as contributing to morbidity in dogs undergoing resection of approximately 70% of the liver.[21]

Most contemporary anesthetic agents are safe to use in patients undergoing liver lobectomy; however, drugs metabolized by hepatocytes (e.g., diazepam) should be avoided when possible.[22] Perioperative antibiotics are generally recommended for liver lobectomy, as intestinal bacteria and endotoxins are delivered through the portal system for hepatic clearance. An antibiotic that covers *Staphylococcus* species and enteric bacteria (*Escherichia coli*; *Enterococcus*, *Bacteroides*, and *Clostridium* species) should be chosen. The authors most commonly use cefoxitin, though there is limited direct primary literature on the subject.

Case selection for surgical candidates is based on facility-dependent factors as well as patient-dependent ones, with the former including clinician surgical experience and knowledge of liver anatomy. An appropriate knowledge base is critical to reduce complications associated with liver surgery, and referral should be pursued as appropriate based on clinical knowledge and skill level.[9] If partial or total liver lobectomy is to be performed, 24-hour patient monitoring is recommended based on the potential for life-threatening complications in the immediate postoperative period.[6,16]

SURGERY

Patient Preparation

The patient should be clipped for a routine abdominal celiotomy, but clipping should extend cranial to the thorax and be wide laterally in case extension of the incision into a sternotomy becomes necessary during surgery. The patient is positioned in dorsal recumbency and draped wide for possible extension of the incision. Additional hepatobiliary exposure can be achieved intraoperatively by performing a diaphragmotomy, although this procedure should be undertaken cautiously in light of its associated risks (e.g., pneumothorax).[23]

Liver Lobectomy

The incision should extend from the xyphoid to the pubis for adequate exposure and manipulation of the liver mass. A complete abdominal exploratory should be done routinely. A partial liver lobectomy can be performed for smaller or more peripheral masses. Complete liver lobectomy is generally performed for larger masses (**FIGURE 4**). Transection of the triangular ligaments aids in mobilization of the liver lobes to allow excision. The lobe with the associated mass is exposed and isolated. Lobectomy is then performed using one of the following techniques.

Blunt Dissection and Vessel Ligation

The liver capsule is incised and the liver parenchyma bluntly dissected using the blunt end of a scalpel handle or the inner cannula of a Poole suction tip to expose and isolate larger blood vessels and bile ducts. Hemostasis can be achieved for smaller vessels using

FIGURE 4. Massive liver mass removed via lobectomy.

Using a surgical stapling device eliminates the need for extensive dissection and isolation of hepatic vessels.

electrocoagulation or surgical clips (hemoclips or Surgiclips [Covidien, medtronic.com]). Larger vessels may need to be ligated.

This dissection technique is slower, less complete, and associated with more hemorrhage than the use of an electrosurgical vessel-sealing device (LigaSure; Covidien, medtronic.com) or ultrasonic scalpel (Ultracision Harmonic Scalpel; Ethicon, ethicon.com). These devices can minimize hemorrhage and lead to shorter surgical times compared with a finger-fracture method.[7]

Surgical Stapling Device

Using a surgical stapling device (Autosuture TA 90, 55, 30; Covidien, medtronic.com) eliminates the need for extensive dissection and isolation of hepatic vessels. The stapling device can be placed across the base of the lobe and the staples deployed. The hepatic parenchyma is then excised distal to the staples with a scalpel or electrosurgical vessel-sealing device.

A narrow (30-mm long) vascular cartridge with small staples (2.5-mm legs, closing to 1-mm diameter) in 3 rows is ideal to achieve maximal hemostasis, but its use should be limited to smaller patients or cases where a more narrow lobar base can be isolated. A 3.5-mm staple that closes to a 1.5-mm inverted B configuration can be used for excision of a liver mass with a wider, thicker base. With this staple, vessels smaller than 1.5 mm may continue to bleed, requiring additional hemostasis (electrocautery or clips).

Self-Ligating Loop

The use of a self-ligating loop has been reported for partial or complete liver lobectomy.[24] It was shown to be effective and associated with low morbidity and mortality rates, and it can be a more economical option since the loop is approximately one-third the cost of a stapler cartridge.

