Morphological classification of neoplastic disorders of the canine and feline liver

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ABSTRACT

Hepatic neoplastic disorders in dogs and cats can be classified as 1. nodular hyperplasia, 2. primary epithelial hepatic neoplasia including hepatocellular adenoma, hepatocellular carcinoma, cholangiocellular adenoma, cholangiocellular carcinoma, cholangiolocarcinoma (dog), neuroendocrine carcinoma (dog) and small cell carcinomas either with neuroendocrine or hepatic progenitor cell characteristics (cat), 3. primary vascular and mesenchymal neoplasia of the liver, 4. hemopoietic neoplasia, and 5. metastatic neoplasia.

INTRODUCTION

Hepatic progenitor cells (HPC) are multipotent cells located within the liver's stem cell compartment, the ductal plates of fetal and neonatal livers, and canals of Hering in pediatric and adult livers [1,2,3,4,5]. They are the only non-parenchymal liver cells with both the capacity for self-renewal as well the capacity to generate numerous reactive precursor cells, committed progenitors and their descendants. These become, governed by their mesenchymal microenvironment, mature hepatocytes and cholangiocytes [6,7]. They may also demonstrate autonomous growth and develop into primary hepatic neoplasms, where depending on the presence of further maturation and differentiation various morphological entities may be seen.

Over the past decade, many advances have been made in the characterisation of primary liver tumours in man, in particular regarding the identification of HPC and their prognostic significance in hepatocellular tumours [4,5,8]. A comparable finding with regard to the presence and prognostic significance of hepatic progenitor cells was made in primary hepatocellular tumours in dogs [9]. More recently, the role of hepatic progenitor cells in the development and differentiation of the various forms of intrahepatic cholangiocellular tumours in man has been elucidated [10]. This knowledge has resulted in a proposal for a morphological and immunohistochemical classification of primary liver tumours in man [10,11], which facilitates the diagnosis and categorisation of these tumours including their aggressiveness and prognosis.

Recently, primary epithelial hepatic neoplasms in dogs and cats have been morphologically and immunohistochemically classified and differentiated in a similar system that includes hepatic

progenitor cells [12,13]. The various morphological types of primary epithelial hepatic neoplasms in the dog is in accordance with the recent classification scheme in humans. Although overlapping features exist between canine and feline neoplasms, there are also marked morphological and immunohistochemical differences present between the canine and feline primary epithelial neoplasms. Therefore the feline primary epithelial hepatic neoplasms are classified and described separately. For the immunohistochemical differentiation, markers representative of hepatocytic and cholangiocytic lineages as well as HPC and neuroendocrine markers were used (Table 1) [12,13].

Table 1. Markers used for immunohistochemical differentiation of primary epithelial hepatic neoplasms in the dog and cat

Markers	Hepatocellular	Cholangiocellular	HPC	Neuroendocrine
Dog	**HepPar-1** cytoplasmic	**K19** cytoplasmic-membranous	**K19** cytoplasmic	**Cg-A** cytoplasmic
	CD10 canalicular	**EMA/MUC-1** cytoplasmic		**NSE** Cytoplasmic
	K19 *Intermediate hepatocyte* submembranous	**CD10** apical / cytoplasmic		
Cat	**HepPar-1** cytoplasmic	**K19** cytoplasmic-membranous	**K19** cytoplasmic	**Cg-A** cytoplasmic
	MRP2 canalicular	**pCEA** apical / cytoplasmic		**NSE** cytoplasmic
	pCEA canalicular			
	K19 **Intermediate hepatocyte** Submembranous			

Cg-A, chromogranin-A; K19, keratin 19, NSE, neuron-specific enolase; MRP2, multidrug resistance-associated protein 2; pCEA, polyclonal carcinoembryonic antigen; EMA/MUC-1, epithelial membrane antigen/mucin-1.

The neoplastic disorders of the liver in dogs and cats can be classified as:

1 Primary epithelial hepatic neoplasia in the dog
   a. Hepatocellular adenoma
   b. Hepatocellular carcinoma
   c. Scirrhous hepatocellular tumour
   d. Cholangiocellular adenoma
   e. Cholangiocellular carcinoma
   f. Cholangiolocarcinoma
   g. Neuroendocrine carcinoma

2 Primary epithelial hepatic neoplasia in the cat
   a. Hepatocellular adenoma
   b. Hepatocellular carcinoma
   c. Cholangiocellular adenoma
   d. Cholangiocellular carcinoma
   e. Small cell carcinoma
      i. Neuroendocrine carcinoma
      ii. Small cell carcinoma with HPC characteristics

3 Mixed hepatocellular and cholangiocellular carcinoma
4 Hepatoblastoma
5 Primary hepatic vascular and mesenchymal neoplasia
6 Hematopoietic neoplasia
7 Metastatic neoplasia

Nodular hyperplasia

Nodular hyperplasia is a non-neoplastic, benign hepatocellular proliferation and a common disorder in older dogs, but occurs less often in cats [14,15]. The incidence increases with age and most of the dogs above the age of 10 years have multiple hyperplastic nodules. The hyperplasia can be found as single or as multiple nodules which can range in size from 0.2 – 3.0 cm diameter (Fig. 1). Nodular hyperplasia is encountered often as an incidental finding during laparotomy or at postmortem examination [16,17]. Histologically, the lesion presents as a non-encapsulated nodule with a rather well retained lobular arrangement, consisting of bi-layered cords of well-differentiated hepatocytes and slight compression of the surrounding parenchyma (Fig. 2). Portal areas may be present within or at the periphery of the nodule, depending on the size of the nodular hyperplasia and its origin within the lobule. The nodules often show focal or diffuse lipidosis or glycogen accumulation of the hepatocytes. Nodular hyperplasia should be distinguished from regenerative nodules as seen in macronodular cirrhosis of the liver. In macronodular cirrhosis affected livers are grossly characterised by collapsed fibrotic areas and multiple nodules of varying size ranging from 0.2 to several centimeters in diameter.

Immunohistochemically, nodular hyperplasia shows a cytoplasmic positivity of hepatocytes for HepPar-1, and a canalicular staining for CD10 in the dog and for MRP2 and pCEA in the cat, but are negative for K19.

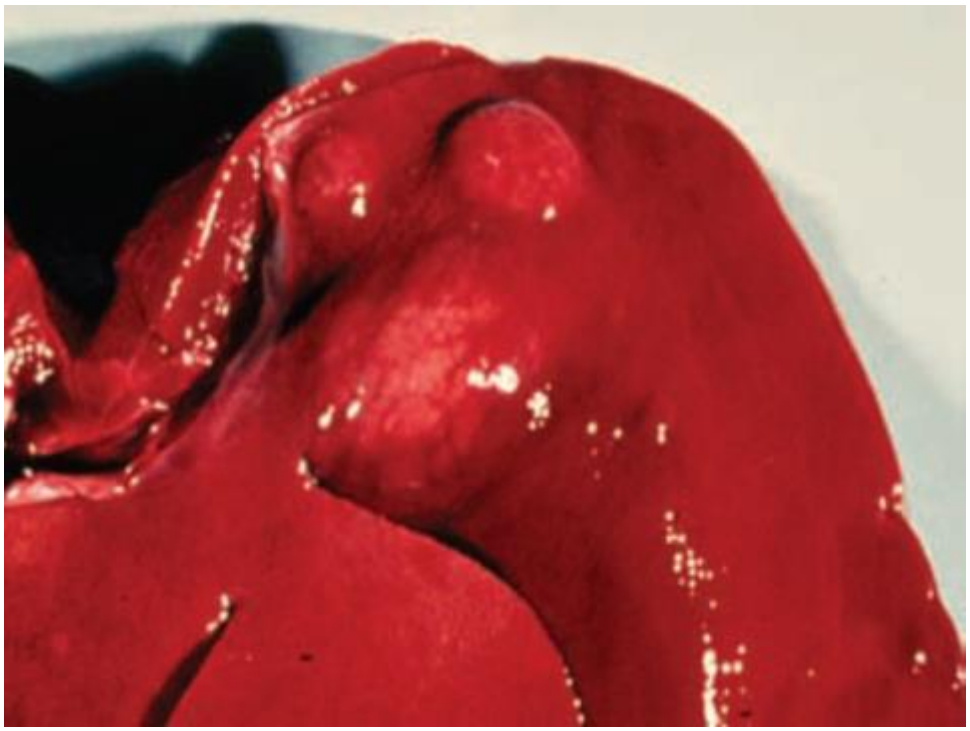


Fig. 1. Dog. Nodular hyperplasia. (Reproduced from Mouwen JMVM, De Groot ECBM, eds. Atlas of veterinary pathology. Utrecht: Bunge; 1982)

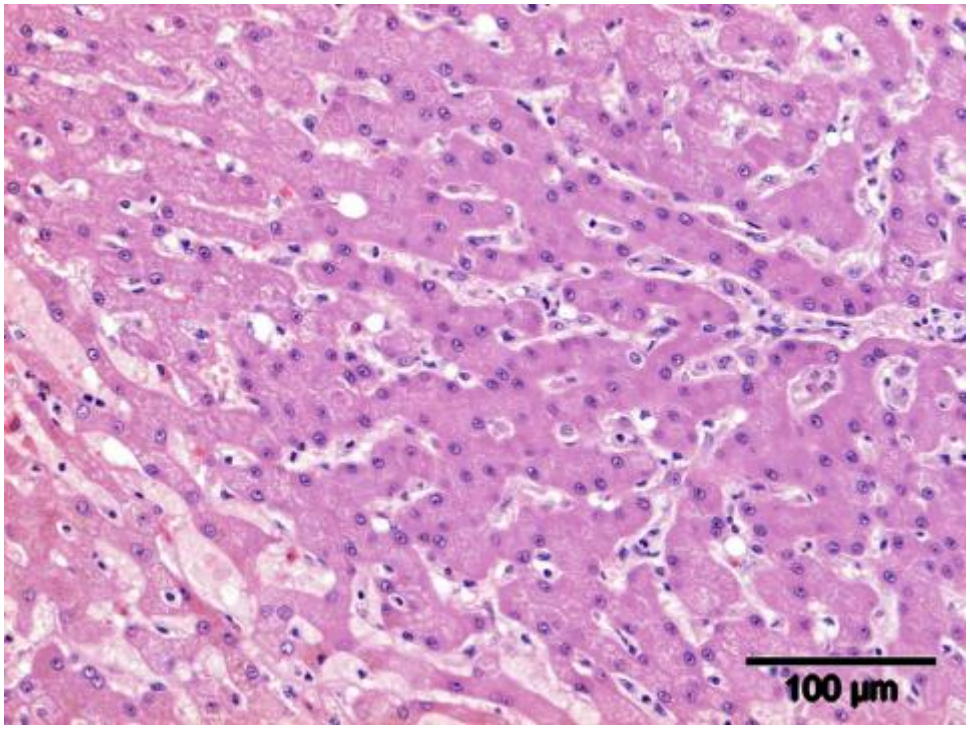


Fig. 2. Dog. Nodular hyperplasia. Non-encapsulated nodule of double layered cords of hepatocytes. HE.

Primary epithelial hepatic neoplasia in the dog [12]

Primary epithelial liver tumours in dogs are relatively rare and represent only 0.6-1.5% of all tumours in dogs; affected animals are mostly older dogs. In the dog no predisposing factors are known, and in almost all canine primary liver tumours no additional liver pathology is present [12].

Hepatocellular adenoma

Hepatocellular adenomas [14,15,18] are rather common in the dog. They are usually restricted to one or two liver lobes and consist of friable pale tumours that closely resemble normal liver tissue. Histologically, these tumours are well demarcated, often encapsulated and lack portal tracts and bile ducts. They consist of broad trabeculae of well-differentiated hepatocytes (Fig. 3), separated by sometimes markedly dilated sinusoids and cystic blood and/or serum filled spaces. The hepatocytes have no or limited cellular pleomorphism, the nuclei are similar to those in normal hepatocytes, but nucleoli may be more prominent. Mitotic figures are absent or rare. Often focal or more extensive areas with macrovesicular or mixed type lipidosis or marked glycogen accumulation of the neoplastic hepatocytes are observed; also areas of necrosis may be present. Sometimes foci of extramedullary hemopoiesis and Fe-pigment containing macrophages can be seen.

Immunohistochemically, hepatocellular adenomas show marked cytoplasmic positivity of hepatocytes for HepPar-1 and a canalicular staining for CD10. In some tumours few hepatocytes with slight cytoplasmic or submembranous positivity for K19 (< 5%) can be seen but most of the hepatocellular adenomas are negative for K19. Some positivity for NSE and Cg-A can occasionally be seen in hepatocellular adenomas, but they are negative for EMA/MUC-1.

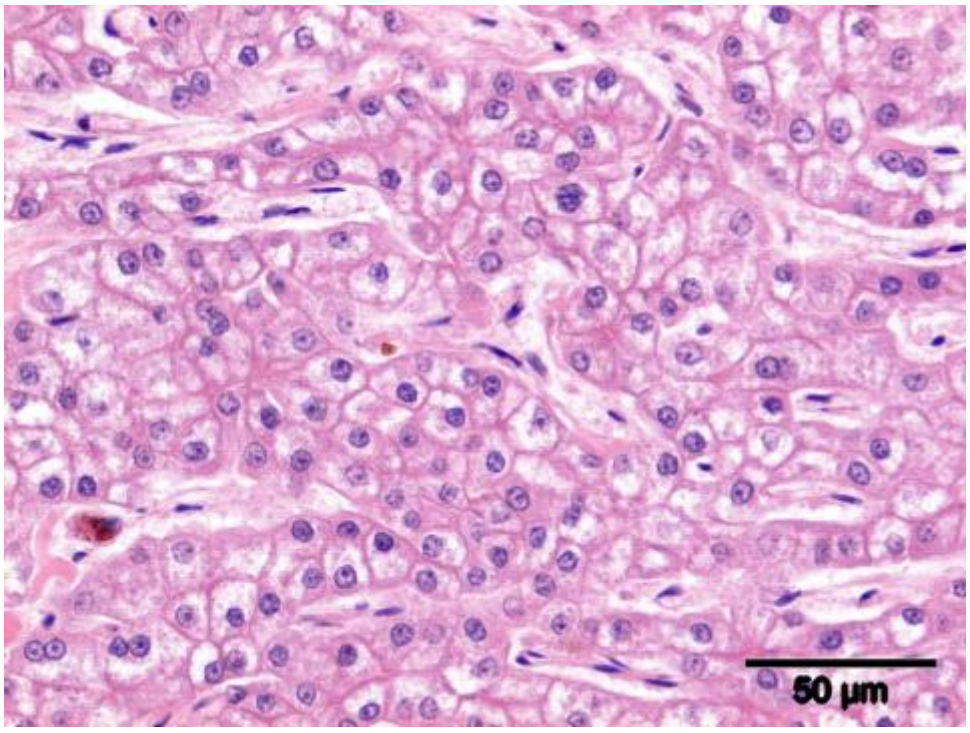


Fig. 3. Dog. Hepatocellular adenoma. Broad trabeculae of well-differentiated hepatocytes with a uniform appearance. HE.

