

A histological section of a bile duct, stained with hematoxylin and eosin (H&E). The duct lumen is visible in the center, surrounded by a thick, multi-layered wall of columnar epithelial cells. The nuclei are stained purple, and the cytoplasm and surrounding connective tissue are stained pink. The text overlay is centered over the duct wall.

CHAPTER 9

Tumours of the Gallbladder and Extrahepatic Bile Ducts

These two closely related tumour sites show remarkable differences in terms of epidemiology, aetiology, and clinical presentation. The incidence of gallbladder carcinoma shows prominent geographic, gender, and racial differences, while extrahepatic bile duct carcinomas show none of these variations. Aetiologic associations include gall stones, sclerosing cholangitis, ulcerative colitis, abnormal choledochopancreatic junction, choledochal cysts, and infestation with liver flukes.

WHO histological classification of tumours of the gallbladder and extrahepatic bile ducts

Epithelial tumours		Small cell carcinoma		8041/3
<i>Benign</i>		Large cell neuroendocrine carcinoma		8013/3
Adenoma		Undifferentiated carcinoma		8020/3
	8140/0 ¹	Biliary cystadenocarcinoma		8161/3
	Tubular			
	8211/0	Carcinoid tumour		8240/3
	Papillary	Goblet cell carcinoid		8243/3
	8260/0	Tubular carcinoid		8245/1
	Tubulopapillary	Mixed carcinoid-adenocarcinoma		8244/3
	8263/0	Others		
	Biliary cystadenoma			
	8161/0			
	Papillomatosis (adenomatosis)			
	8264/0			
Intraepithelial neoplasia (dysplasia and carcinoma in situ)				
<i>Malignant</i>		Non-epithelial tumours		
Carcinoma		Granular cell tumour		9580/0
	Adenocarcinoma	Leiomyoma		8890/0
	8140/3	Leiomyosarcoma		8890/3
	Papillary adenocarcinoma	Rhabdomyosarcoma		8900/3
	8260/3	Kaposi sarcoma		9140/3
	Adenocarcinoma, intestinal type	Others		
	8144/3			
	Adenocarcinoma, gastric foveolar type	Malignant lymphoma		
	8480/3			
	Mucinous adenocarcinoma			
	8310/3			
	Clear cell adenocarcinoma			
	8490/3			
	Signet-ring cell carcinoma			
	8560/3			
	Adenosquamous carcinoma			
	8070/3			
	Squamous cell carcinoma			
Secondary tumours				

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline, or uncertain behaviour, /2 for in situ carcinomas and grade III intraepithelial neoplasia and /3 for malignant tumours.

TNM classification of tumours of the gallbladder

TNM classification ^{1,2}			
T – Primary Tumour		M – Distant Metastasis	
TX	Primary tumour cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumour	M0	No distant metastasis
Tis	Carcinoma in situ	M1	Distant metastasis
T1	Tumour invades lamina propria or muscle layer	Stage Grouping	
T1a	Tumour invades lamina propria	Stage 0	Tis N0 M0
T1b	Tumour invades muscle layer	Stage I	T1 N0 M0
T2	Tumour invades perimuscular connective tissue, no extension beyond serosa or into liver	Stage II	T2 N0 M0
T3	Tumour perforates serosa (visceral peritoneum) or directly invades into one adjacent organ or both (extension 2 cm or less into liver)	Stage III	T1 T2 N1 M0
T4	Tumour extends more than 2 cm into liver and/or into two or more adjacent organs (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, any involvement of liver)		T3 N0, N1 M0
N – Regional Lymph Nodes		Stage IVA	T4 N0, N1 M0
NX	Regional lymph nodes cannot be assessed	Stage IVB	Any T N2 M0
N0	No regional lymph node metastasis		Any T Any N M1
N1	Metastasis in cystic duct, pericholedochal, and/or hilar lymph nodes (i.e., in the hepatoduodenal ligament)		
N2	Metastasis in peripancreatic (head only), periduodenal, periportal, coeliac, and/or superior mesenteric lymph nodes		

¹ {1, 66}. The classification applies only to carcinomas.

² A help desk for specific questions about the TNM classification is available at <http://tnm.uicc.org>.

TNM classification of tumours of the extrahepatic bile ducts

TNM classification^{1,2}

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour invades subepithelial connective tissue or fibromuscular layer
T1a	Tumour invades subepithelial connective tissue
T1b	Tumour invades fibromuscular layer
T2	Tumour invades perifibromuscular connective tissue
T3	Tumour invades adjacent structures: liver, pancreas, duodenum, gallbladder, colon, stomach

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in cystic duct, pericholedochal, and/or hilar lymph nodes (i.e., in the hepatoduodenal ligament)
N2	Metastasis in peripancreatic (head only), periduodenal, periportal, coeliac, superior mesenteric, posterior peripancreatico-duodenal lymph nodes

M – Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1, N2	M0
	T2	N1, N2	M0
Stage IVA	T3	Any N	M0
Stage IVB	Any T	Any N	M1

¹{1, 66}. The classification applies to carcinomas of extrahepatic bile ducts and those of choledochal cysts.