Overlapping Mattress Sutures

The overlapping mattress suture technique has been used for partial lobectomies and for removal of peripherally located masses.[6,25] The technique involves placing 2 overlapping rows of horizontal mattress sutures around the area to be excised, with the sutures tightened to ligate the vasculature within the liver parenchyma; the liver can then be transected within the boundaries of the sutures, or a blunt dissection with vessel ligation technique (as described above) can be performed.[25]

Additional Considerations

Regardless of the surgical technique used, additional hemostasis can be achieved after liver lobectomy by placing topical hemostatic agents such as a gelatin sponge (Gelfoam; Pfizer, pfizer.com) or oxidized regenerated cellulose (Surgicel; Johnson & Johnson, jnjmedicaldevices.com) on the remaining cut surface of the liver parenchyma.

A laparoscopic approach, providing access to the hilar region of all liver lobes, has been described as allowing adequate evaluation of the liver; however, to the authors' knowledge, there is no current description of a laparoscopic approach for performing a liver lobectomy in dogs.[26] It has been proposed that resection of large liver masses may result in a higher incidence of gastric dilatation–volvulus; a recommendation for a prophylactic gastropexy based on case-specific information may be warranted, as in dogs undergoing splenectomy.[27]

ALTERNATIVE MANAGEMENT TECHNIQUES

Development of nonsurgical management techniques is needed for unresectable liver tumors, such as diffuse and nodular forms.[15] Hepatic chemoembolization and intra-arterial chemotherapy using minimally invasive interventional radiology have been proposed;[28] however, the true benefits of these treatments are yet unknown.

Little literature exists regarding the use of chemotherapeutic agents for dogs with incompletely excised, nonresectable, or metastatic hepatocellular carcinoma.[14] While significant research is still needed, designing therapeutics to specifically target aberrant

microRNA and gene expression is a potential avenue to develop new medical treatments for hepatocellular carcinoma.[11] Radiation therapy traditionally has not had a significant role in the management of inoperable liver tumors; however, 3D conformal radiation therapy, which allows targeting of a high dose of radiation to the area of interest, has demonstrated some promise, with 5 of 6 dogs with massive hepatocellular carcinoma that was deemed nonresectable having an objective response in a case series.[29]

While stem cell therapy has been considered as a potential treatment for a variety of disease processes, soluble factors from adipose tissue–derived mesenchymal stem cells may actually promote proliferative as well as invasive characteristics of hepatocellular carcinoma based on in vitro studies.[15]

The feasibility of microwave ablation, which uses thermal energy to cause cell death, has been demonstrated in a case series that included 2 dogs with primary hepatic tumors; both underwent laparotomy with subsequent microwave ablation.[30] A laparoscopic approach for microwave ablation was recently demonstrated to be possible in a clinical setting in a case report including a dog with primary hepatocellular carcinoma.[26] Further studies are needed to evaluate the indications and clinical outcomes of dogs undergoing microwave ablation.

POSTOPERATIVE CARE

Many postoperative care decisions are based on addressing concerns associated with the specific patient, and the level of care needed can vary widely; however, hospitalization with 24-hour monitoring is recommended during the immediate postoperative period for all patients.[2,16,21] It is important to monitor the dog's perfusion parameters as well as perform serial blood work assessment to aid in the postoperative treatment plan.

Complications of liver lobectomy include hemorrhage, vascular compromise to adjacent liver lobes, transient hypoglycemia, and reduced hepatic function. Appropriate understanding of the blood supply and biliary drainage of the canine liver can help reduce the likelihood of some complications, such as devascularizing liver tissue and hemorrhage.[9]

The prognosis is good for dogs with massive hepatocellular carcinoma, with median survival times of more than 1460 days, a 0% to 6% local tumor recurrence rate, and a 0% to 37% distant metastatic rate. Neither size of tumor nor microscopically complete resection is prognostic.[2] The liver has an enormous capacity for regeneration. Up to three-quarters of the liver can be removed without ill effect, provided the function of the remaining liver is uncompromised. Within 6 to 8 weeks, hypertrophy and hyperplasia will result in significant enlargement of the remaining parts of the liver. TVP

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CONTINUING EDUCATION

Surgical Management of Canine Liver Masses

LEARNING OBJECTIVES

This article provides information on canine liver tumors as well as an overview of the clinical presentation, diagnostic plan, presurgical considerations, surgical treatment options, and postoperative care for dogs undergoing a liver lobectomy for primary liver tumors.