Hepatocellular carcinoma

Hepatocellular carcinomas represent about 20% of all hepatocellular tumours in the dog and usually present as a nodular or diffusely affected liver (Fig. 4) [12]. Histologically, they form irregular trabeculae of relative small cells, compared to normal hepatocytes, and are poorly differentiated with marked cellular and nuclear pleomorphism, and many mitotic figures (Fig. 5). They show marked infiltrative growth, exhibit lymphatic and vascular invasion in portal tracts and have intrahepatic and very often distant metastases.

Immunohistochemically they have all the characteristics of tumours derived from HPC as they show extensively (40-100%) and marked cytoplasmic staining for K19 (Fig. 6), stain negative or rarely and then only locally positive for HepPar-1, and are negative for CD10 and EMA/MUC1. Positive staining for NSE and Cg-A of single or small groups of tumour cells can occasionally be seen.

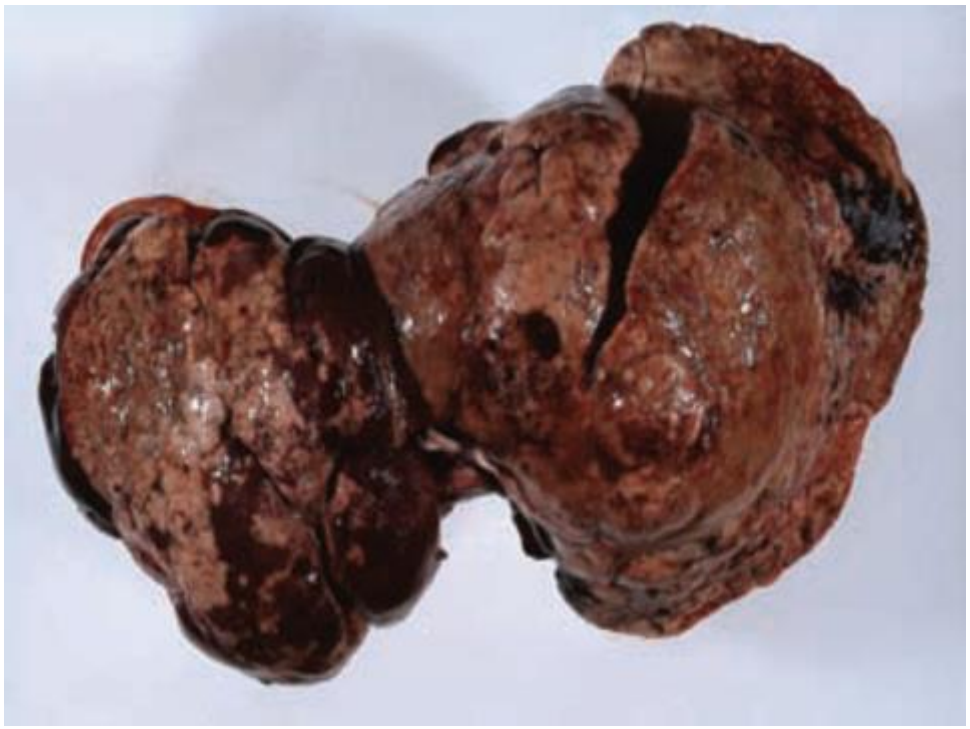


Fig. 4. Dog. Hepatocellular carcinoma

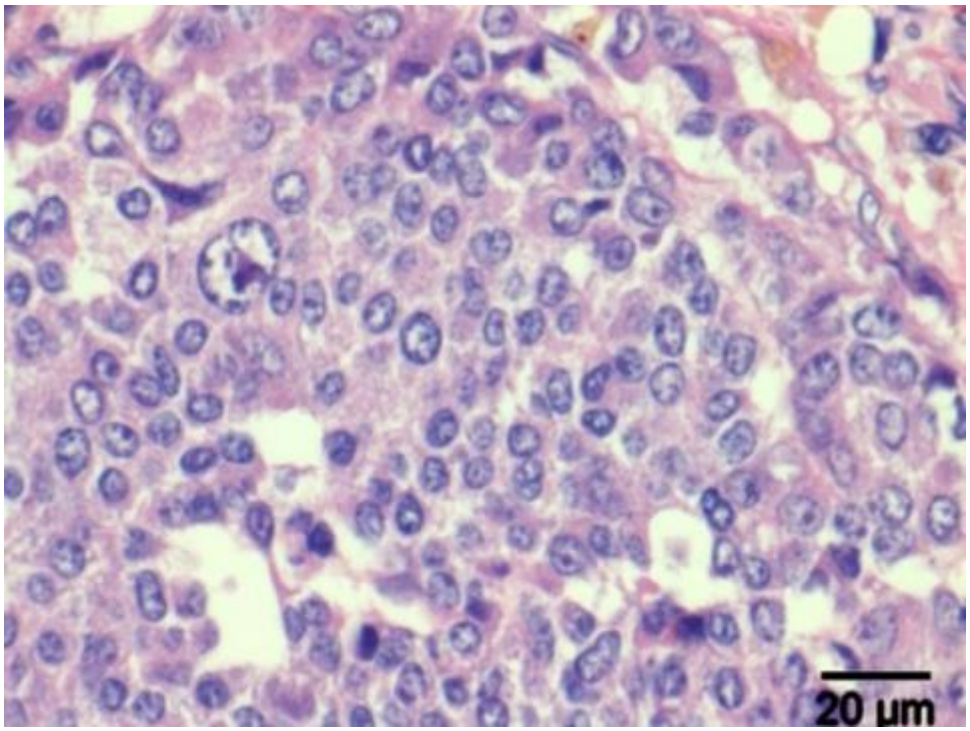


Fig. 5. Dog. Hepatocellular carcinoma. Relatively small undifferentiated tumour cells. HE.

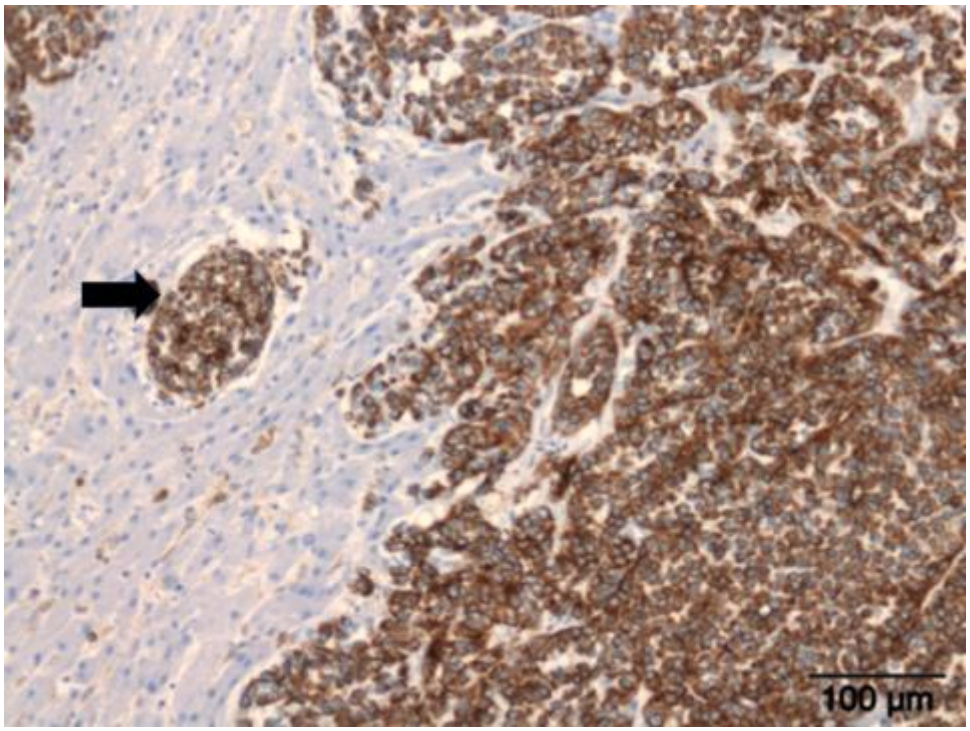


Fig. 6. Dog. Hepatocellular carcinoma with infiltrative growth and intravascular metastasis (arrow). Marked cytoplasmic staining of tumour cells. K19.

The canine hepatocellular tumours which do not express K19 or have less than 5% positivity for K19 in principle have a benign character [(12)]. However, one of the authors with a longstanding experience in liver pathology (TvdI) has once seen an exceptional case with a well differentiated hepatocellular tumour, which proved HepPar-1 positive and K19 negative and had metastasized to

the lungs; also the metastasis was HepPar-1 positive and K19 negative. In addition, it cannot be excluded that in progression of the disease a tumour with less than 5% K19 staining might develop increased K19 positivity and hence conceive malignant characteristics.

Scirrhous hepatocellular tumour

Scirrhous hepatocellular tumours are very rare and have an intermediate position with respect to histomorphology and immunohistochemistry and probably prognosis. They present as large solitary structures that resemble normal liver tissue. These hepatocellular tumours mainly consist of trabecular structures of well-differentiated hepatocytes similar to a hepatocellular adenoma, and multifocal areas with a fibrous stromal component and ductular structures, whereby the trabecular areas are continuous with the ductular structures (Fig. 7)[12].

Immunohistochemically, the trabecular areas are positive for HepPar-1 and CD10, but negative for K19. The ductular structures in the areas of fibrosis are positive for K19 (Fig. 8) and NSE, but negative for HepPar-1 and CD10. In two out of three tumours described, the ductular/fibrotic areas were well circumscribed and present within the well-differentiated trabecular component [12]. In one tumour the ductular component had infiltrative growth suggesting malignant transformation. A similar morphological entity has been described in humans as scrirrhous hepatocellular carcinoma, in which the stromal proliferation possibly drives the K19 positive ductular differentiation [6].

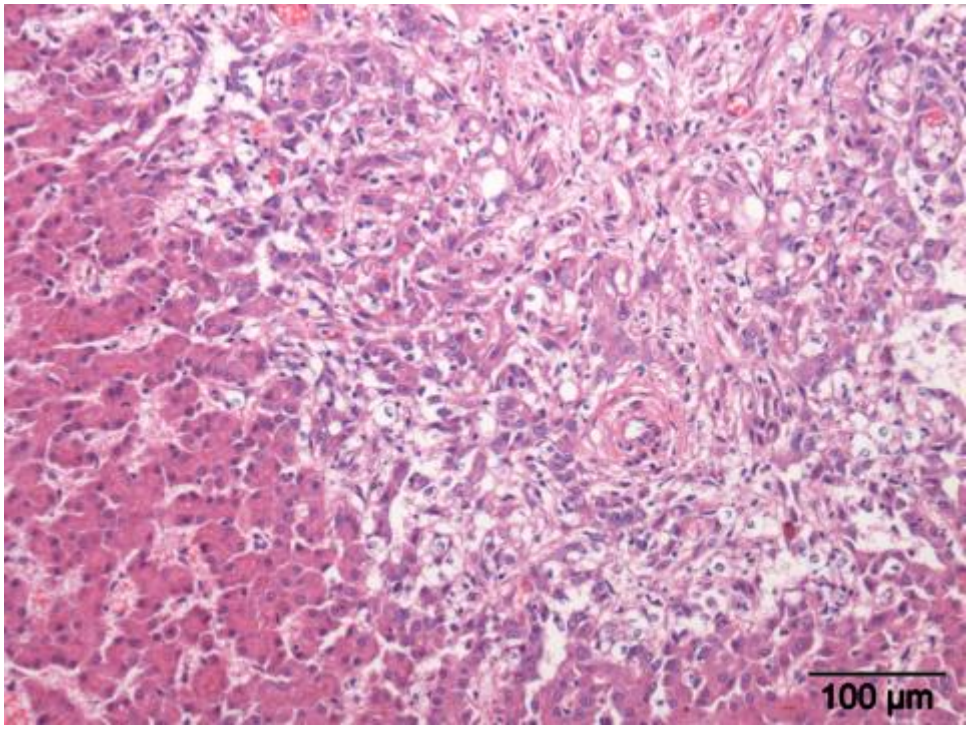


Fig. 7. Dog. Scirrhous hepatocellular tumour. Trabecular area with transition to ductular structures in fibrotic tissue. HE.

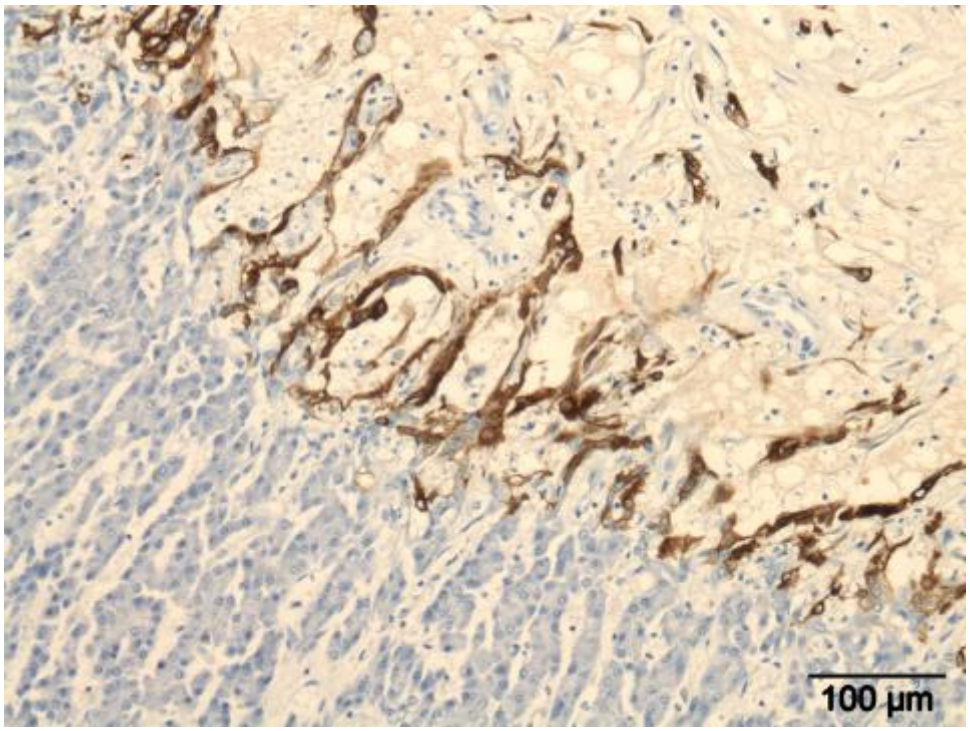


Fig. 8. Dog. Scirrhous hepatocellular tumour. Positive ductular structures in fibrotic area with negative staining hepatocytes in trabecular area. K19

Cholangiocellular adenoma

Cholangiocellular adenomas are solitary, well circumscribed tumours composed of biliary epithelial cells. Cholangiocellular adenomas are extremely rare in dogs [14,15]. They show expansive growth and consist of slightly dilated, occasionally cystic structures lined with cuboidal or flattened well-differentiated biliary epithelium. They should be differentiated from unilocular or multilocular cysts or Von Meyenburg complexes as seen in congenital cystic 2disease of the liver. These cystic lesions, (which are often mistaken for cholangiocellular adenomas), typically show irregular cystic spaces lined with cuboidal to flattened epithelium, varying amounts of fibrous tissue, and often islands of hepatocytes that are interspersed between the cysts.