²A help desk for specific questions about the TNM classification is available at <http://tnm.uicc.org>.

TNM classification of tumours of the Ampulla of Vater

TNM classification^{1,2}

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour limited to ampulla of Vater or sphincter of Oddi
T2	Tumour invades duodenal wall
T3	Tumour invades 2 cm or less into pancreas
T4	Tumour invades more than 2 cm into pancreas and/or into other adjacent organs

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M – Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

¹{1, 66}. The classification applies only to carcinomas.

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Carcinoma of the gallbladder and extrahepatic bile ducts

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Definition

A malignant epithelial tumour with glandular differentiation, arising in the gallbladder or extrahepatic biliary system.

Epidemiology

Most tumours of the gallbladder and extrahepatic bile ducts are carcinomas. Only a small proportion are adenomas, carcinoid and stromal tumours [35].

Geographic distribution

The incidence of carcinoma of the gallbladder varies in different parts of the world and also differs among different ethnic groups within the same country. In the United States, carcinoma of the gallbladder is more common in Native Americans and Hispanic Americans than in whites or blacks; the rate among female Native Americans is 21 per 100,000 compared with 1.4 per 100,000 among white females. In Latin American countries, the highest rates are found in Chile, Mexico and Bolivia. In Japan, the incidence rates are intermediate. In the general population of the United States cancer of the gallbladder accounts for 0.17% for all cancers in males and 0.49% in females.

There are no geographic variations in the incidence of extrahepatic bile duct carcinoma which accounts for 0.16% of all invasive cancers in males and 0.15% in females in the general population of the United States [35].



Fig. 9.01 Gallbladder carcinoma with a white, irregular cut surface next to a large gall stone.

Age and sex distribution

Carcinomas of the gallbladder and extrahepatic bile ducts are diseases of older age groups. Most patients are in the 6th or 7th decades of life. Gallbladder carcinomas have a strong female predominance, whereas extrahepatic bile duct carcinomas occur more frequently in males.

Aetiology

Unlike carcinoma of the extrahepatic bile ducts, gallbladder carcinomas are not associated with primary sclerosing cholangitis or ulcerative colitis.

Gallbladder carcinoma

Gallstones. The incidence of gallbladder cancer is higher in patients with gallstones than in patients without stones [35], and stones are present in over 80% of gallbladder carcinomas. The incidence of gallbladder carcinoma parallels that of gallstones, being more frequent in females and in certain ethnic groups, e.g. Native Americans, who have a high incidence of stones. Nevertheless, although gall stones are considered a risk factor, the overall incidence of carcinoma of the gallbladder in patients with cholelithiasis is less than 0.2%; this percentage varies with race, sex, and length of exposure to the stones [35]. While some authors have reported a correlation between gallstone size and the risk of cancer, others have not found such a correlation [35].

Abnormal choledochopancreatic junction. Data largely reported from Japan indicate an association between gallbladder cancer and an abnormal junction of the pancreatic and common bile ducts [1248]. Normally, the main pancreatic duct and the common bile duct unite within the sphincter to form the pancreaticobiliary duct. The abnormal junction is defined as the union of the pancreatic and common bile ducts outside the wall of the duodenum beyond the influence of the sphincter of Oddi. As a result, pancreatic juice can reflux into the common bile duct, resulting in hyperplastic, meta-

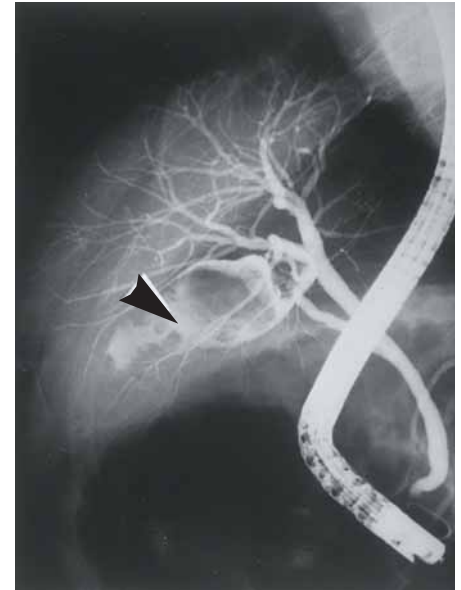


Fig. 9.02 Carcinoma of the gallbladder involving the fundus (arrow). Bile ducts are normal.