TOPIC OVERVIEW

After reviewing this article, readers should be able to describe normal liver anatomy, name common liver tumors and their associated characteristics, list common surgical techniques for liver lobectomy, and discuss perioperative considerations as well as prognosis.

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1. **Which of the following can be a primary hepatic tumor?**
   a. Hepatocellular carcinoma
   b. Cholangiocellular carcinoma
   c. Neuroendocrine carcinoma
   d. All of the above

2. **Which statement regarding liver anatomy is false?**
   a. The liver consists of 7 lobes.
   b. The gallbladder lies within the gallbladder fossa between the quadrate and right medial lobes.
   c. The liver has blood supplied by the hepatic artery and portal vein.
   d. Biliary collection is through 3 or 4 major divisional ducts emptying into the common bile duct.

3. **Which statement regarding hepatocellular tumors is false?**
   a. Hepatocellular adenomas are benign masses.
   b. Hepatocellular tumors are the most common primary hepatic tumors in dogs.
   c. Hepatocellular carcinoma can be divided into massive, nodular, and diffuse morphologic distributions.
   d. Massive hepatocellular carcinoma tumors most commonly arise from the right lateral liver lobe.

4. **Which statement regarding liver tumors is false?**
   a. Cholangiocellular tumors arise from hepatocytes.
   b. Cholangiocellular carcinomas can be divided into massive, nodular, and diffuse morphologic distributions.
   c. Primary hepatic neuroendocrine tumors arise from cells in the biliary epithelium.
   d. Sarcomas are potential primary malignant tumors of the liver.

5. **Which statement regarding surgical indications for liver tumors is false?**
   a. Surgery is the treatment of choice for massive, solitary liver tumors.
   b. Surgery for left-division tumors is generally less technically challenging than right- or central-division lobectomies.
   c. Biliary carcinomas are suspected to have a better prognosis than hepatocellular carcinomas.
   d. Increased serum alanine aminotransferase and aspartate aminotransferase activities are considered a negative prognostic indicator for dogs undergoing surgery for massive hepatocellular carcinoma.

6. **Which statement regarding the clinical presentation for dogs with liver tumors is false?**
   a. The mean age of dogs presenting for hepatocellular carcinoma is 11 to 13 years.
   b. Masses may be found incidentally.
   c. Hemoabdomen is commonly noted at the time of presentation.
   d. Potential clinical signs include hepatomegaly, abdominal distention, icterus, and seizures.

7. **Which statement regarding the diagnosis of liver tumors is false?**
   a. Pre- and post-prandial bile acid levels are often increased in patients with liver tumors.
   b. A definitive diagnosis of neoplasia can always be achieved on cytology of liver aspirates.
   c. Computed tomography and ultrasound can be used for localizing solitary hepatic masses.
   d. Ultrasound imaging alone should not be used for diagnosis.

8. **Which statement regarding presurgical planning is false?**
   a. Blood products should be readily available due to the risk of hemorrhage.
   b. Hypoglycemia has been associated with hepatocellular carcinoma.
   c. Perioperative antibiotics are typically not indicated.
   d. Most contemporary anesthetic agents are safe to use for patients undergoing liver lobectomy.

9. **Which statement regarding surgical intervention for liver lobectomy is false?**
   a. Diaphragmotomy can be used to increase hepatobiliary exposure.
   b. A partial liver lobectomy can be performed for smaller or more peripheral masses.
   c. Blunt dissection and vessel ligation is generally considered to be slower, less complete, and associated with more hemorrhage compared with other techniques.
   d. The use of a self-ligating loop has been demonstrated to be inferior to other techniques such as stapling.

10. **Which statement regarding postoperative care and management is false?**
    a. Complications include hemorrhage, vascular compromise to adjacent liver lobes, transient hypoglycemia, and reduced hepatic function.
    b. Patients undergoing surgery for massive hepatocellular carcinoma have a median survival time of more than 1400 days.
    c. Up to three-quarters of the liver can be removed without complication provided that the function of the remaining liver is uncompromised.
    d. Massive hepatocellular carcinoma has a local tumor recurrence rate of 30% to 40%.