Cholangiocellular carcinoma

Cholangiocellular carcinomas are malignant neoplasms of biliary epithelium and usually arise from the intrahepatic bile ducts. They are relatively rare in dogs [14,15,18,19] and may occur as a large single mass, but often present as multiple irregularly formed tumour nodules. They have a whitish appearance and firm consistency and often show central umbilication (Fig. 9). Microscopically they are monomorphic with an acinar, ductular and/or papillary growth pattern (Fig. 10) and often are associated with marked fibroplasia. The neoplastic cells are cuboidal to columnar, with a relative small amount of cytoplasm, and usually there is marked cellular and nuclear pleiomorphism and mitotic figures are encountered regularly. In well differentiated areas in the lumen of the cholangiocellular carcinoma mucin may be detected. The margins of the tumour clearly show invasion of tumour cells in the surrounding parenchyma. Spread within the liver particularly results from metastases along the portal lymphatics and the portal vein. Metastases to the regional (hepatic) lymph nodes as well as distant metastases are frequently seen.

Cholangiocellular carcinomas may also arise from the extrahepatic bile ducts and, apart from metastases, may cause obstruction of the common bile duct and thus extrahepatic cholestasis.

Immunohistochemically, cholangiocellular carcinomas are positive for K19 with a cytoplasmic-membranous staining pattern (Figure 11) and are also strongly positive for EMA/MUC-1 with an apical membranous and/or diffuse cytoplasmic staining pattern; they are negative for HepPar-1. Some of the cholangiocellular carcinomas show some positivity for CD10, but most of these tumours are negative for this marker. Cytoplasmic staining for EMA/MUC-1, as seen in most cholangiocellular carcinomas, suggests that these tumours are derived from differentiated mucin producing cholangiocytes, which are normally present in the larger bile ducts. Apical membranous staining for EMA/MUC-1 as well as positive staining for CD10 suggest a ductular origin as in the normal liver only the smallest bile ducts show apical membranous staining for EMA/MUC-1 and stain for CD10. In some cholangiocellular carcinomas some positivity for NSE can be observed.

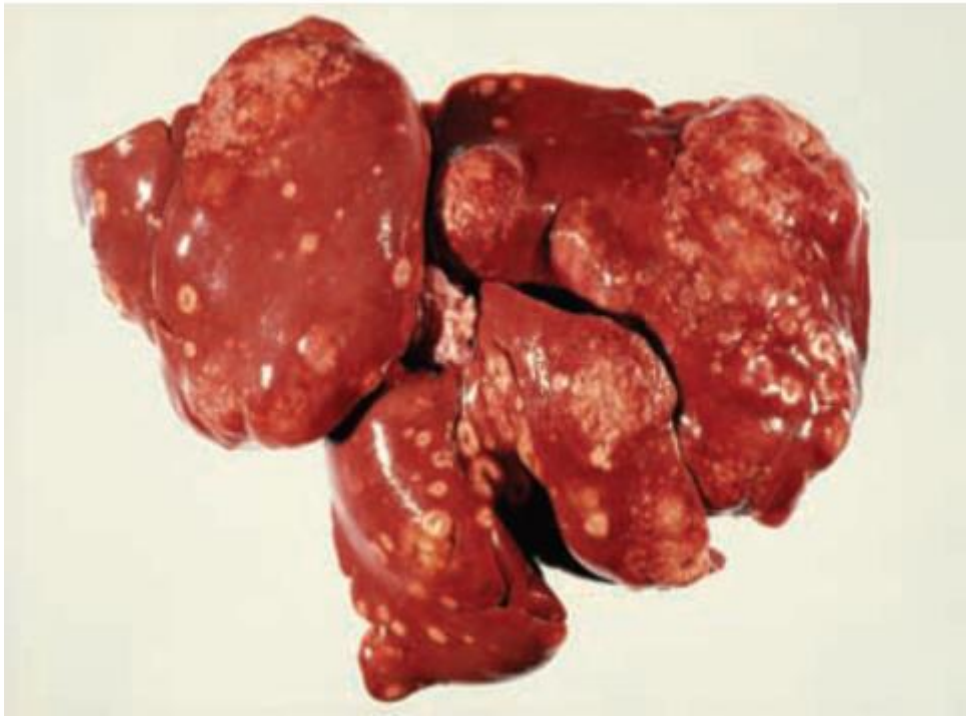


Fig. 9. Dog. Cholangiocellular carcinoma. Multiple irregularly formed tumours, often showing central umbilication

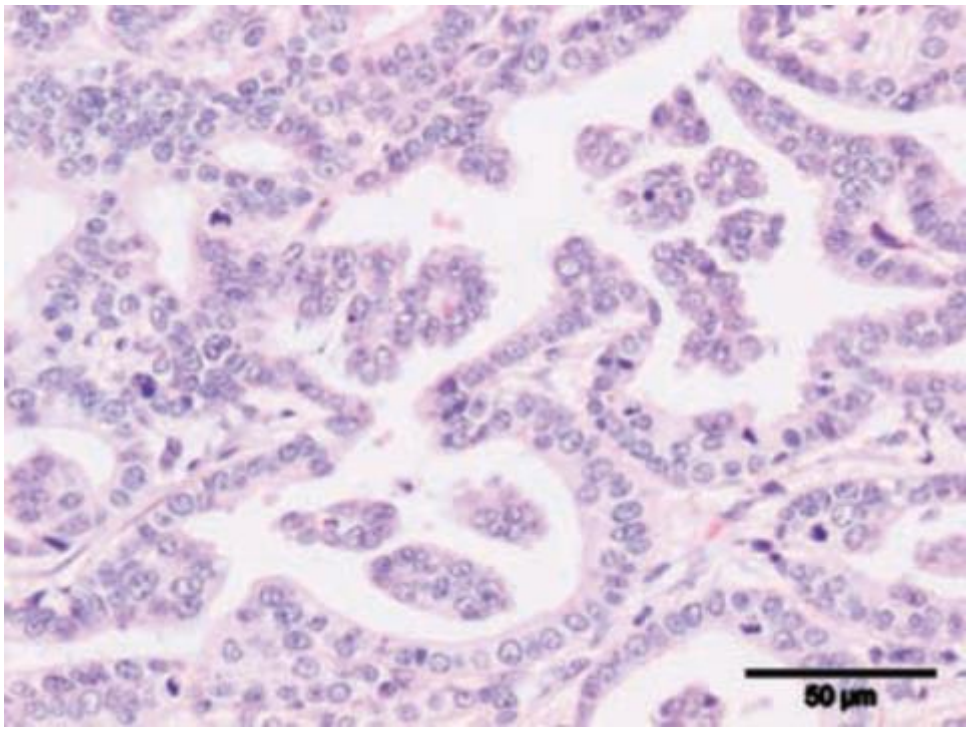


Fig. 10. Dog. Cholangiocellular carcinoma. Papillary growth of rather well-differentiated bile duct epithelium with multiple mitotic figures. HE.

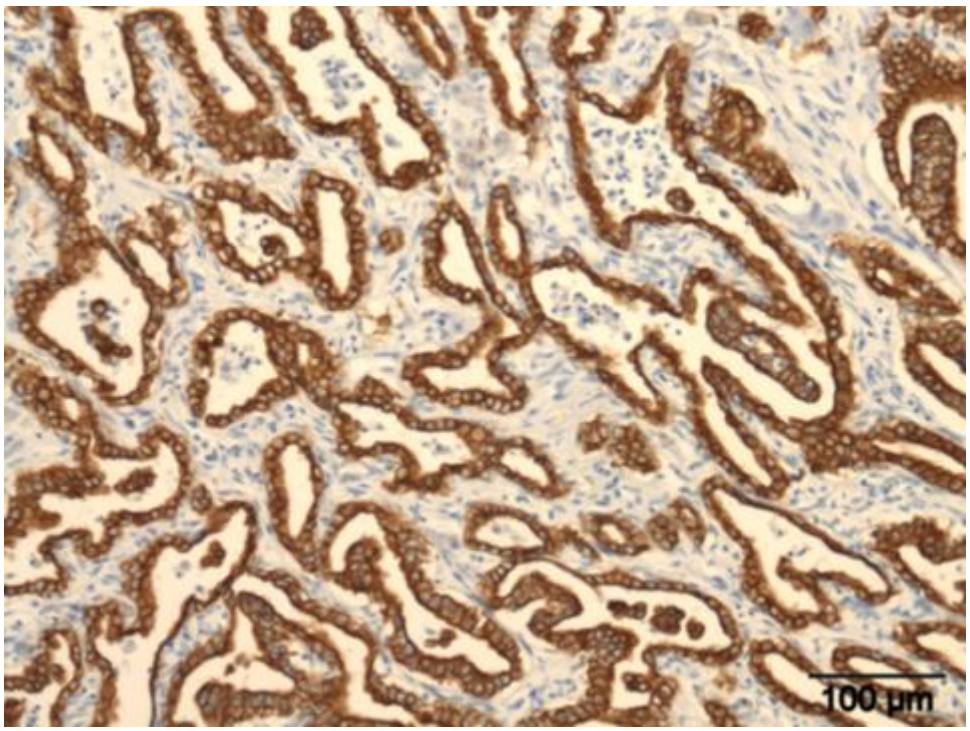


Fig. 11. Dog. Cholangiocellular carcinoma with marked fibroplasia. Marked cytoplasmic and membranous staining of neoplastic epithelium. K19.

Cholangiolocarcinoma

Cholangiolocarcinoma is a very rare malignant tumour in the dog with a different morphological and immunohistochemical pattern in comparison with the cholangiocellular carcinomas. The tumour is characterised by a combination of, usually centrally located, tubular structures with or without fibrosis, and solid areas with a more hepatocellular appearance (Fig. 12). They show moderate to marked cellular and nuclear pleomorphism and have a high mitotic activity. Intrahepatic metastases, metastases to the regional (hepatic) lymph nodes as well as distant metastases are seen.

Immunohistochemically, the tubular areas of the cholangiolocarcinoma show cytoplasmic and membranous staining for K19 (Fig. 13) and an apical and/or cytoplasmic staining for EMA/MUC-1 and CD10. The solid hepatocyte-like areas show a moderate cytoplasmic staining for K19 (Fig, 13), a focal cytoplasmic staining for Cg-A and are negative for EMA/MUC-1 and CD10. The appearance of the cholangiolocarcinoma is suggestive for bidirectional differentiation of neoplastic HPC to hepatocytes and cholangiocytes [10,11].

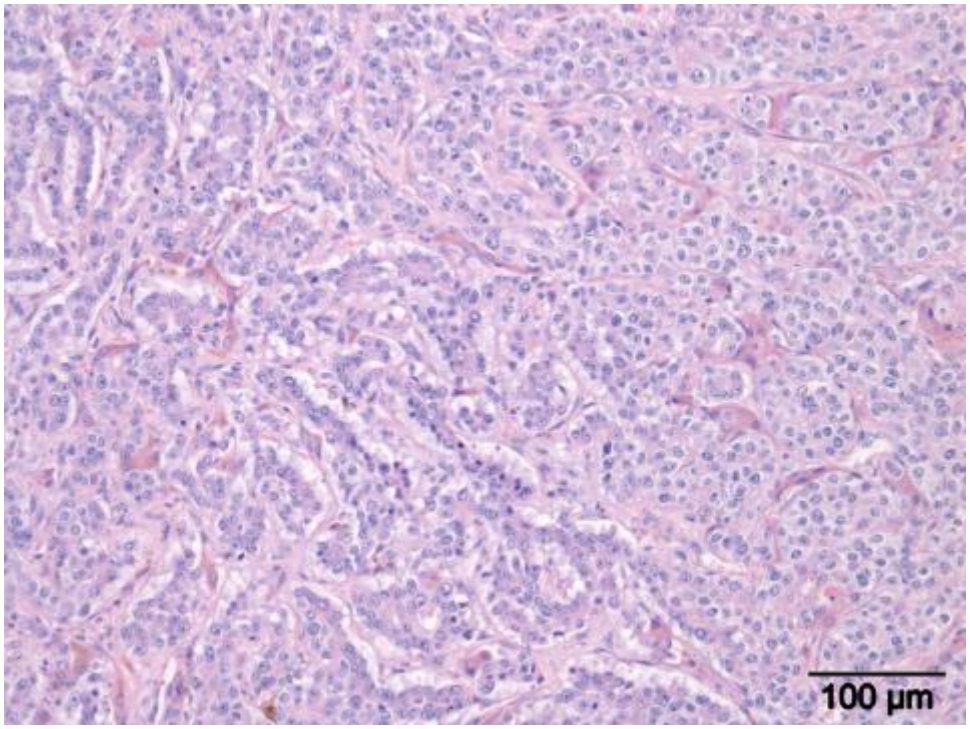


Fig. 12. Dog. Cholangiolocarcinoma. Tubular area (left) and sold area (upper right). HE.

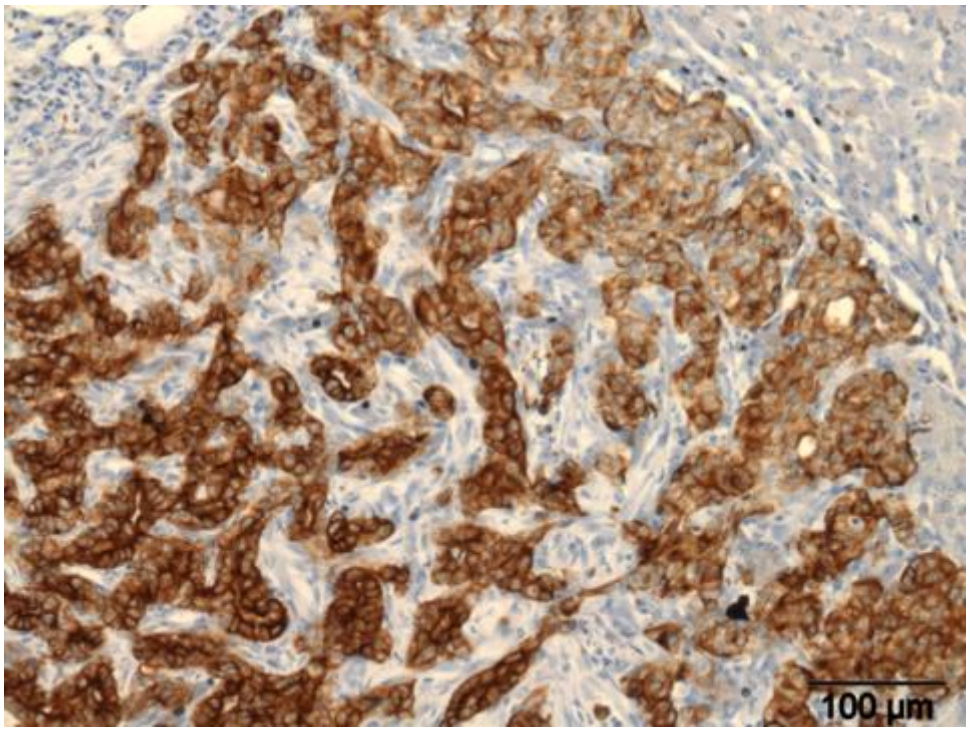


Fig. 13. Dog. Cholangiolocarcinoma. Marked cytoplasmic-membranous staining of tubular areas (lower left) and less intense, cytoplasmic staining of solid areas (upper right). K19.