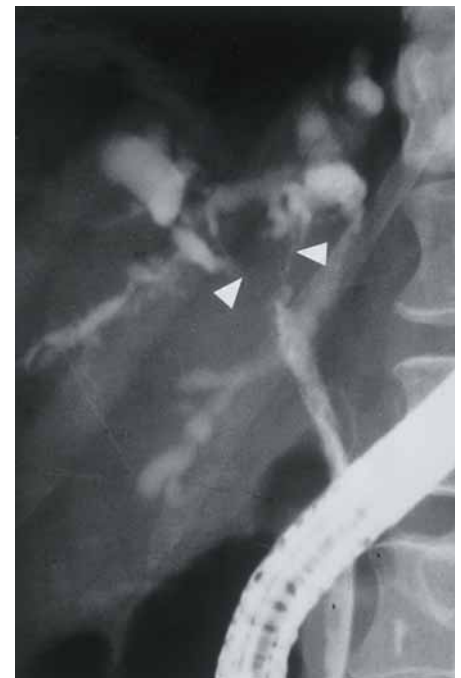


Fig. 9.03 Hilar cholangiocarcinoma extending beyond both the right and left hepatic bile ducts (Klatskin type III) (arrows).

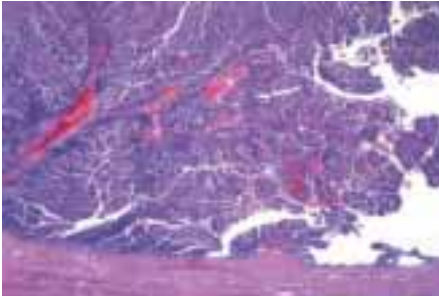


Fig. 9.04 Papillary adenocarcinoma, non-invasive. The tumour projects into the lumen, but does not invade the wall of the gallbladder.

plastic, and neoplastic changes in the gallbladder epithelium.

Porcelain gallbladder. Diffuse calcification of the gallbladder wall (porcelain gallbladder) is associated with carcinoma in 10-25% of cases.

Genetic susceptibility. As discussed above, carcinoma of the gallbladder is concentrated in certain racial and ethnic groups. Familial aggregation of gallbladder cancer has been recorded in the US and in other countries [35].

Carcinoma of extrahepatic bile ducts

Well established risk factors for carcinomas of the extrahepatic bile ducts are sclerosing cholangitis, ulcerative colitis, abnormal choledochopancreatic junction, choledochal cysts and infestation with the liver flukes *C. sinensis* and *O. viverrini*. Choledocholithiasis does not seem to play a role in the pathogenesis of carcinomas of the extrahepatic bile ducts.

Clinical features

Cancer of the gallbladder usually presents late in its course. The signs and symptoms are not specific, often resembling those of chronic cholecystitis. Right upper quadrant pain is common.

Computed tomography and ultrasonography can be used to demonstrate the lesion.

Carcinomas of the extrahepatic bile ducts usually present relatively early with obstructive jaundice, which can rapidly progress or fluctuate. Jaundice usually appears while the tumour is relatively small before widespread dissemination has occurred. Other symptoms include right upper quadrant pain, malaise, weight loss, pruritus, anorexia, nausea, and vomiting. If cholangitis develops, chills and fever appear. In patients with carcinoma of the proximal bile ducts (right and left hepatic ducts, common hepatic duct), the intrahepatic bile ducts are dilated, the gallbladder is not palpable and the common duct often collapses. Patients with carcinoma in the common or cystic ducts have a distended and palpable gallbladder as well as a markedly dilated proximal duct system, as may be shown by ultrasonography and computerised tomography. Transhepatic cholangiograms and endoscopic retrograde cholangiopancreatography are essential for exact localization of carcinomas of the extrahepatic bile ducts.

Macroscopy

Carcinoma of the gallbladder appears as an infiltrating grey white mass. Some carcinomas may cause diffuse thickening and induration of the entire gallbladder wall. The gallbladder may be distended by the tumour, or collapsed due to obstruction of the neck or cystic duct. It can also assume an hourglass deformity when the tumour arises in the body and constricts the lateral walls. Papillary carcinomas are usually sessile and exhibit a polypoid or cauliflower-like appearance. Mucinous and signet ring cell carcinomas have a mucoid or gelatinous cut surface. Although any type of gallbladder

cancer may show necrosis, undifferentiated giant cell and small cell carcinomas are usually the most necrotic. Submucosal growth is an important feature of signet ring and small cell carcinomas.

Carcinomas of the extrahepatic bile ducts have been divided into polypoid, nodular, scirrhous constricting, and diffusely infiltrating types. This separation can provide a guide to the operative procedure, extent of resection, and prognosis. However, except for the polypoid tumours, this separation is rarely possible in practice because of overlapping gross features. The nodular and scirrhous types tend to infiltrate surrounding tissues and are difficult to resect. The diffusely infiltrating types tend to spread linearly along the ducts.