Neuroendocrine carcinoma

Neuroendocrine carcinomas are rare neoplasms in dogs [14,20] and most likely derived from pre-existing neuroendocrine cells in the biliary epithelium. These tumours can be recognized in both intrahepatic and extrahepatic sites. They can form solitary masses, but they can also occur as multiple nodules probably due to intrahepatic metastasis, particularly in intrahepatic tumours. Histologically, neuroendocrine carcinomas consist of medium-sized to large columnar cells with abundant cytoplasm and basal nuclei in a trabecular and/or rosette growth pattern (Fig. 14). The tumour cells show only slight cellular and nuclear pleomorphism; the mitotic activity is moderate to high. Intrahepatic metastases are frequently seen.

Immunohistochemically they have a strong positive cytoplasmic staining for NSE (Fig. 15) while the positivity for Cg-A can be variable. They usually are negative for K19 although sometimes focal staining of a small amount of tumour cells can be seen. They are negative for HepPar-1, CD10 an EMA/MUC1.

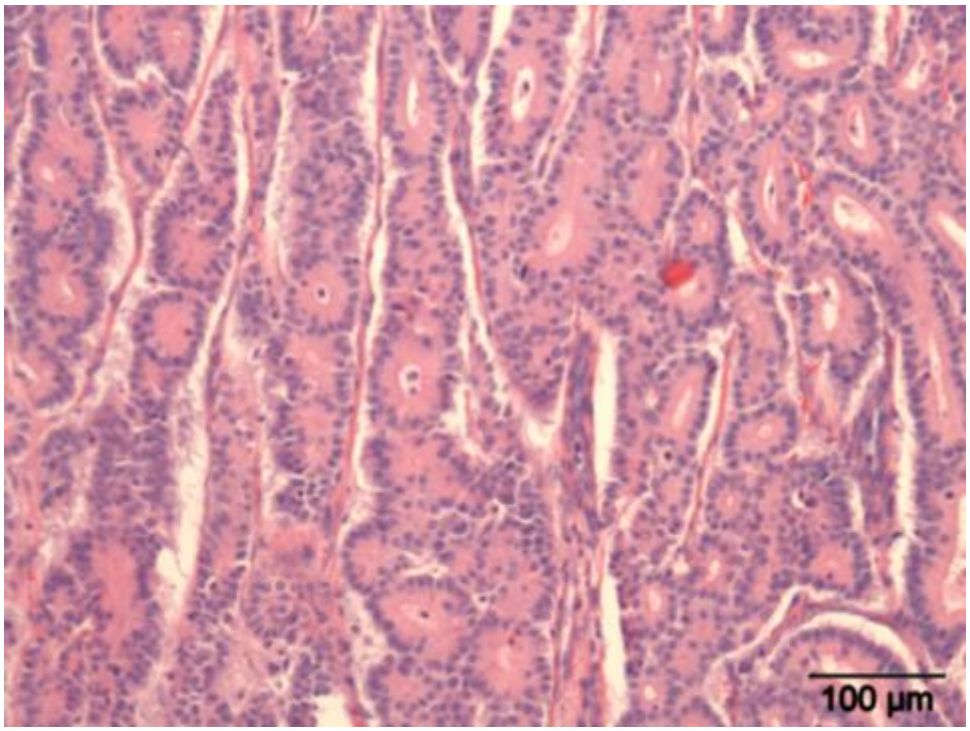


Fig. 14. Dog. Neuroendocrine carcinoma. Rosette pattern with fine fibro-vascular stroma. HE.

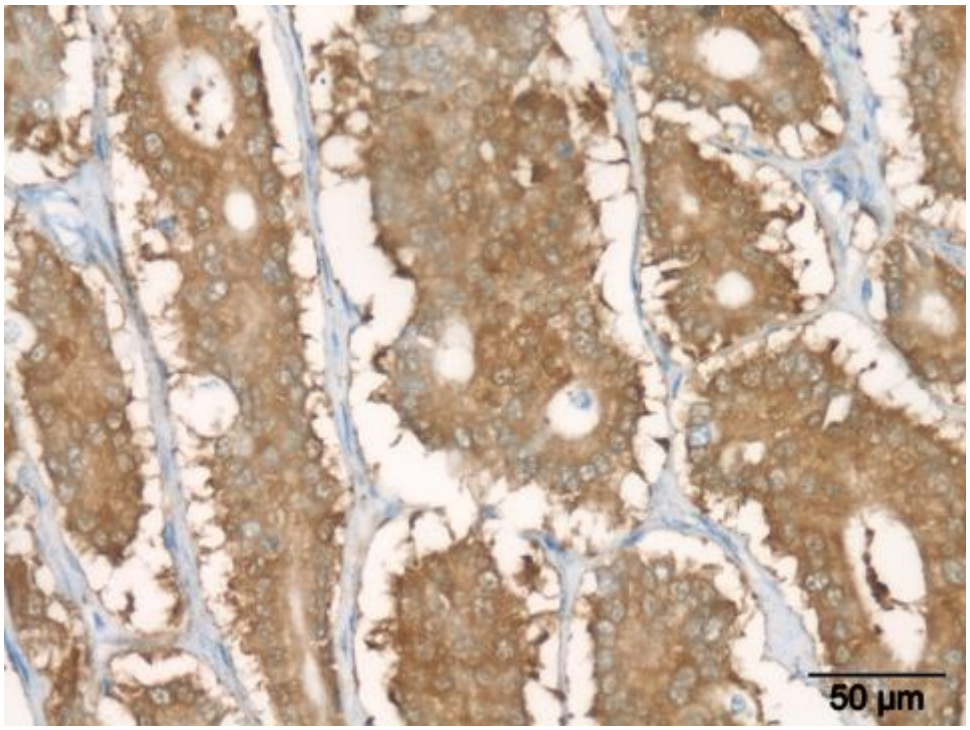


Fig. 15. Dog. Neuroendocrine carcinoma with marked cytoplasmic staining of neoplastic cells. NSE.

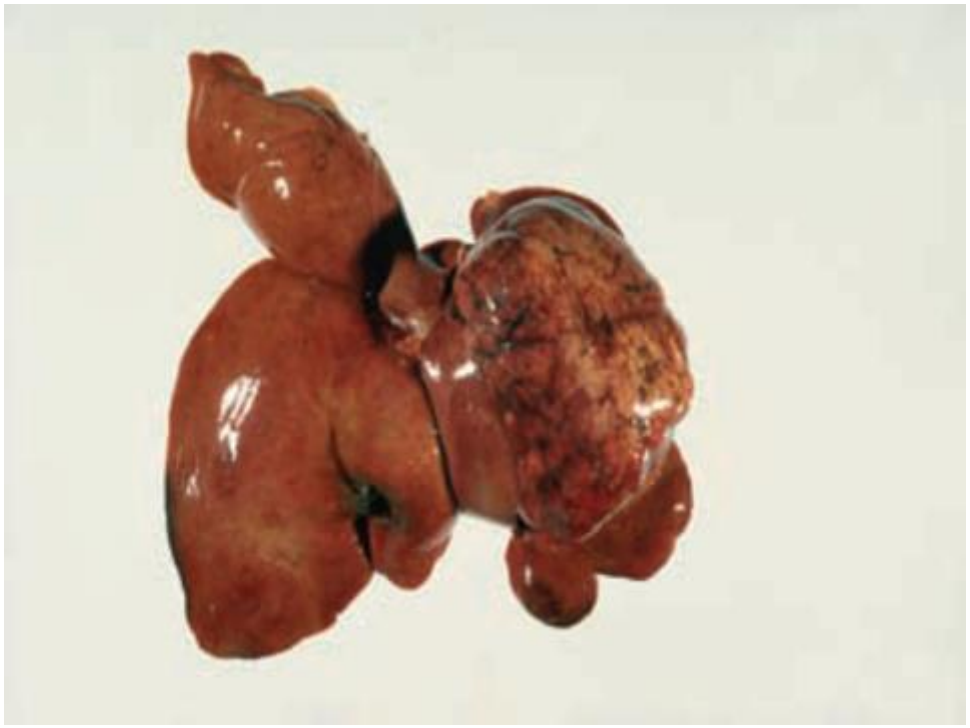
Primary epithelial hepatic neoplasia in the cat [13]

In cats the relative frequency of the various primary epithelial hepatic tumours is quite different compared with dogs. In the dog hepatocellular tumours are much more common than the cholangiocellular tumours. In cats, however, the cholangiocellular tumours are the most common primary epithelial hepatic neoplasm. This difference might be associated with the high prevalence of cholangitis and cystic liver disease in cats, whereas both are infrequently observed in dogs [21,22,23,24,25].

Hepatocellular adenoma

Hepatocellular adenomas are often seen in cats [14,15,17,26] and closely resemble canine hepatocellular adenomas. Grossly they are usually restricted to one or two liver lobes and consist of friable pale tumours that closely resemble normal liver tissue (Fig. 16). Histologically, they are well demarcated, lack portal areas and bile ducts and consist of relatively small trabeculae of well differentiated hepatocytes with no or very limited cellular pleomorphism and no or rare mitotic figures (Fig. 17). In the hepatocellular adenoma sometimes widely dilated sinusoids and cavernous blood-filled spaces as well as extramedullary hematopoiesis can be seen. Hemorrhagic or necrotic areas are frequently observed.

Immunohistochemically, hepatocellular adenomas show marked positive cytoplasmic staining of the hepatocytes for HepPar-1 and a slight to moderate canalicular staining for MRP2 and pCEA. They are negative for K19, NSE and Cg-A. Rarely hepatocellular adenomas with a different aspect can be seen with regional loss of HepPar-1 staining and presence of conglomerates of K19 positive cells with cytoplasmic staining, characteristic for HPC, and possibly indicating transition to malignancy.



Fig, 16. Cat. Hepatocellular adenoma.

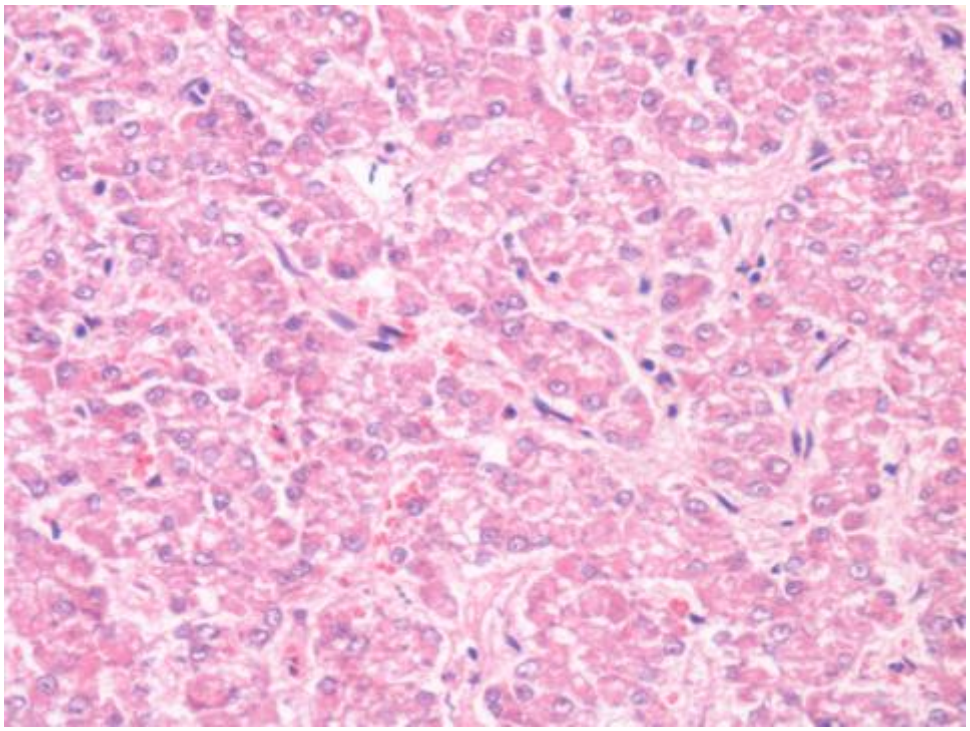


Fig. 17. Cat. Hepatocellular adenoma with relatively small trabeculae of well differentiated hepatocytes. HE.

Hepatocellular carcinoma

Hepatocellular carcinomas are malignant neoplasms of hepatocytes and are infrequently seen in cats [14,15,27]. They may occur as large solitary structures that resemble normal liver tissue, but also may be seen widespread throughout the liver. Histologically, the tumours form trabecular structures of hepatocytes with moderate to marked cellular and nuclear pleomorphism, including large atypical, bizarre and multinucleated hepatocytes (Fig, 18, 19) and moderate to large numbers of mitotic figures. They often show infiltrative growth into the surrounding liver parenchyma and/or have intrahepatic and/or distant metastases.

Immunohistochemically, they maintain their hepatocellular characteristics as they show marked cytoplasmic staining for HepPar-1 and canalicular staining for MRP2 (Fig, 20) and pCEA but are negative or only show a solitary cell with cytoplasmic staining for K19. They are negative for NSE and Cg-A.

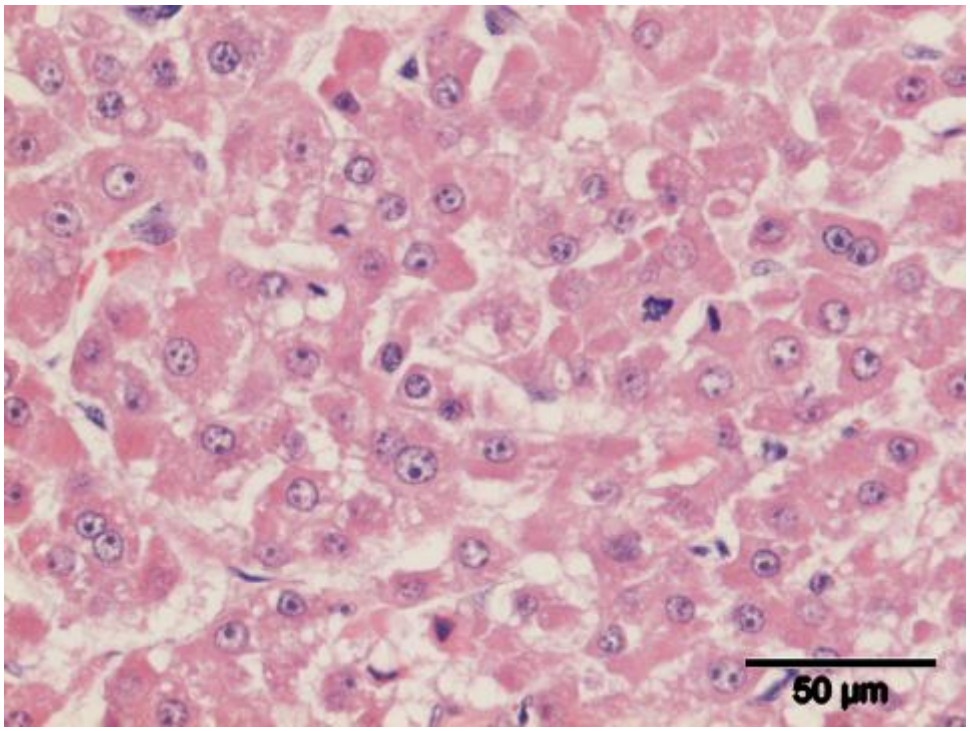


Fig. 18. Cat. Hepatocellular carcinoma. Trabecular structures of hepatocytes with moderate cellular and nuclear pleomorphism and mitotic figures. HE.

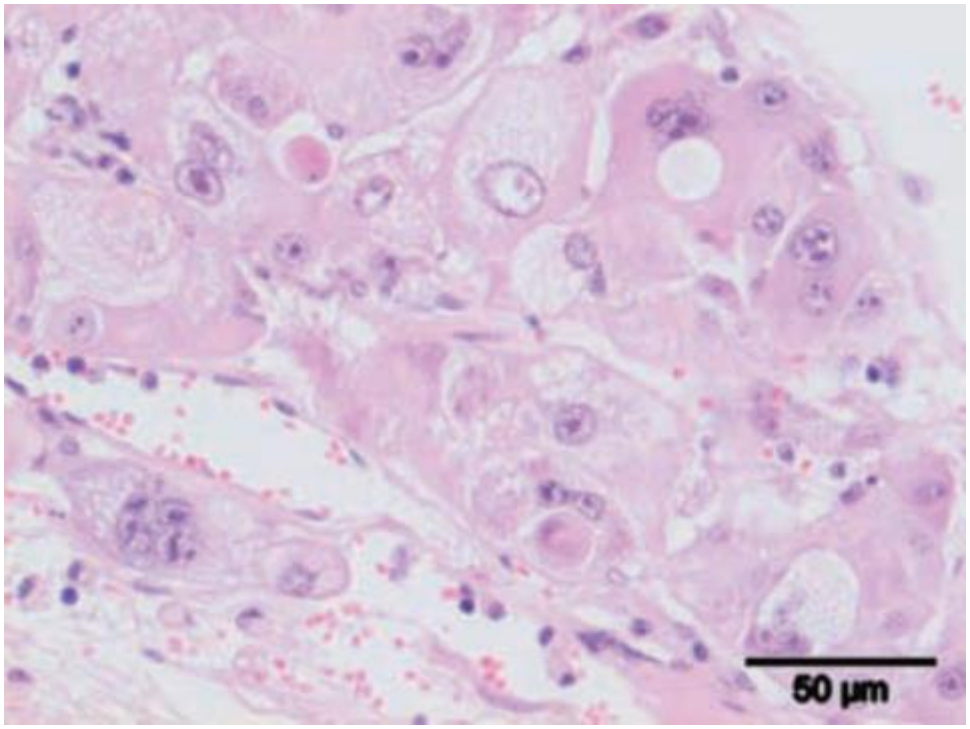


Fig. 19. Cat. Hepatocellular carcinoma. Trabeculae of atypical, bizarre and multinucleated hepatocytes. HE.

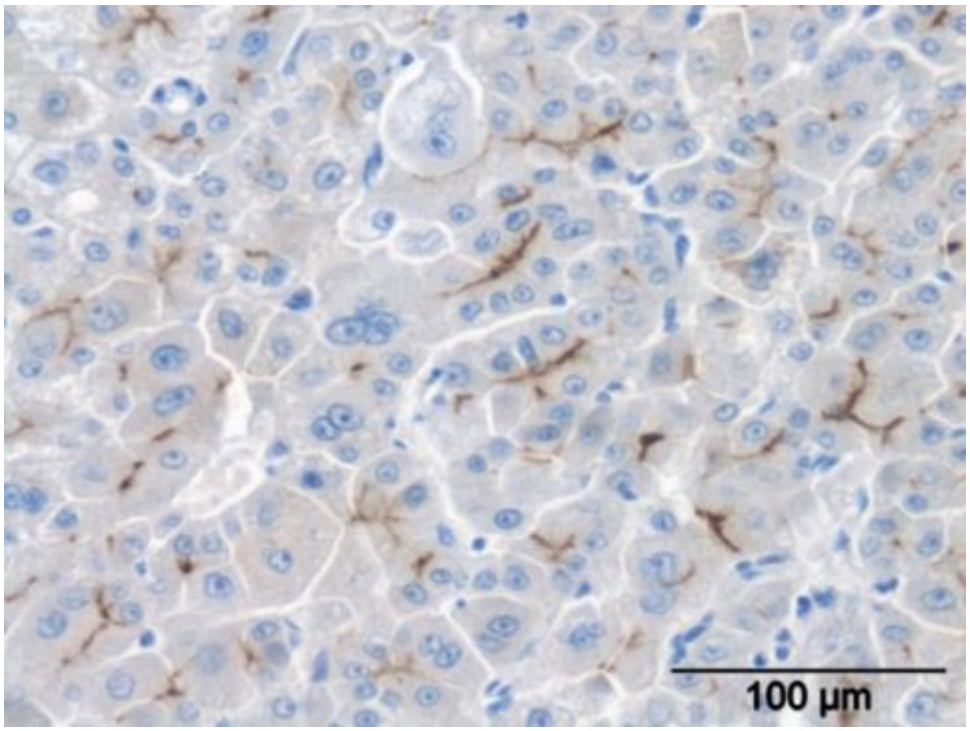


Fig. 20. Cat. Hepatocellular carcinoma with marked canalicular staining. MRP2.

Cholangiocellular adenoma

Cholangiocellular adenomas resemble macroscopically and microscopically cholangiocellular adenomas in dogs. They are extremely rare in the cat [14,15] and probably all feline cholangiocellular adenomas described in veterinary literature represent adult-type cystic liver disease (Fig. 21) [17].

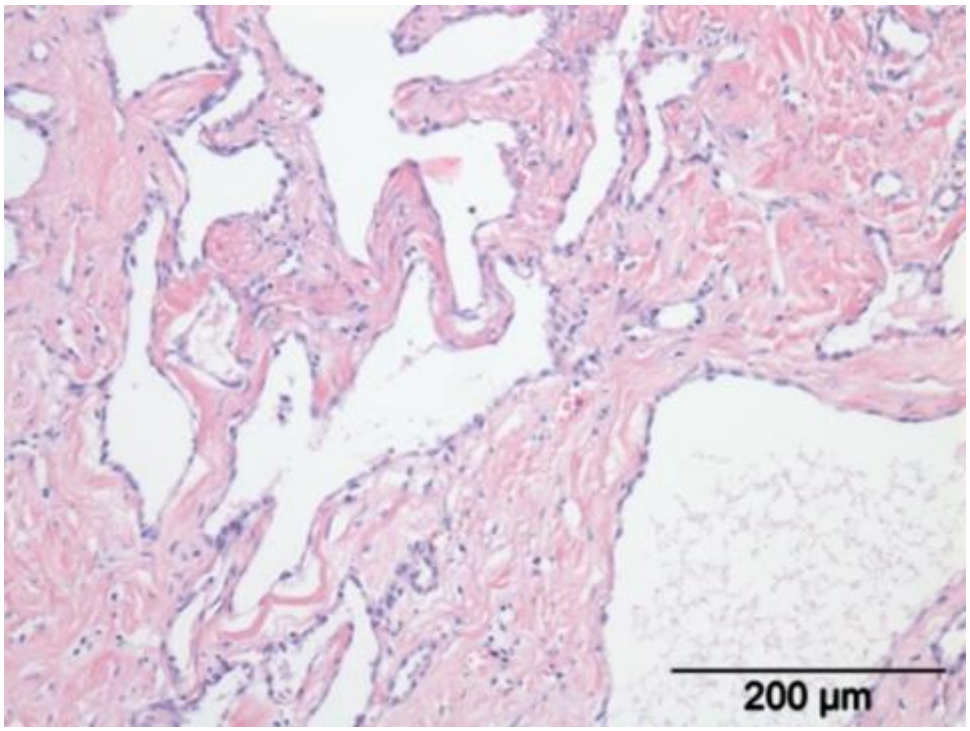


Fig. 21. Cat. Liver. Adult-type polycystic disease. Irregularly formed bile ducts with cystic dilatation. HE.

Cholangiocellular carcinoma

Cholangiocellular carcinomas are the most common primary epithelial hepatic neoplasm in cats and have been associated with chronic cholangitis due to liver fluke infestation [22,25] and with adult-type congenital cystic diseases of the liver [13]. They may occur intrahepatic and in the extrahepatic large bile ducts and closely resemble cholangiocellular carcinomas in dogs macroscopically, microscopically (Fig. 22) and prognostically.

Immunohistochemically, feline cholangiocellular carcinomas are positive for K19 with a cytoplasmic-membranous staining pattern (Fig. 23). They are negative for the hepatocellular markers HepPar-1 and MRP2 as well as for the neuroendocrine markers NSE and Cg-A. A marked variability between neoplasms for pCEA can be seen; this difference in pCEA staining possibly depends on the origin of the neoplasm because in the normal feline liver small bile ducts are negative or show an apical staining and larger bile ducts show a cytoplasmic staining for pCEA [13]. The feline cholangiocellular carcinomas with cytoplasmic staining for pCEA are thought to be derived from mucin-producing cholangiocytes, normally present in larger bile ducts and could be associated with the production of large quantities of mucin as described in a cholangiocarcinoma in a cat [28].

No cholangiolocarcinomas have been observed in cats to date.

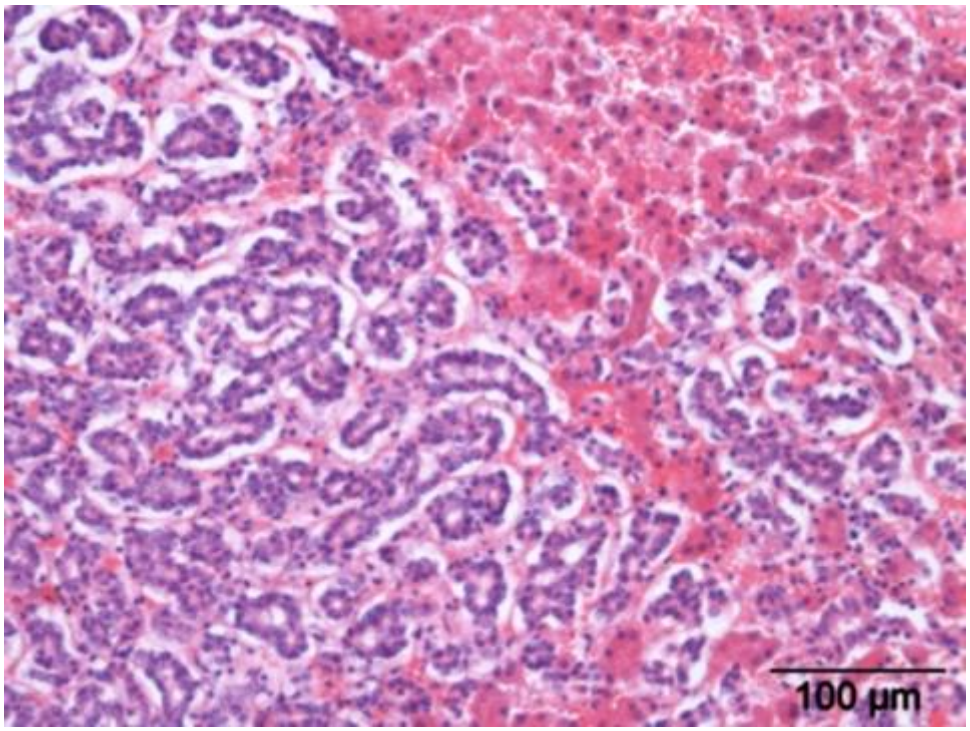


Fig. 22. Cat. Cholangiocellular carcinoma. Tubulopapillary growth pattern and infiltrative growth. HE.

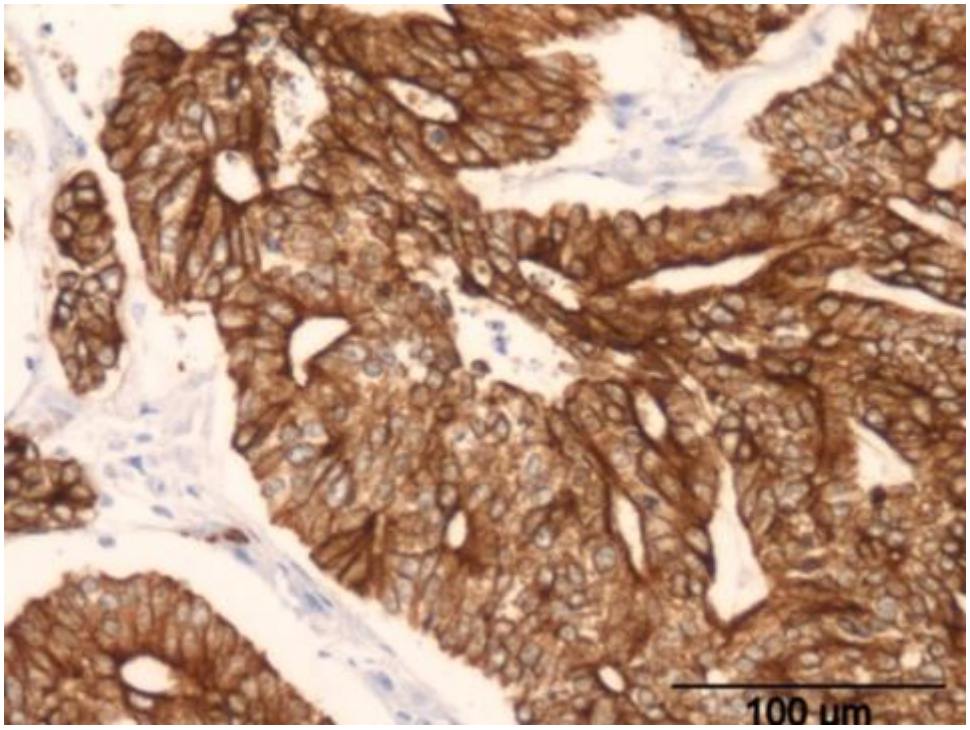


Fig. 23. Cat. Cholangiocellular carcinoma. Marked cytoplasmic and membranous staining of neoplastic tissue. K19.

Small cell carcinoma

Small cell carcinomas are rare neoplasms in cats [14,27]. These tumours can be recognized in both intrahepatic and extrahepatic bile ducts and the gall bladder. They can form solitary masses, but particularly in intrahepatic tumours they can also occur as multiple nodules (Fig. 24) probably due to intrahepatic metastasis. Histologically, these small cell carcinomas consist of relatively small cells with varying amounts of cytoplasm and hyperchromatic nuclei, and a trabecular and/or rosette growth pattern. The tumour cells show only slight cellular and nuclear pleomorphism and the mitotic activity is moderate to high. Small cell carcinomas often show lymphatic and vascular invasion and intrahepatic metastases; sometimes also distant metastases can be seen.

Immunohistochemically they show diffuse or variable positive cytoplasmic staining for NSE and less for Cg-A. Although comparable in histology and behaviour, the feline small cell carcinomas can be subdivided based on their immunohistochemical staining for K19 into K19 negative neuroendocrine carcinomas probably originating from neuroendocrine cells in the epithelium of the intrahepatic or extrahepatic bile duct [29] (Fig. 25) and K19 positive small cell carcinomas with HPC characteristics (Fig. 28).

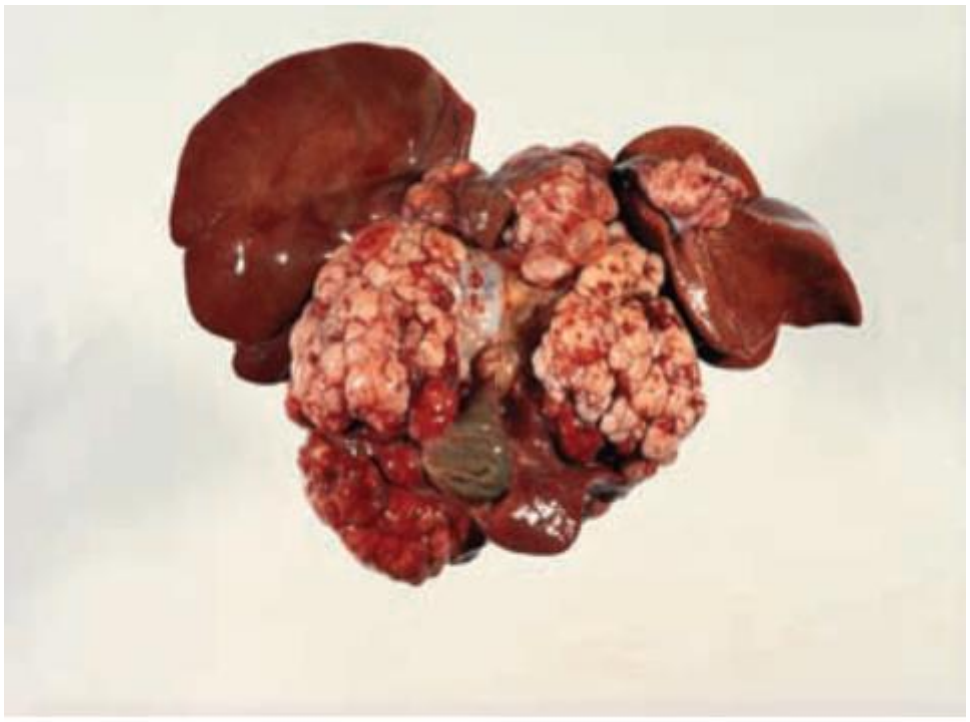


Fig. 24. Cat. Hepatic small cell carcinoma.

Neuroendocrine carcinoma

The K19 negative small cell carcinomas probably originating from neuroendocrine cells (Fig. 27) are also negative for HepPar-1 and MRP2 but are highly positive for NSE (Fig. 26) and show variable positivity for Cg-A and pCEA.

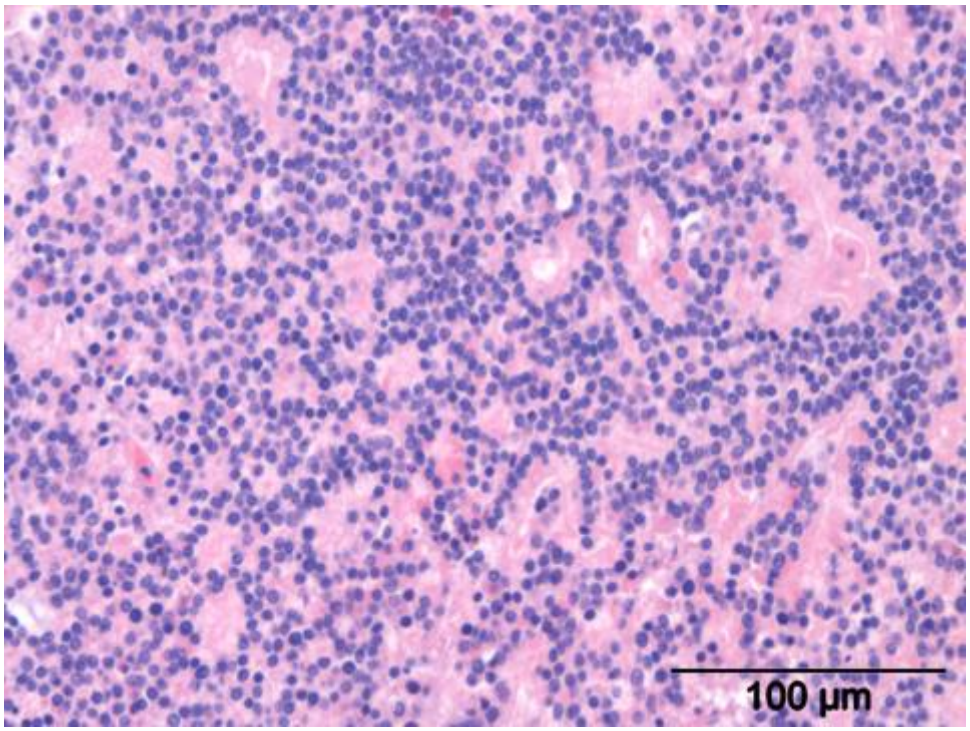


Fig. 25. Cat. Neuroendocrine carcinoma. Small cells in a trabecular and rosette growth pattern. HE..

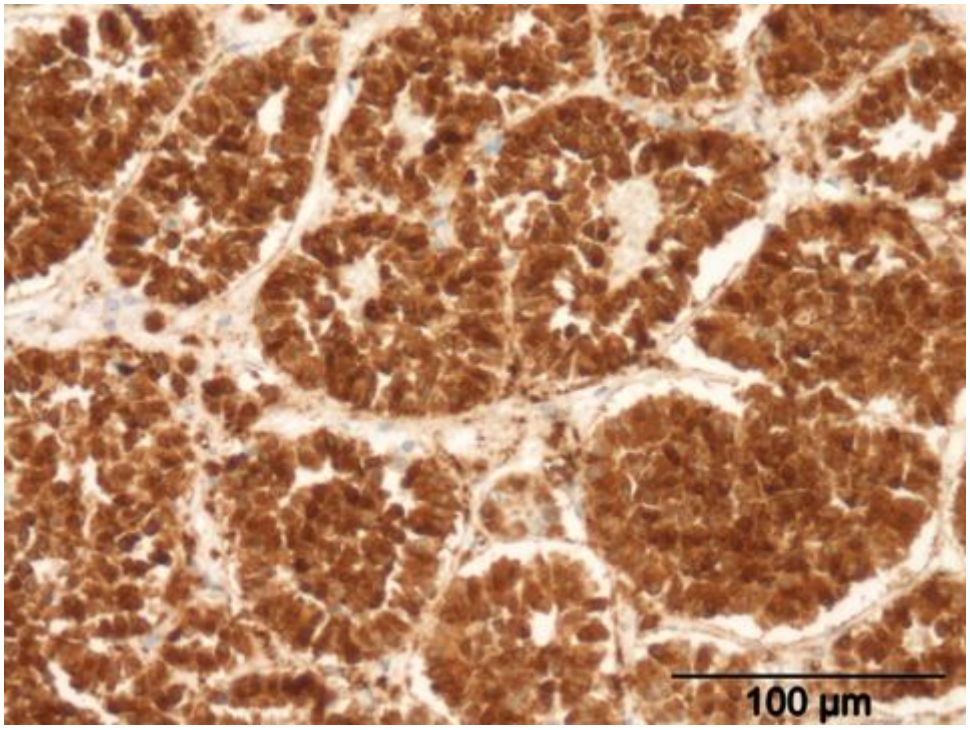


Fig. 26. Cat. Neuroendocrine carcinoma Marked cytoplasmic staining of neoplastic tissue NSE.

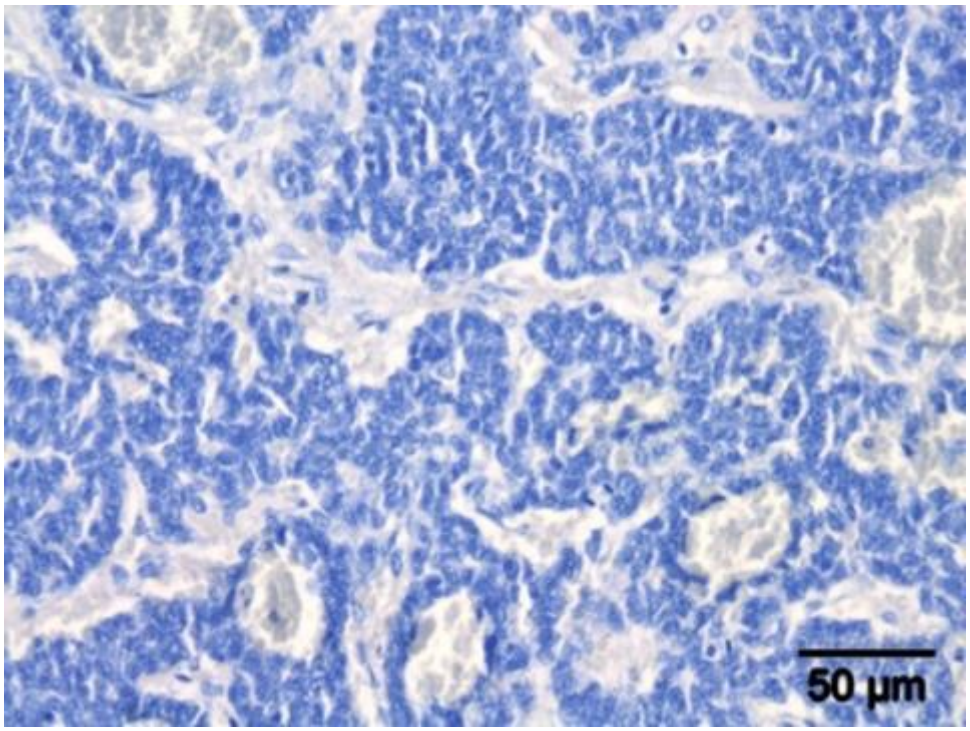


Fig. 27. Cat. Neuroendocrine carcinoma. Negative staining of neoplastic tissue. K19.

Small cell carcinoma with HPC characteristics

The small cell carcinomas with HPC characteristics show variable cytoplasmic staining for K19 (Fig. 30), are negative for HepPar-1, MRP2 and pCEA and show a variable positive staining for NSE (Fig. 29) and Cg-A.

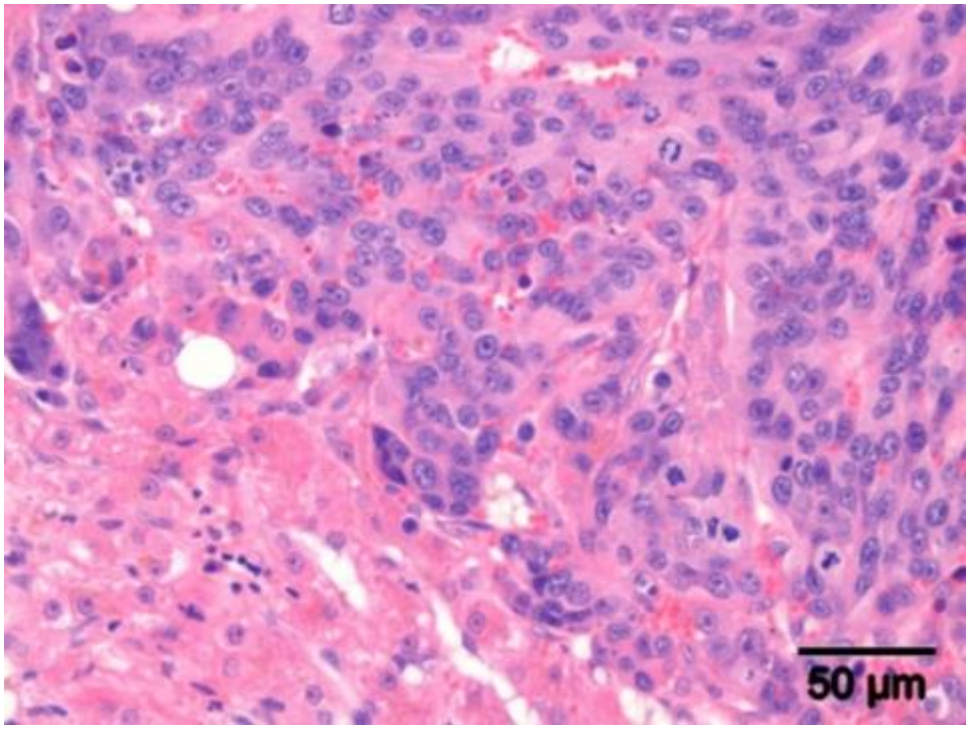


Fig. 28. Cat. Small cell carcinoma with HPC characteristics. Small cells with slight cellular and nuclear pleomorphism with a high mitotic activity; infiltrative growth. HE

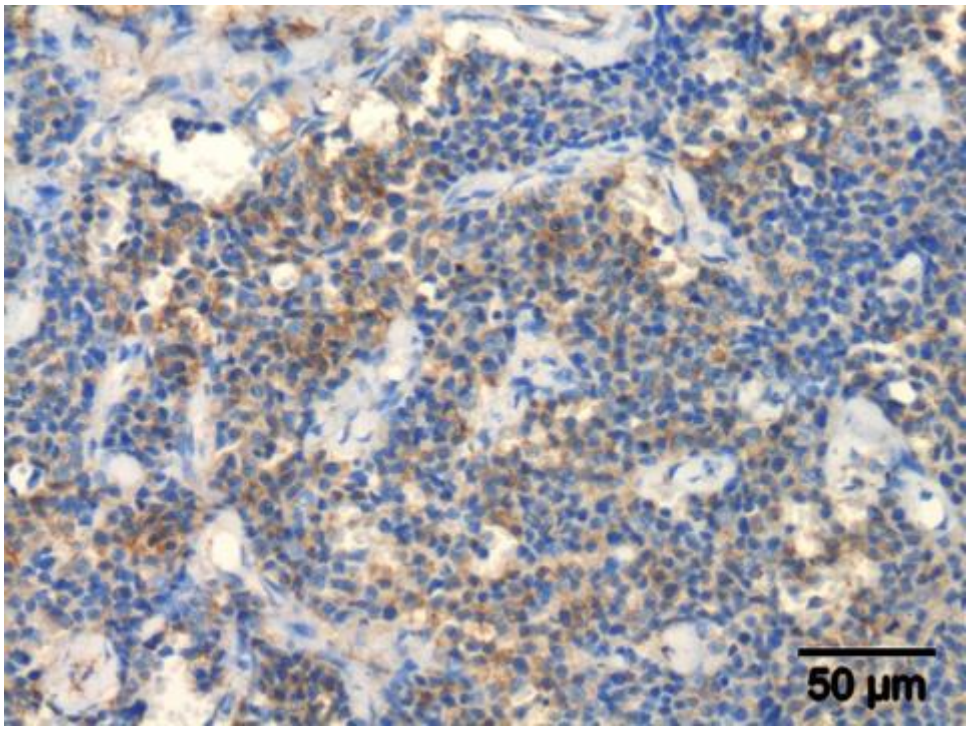


Fig. 29. Cat. Small cell carcinoma with HPC characteristics. Moderate positive cytoplasmic staining of neoplastic tissue. NSE.

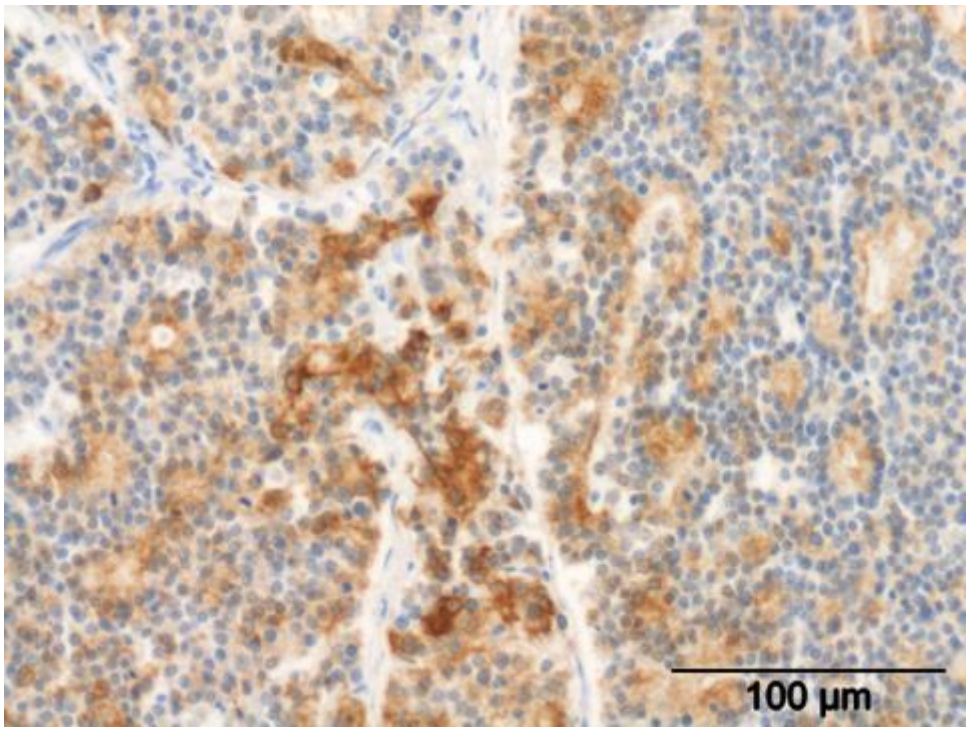


Fig. 30. Cat. Small cell carcinoma with HPC characteristics. Positive cytoplasmic staining of neoplastic tissue. K19

Mixed hepatocellular and cholangiocellular carcinoma

Sometimes primary hepatic tumours with a mixed histological pattern of hepatocellular differentiation and cholangiocellular differentiation are observed [18]. Immunohistochemical evaluation of future cases will reveal whether they all represent scirrhous hepatocellular carcinomas or cholangiolocarcinomas or whether mixed hepatocellular and cholangiocellular carcinoma should be maintained as a separate group.

Hepatoblastoma

Hepatoblastomas frequently occur in children and are composed of epithelial elements at various stages of differentiation or are mixed and composed of epithelial and mesenchymal elements in varying proportions. The epithelial element recapitulates the stages of hepatocyte development from the primitive blastema through embryonal hepatocytes fetal hepatocytes. The blastemal or undifferentiated cells have been postulated to represent neoplastic hepatocytic progenitor cells. The hepatoblastomas display differing immunoreactivity within and between tumours, probably based on their degree of differentiation [30]

Hepatoblastomas have been described in domestic animals in lambs [31] and in foals [32,33] but until now have not been unequivocally recognized in dogs and cats. In the literature a neoplasm in a 8-year old cat with positivity for K7 is described as hepatoblastoma [34].. However, this tumour may represent a small cell carcinoma with HPC characteristics.

Primary vascular and mesenchymal tumours in dogs and cats

Primary vascular and mesenchymal tumours, except for hemangiosarcoma, are extremely rare in dogs and cats [14]. Apart from the already mentioned hemangiosarcoma (Fig. 31), they include lymphangioma, lymphangiosarcoma (Fig. 32), fibrosarcoma, leiomyosarcoma, malignant mesenchymoma, osteosarcoma and rhabdomyosarcoma. These tumours have the same gross and histological characteristics as those that arise at other more commonly affected sites of the body.

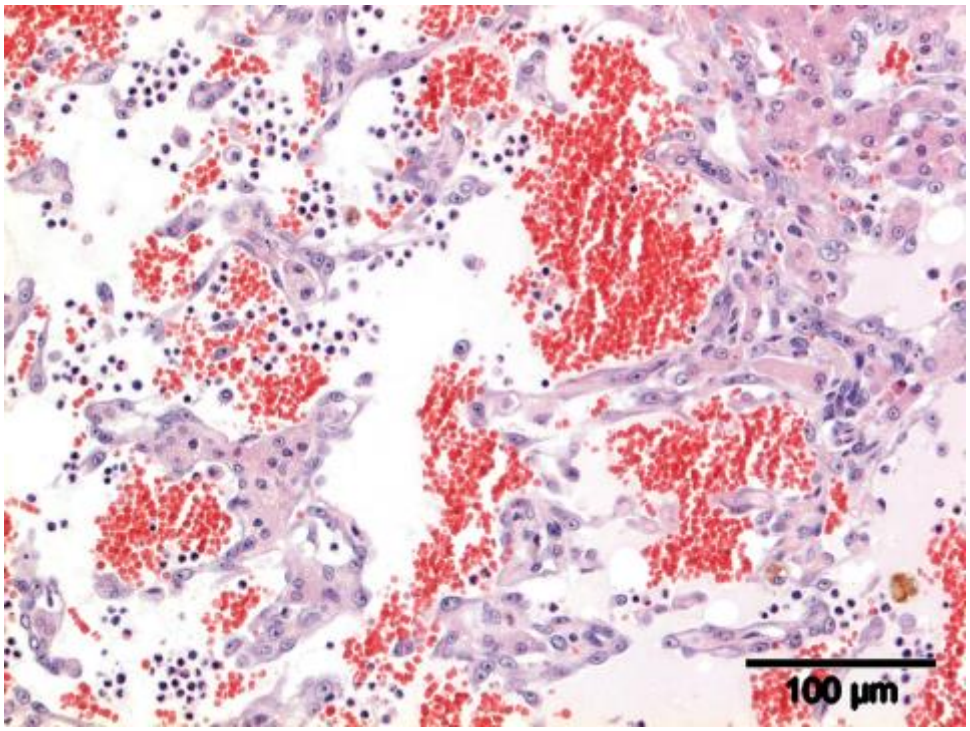


Fig. 31. Dog. Liver. Hemangiosarcoma. HE.

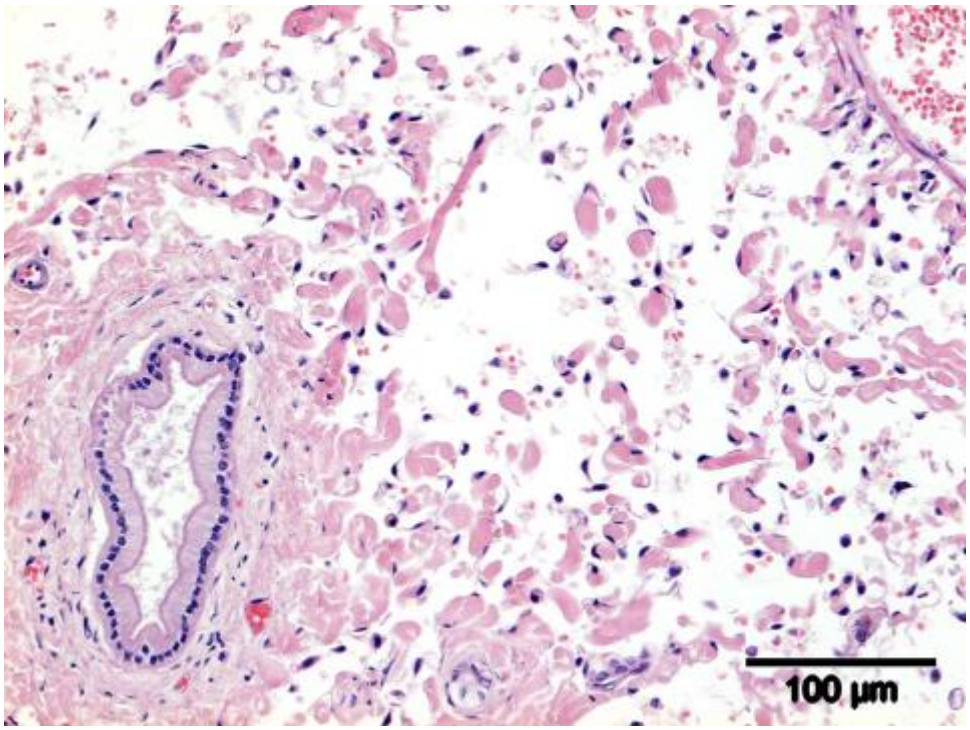


Fig. 32. Dog. Liver. Lymphangiosarcoma; extension in the portal area. HE.

Myelolipoma

Myelolipoma of the liver is a very rare benign tumour or tumour-like lesion and has only been reported in cats and wild felids [14,15]. They are usually found as multiple growths that may be

located in more than one lobe of the liver. Myelolipomas are rather well delineated or surrounded by a thin capsule and are composed of mature and normal appearing adipose and myeloid tissue resembling normal bone marrow (Fig. 33).

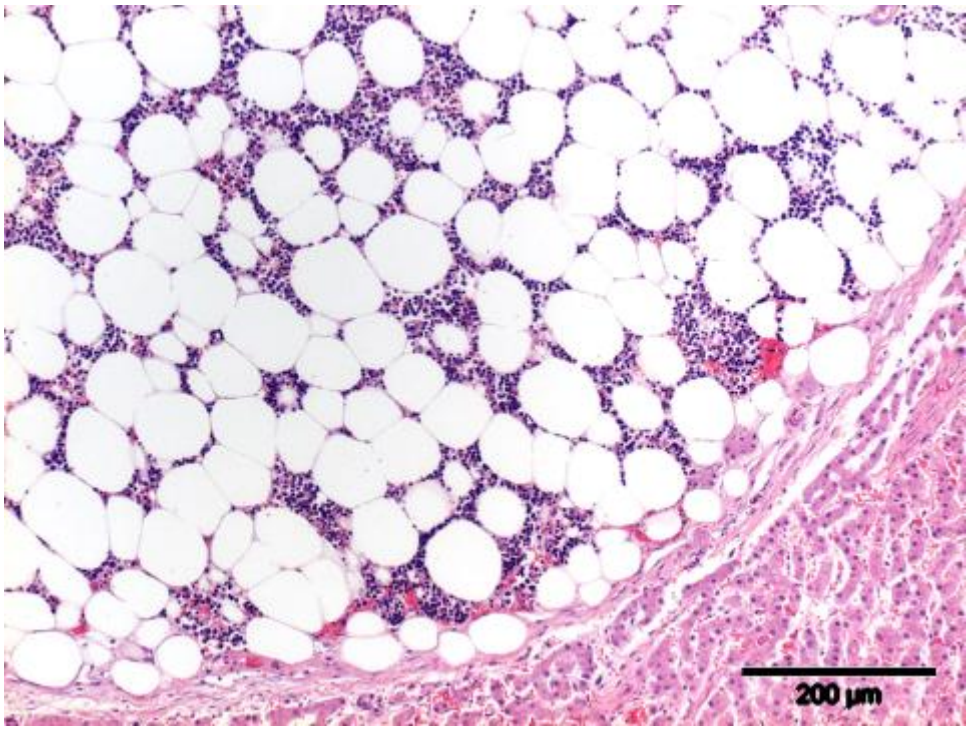


Fig. 33. Cat. Liver. Myelolipoma. HE.

Hematopoietic neoplasms

The liver is often involved in hematopoietic neoplasia usually as part of generalized or visceral forms of the disease. The organ usually is affected diffusely and has a swollen, pale appearance, often with a zonal (lobular) pattern, but nodular infiltration can also occur.

Lymphoma is the most frequent type observed and histologically often shows particular involvement of the portal areas and the connective tissue around the hepatic veins (Fig. 34). Both B and T cell lymphomas are seen. Rarely an epitheliotropic variant of T-cell lymphoma is observed with marked emperipolesis of tumour cells by the hepatocytes (Fig. 35) [(35)].

Other types of hematopoietic neoplasms involving the liver include the whole spectrum of hematopoietic cells and include histiocytic sarcoma (Fig. 36), systemic mastocytosis (malignant mastocytosis) (Fig. 37), erythremic myelosis (Fig. 38), megakaryocytic leukemia, a neutrophilic -, eosinophilic - and basophilic myeloid leukemia (Fig. 39), monocytic leukemia, and systemic plasmacytosis (Fig. 40).

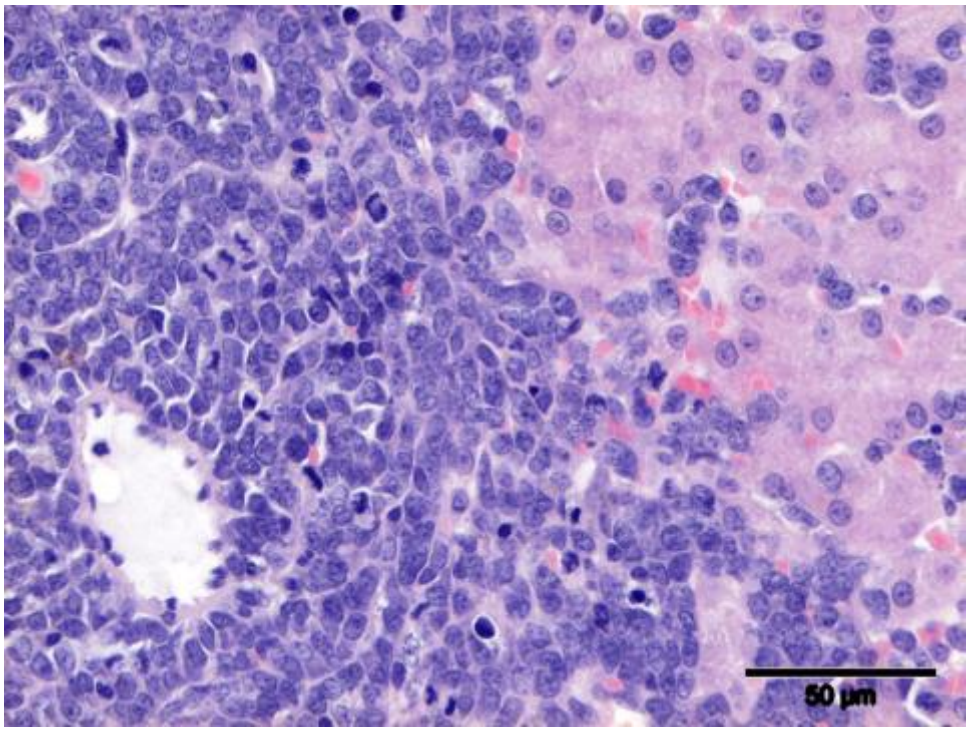


Fig. 34. Dog. Liver centrolobular area. Lymphoma. Infiltrates of neoplastic cells around the central vein and in the sinusoids. HE.

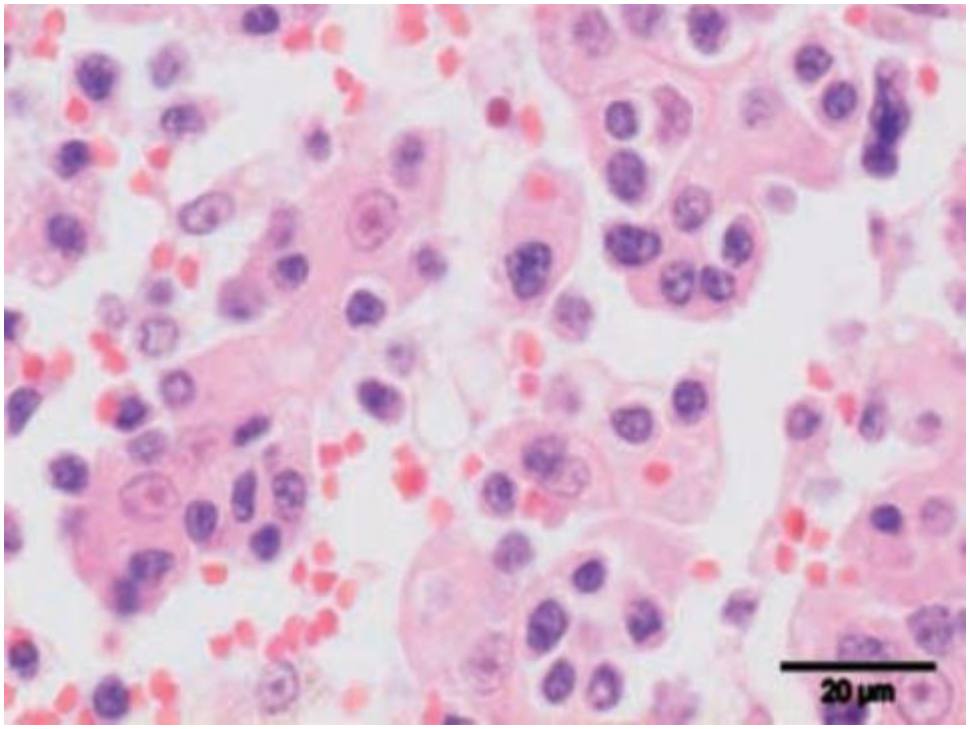


Fig. 35. Cat. Liver. Epitheliotropic lymphoma with emperipolesis of neoplastic lymphocytes by hepatocytes. HE.

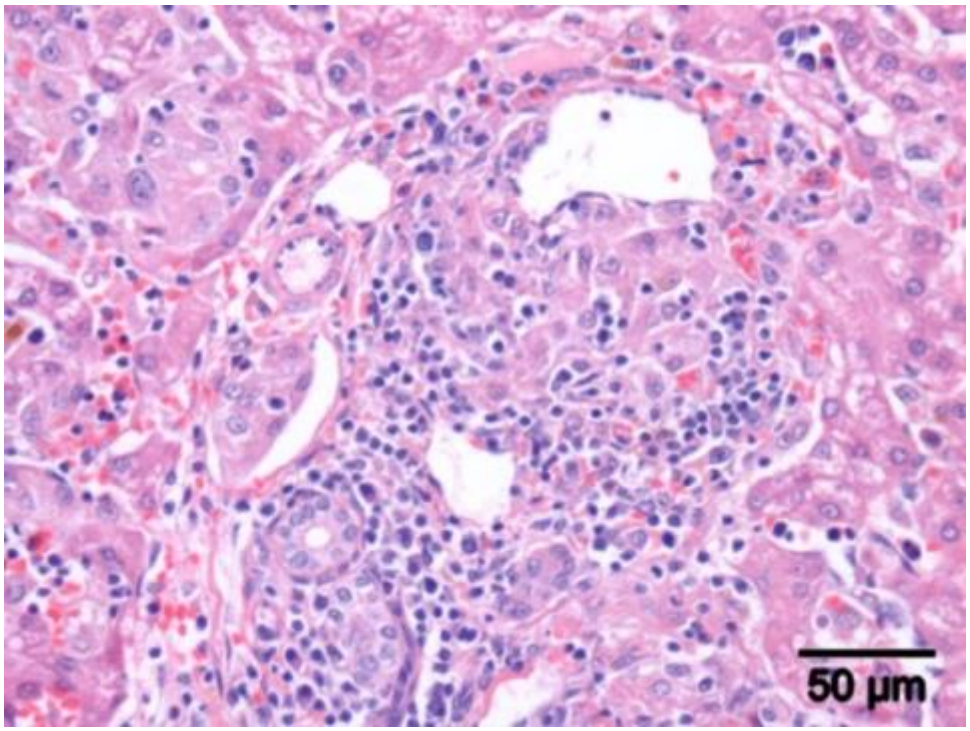


Fig. 36. Dog, Berner Sennen dog.. Liver. Histiocytic sarcoma with parenchymal and portal infiltrates of neoplastic histiocytic cells, and extramedullary erythropoiesis. HE

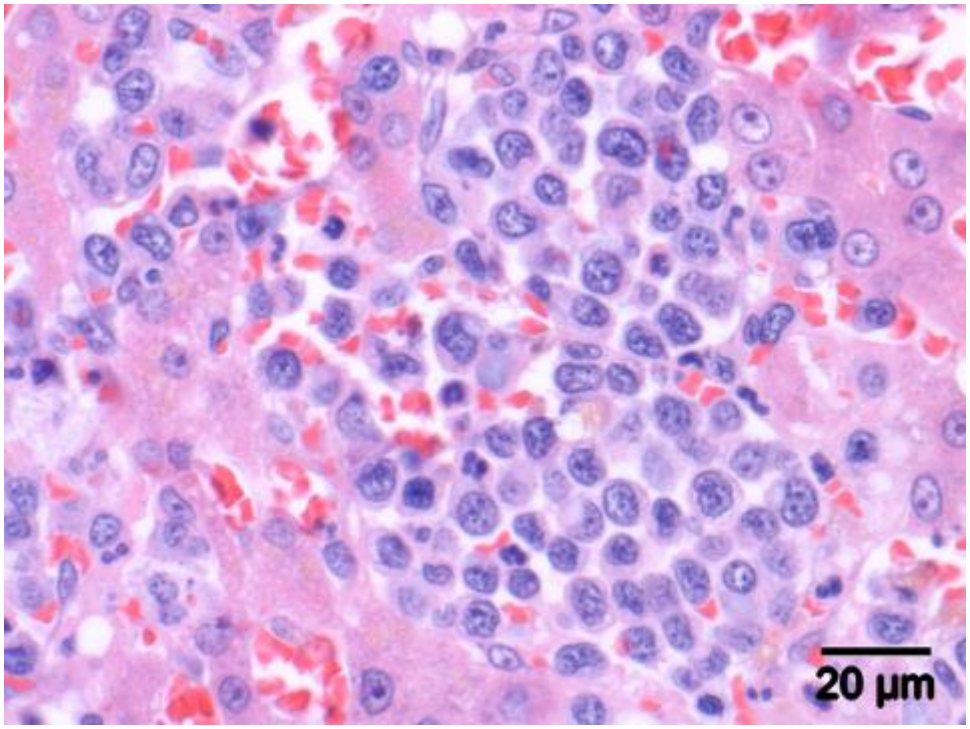


Fig. 37. Dog. Liver. Systemic mastocytosis. Pleomorphic neoplastic mast cells and some eosinophilic leukocytes. HE

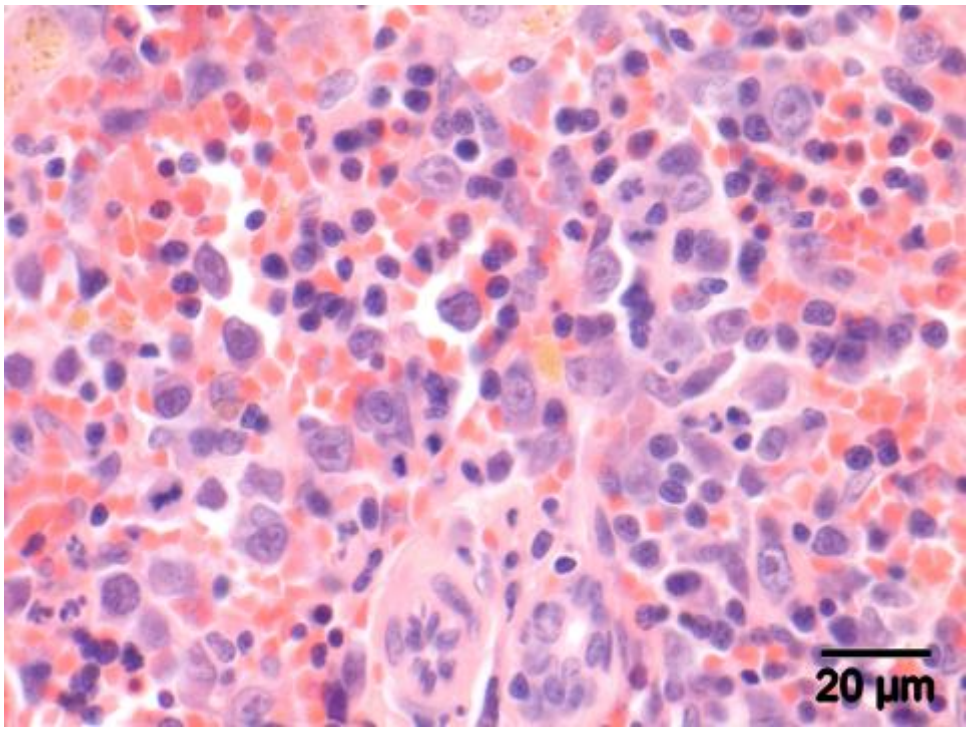


Fig. 38. Cat. Liver. Erythremic myelosis.

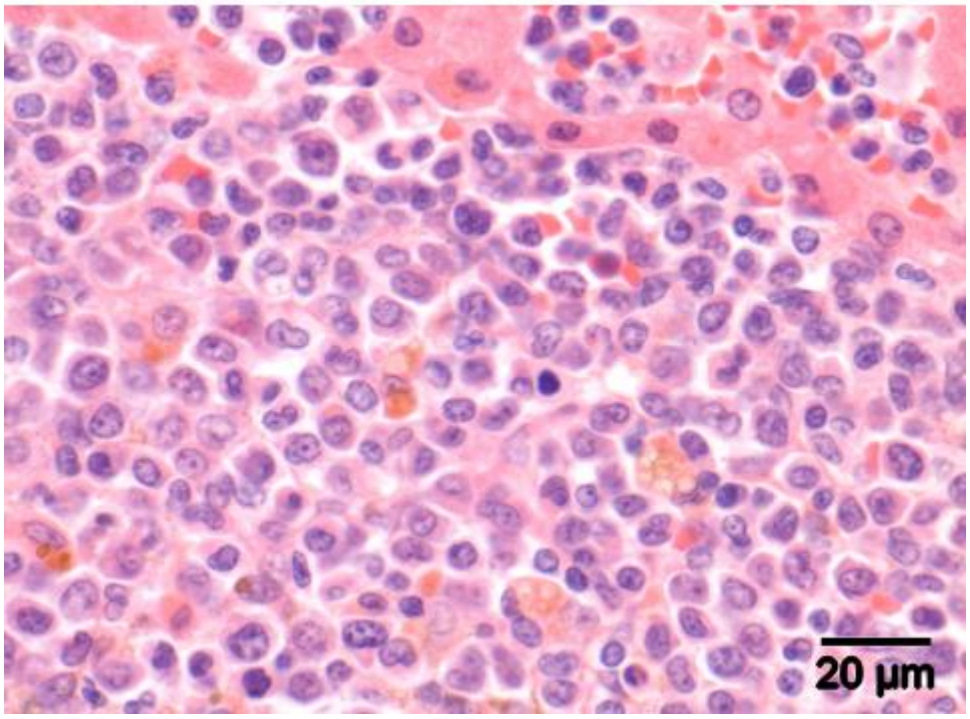


Fig. 39. Dog. Liver. Neutrophilic myeloid leukemia.

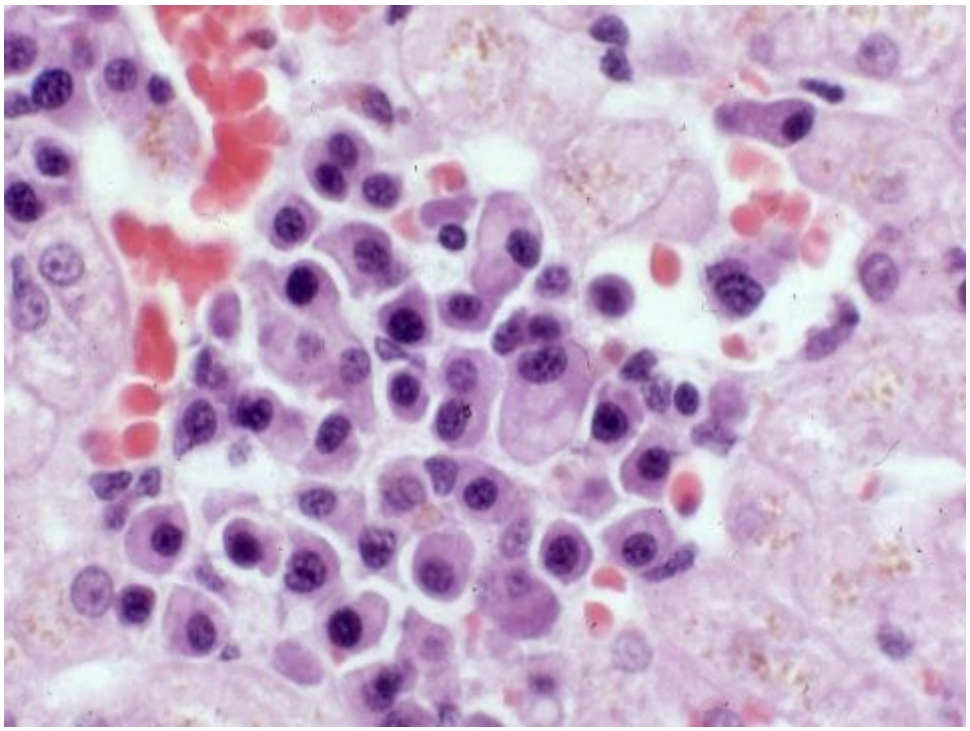


Fig. 40. Dog. Liver. Systemic plamacytosis

Metastatic neoplasia

Metastatic neoplasia in the liver in the dog and cat are more common than primary neoplasia. Metastases usually occur as multiple foci of different sizes and histologically resemble the primary tumour.

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