Tumour staging

There are separate TNM classifications for carcinomas of the gallbladder, extrahepatic bile ducts, and the ampulla of Vater.

Histopathology

The histological classification of tumours of the gallbladder and extrahepatic bile ducts is essentially similar to the previous WHO classification published in 1991 [1774] and to the classification adopted by the AFIP fascicle published in 2000 [35].

Adenocarcinoma

Well to moderately differentiated adenocarcinomas are the most common malignant epithelial tumours of the gallbladder and extrahepatic bile ducts. They are composed of short or long tubular glands lined by cells that vary in height from low cuboidal to tall columnar, superficially resembling biliary epithelium. Mucin is frequently present in the cells and glands. Rarely, the extracellular mucin may

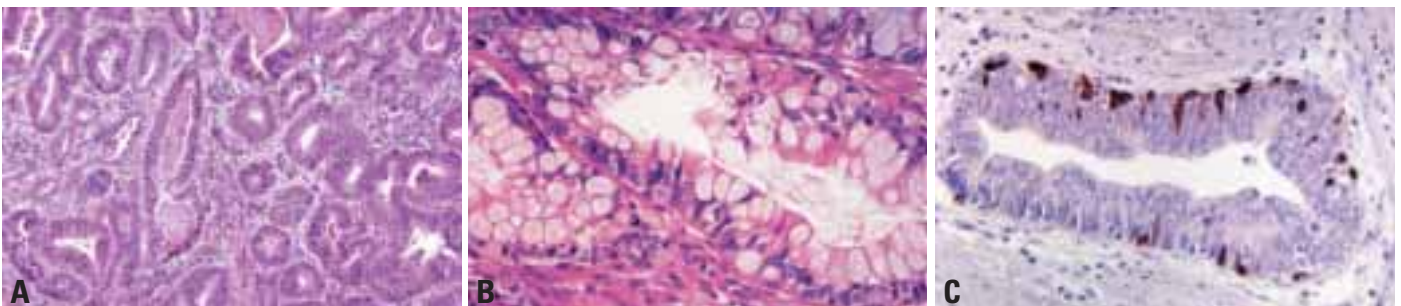


Fig. 9.05 Intestinal type adenocarcinoma. **A** Tubular glands similar to colonic adenocarcinoma. **B** Goblet cell type of adenocarcinoma. **C** Numerous serotonin containing cells in a neoplastic gland.

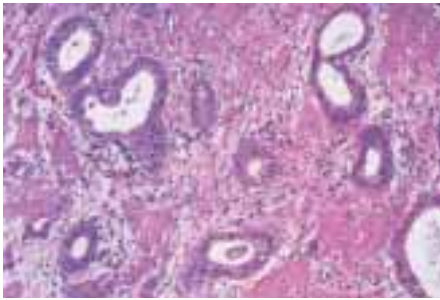


Fig. 9.06 Well differentiated adenocarcinoma infiltrating gallbladder wall.

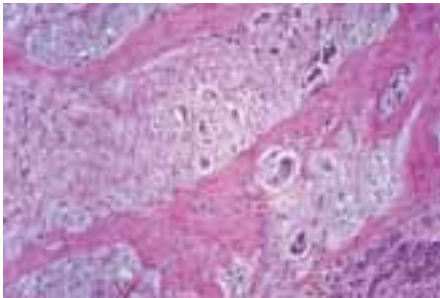


Fig. 9.07 Mucinous adenocarcinoma of gallbladder.

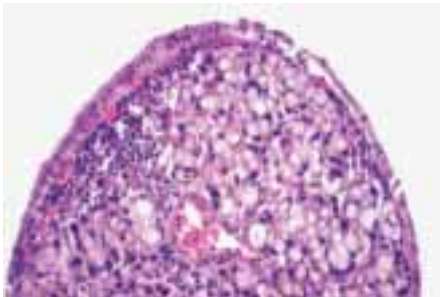


Fig. 9.08 Signet-ring cell carcinoma of gallbladder.

become calcified {1465, 1606}. About one-third of the well differentiated tumours show focal intestinal differentiation and contain goblet and endocrine cells {36, 2152, 2158}. The endocrine cells may be numerous and show immunoreactivity for serotonin and peptide hormones, but a diagnosis of neuroendocrine neoplasm is not warranted. Paneth cells may rarely be seen. An extremely well differentiated adenocarcinoma with gastric foveolar phenotype that simulates adenoma has been described in the extrahepatic bile ducts {39}. Adenocarcinomas may show cribriform or angiosarcomatous patterns. They may also contain cyto- and syncytiotrophoblast cells.

Extrahepatic bile duct adenocarcinomas tend to be better differentiated than their gallbladder counterparts. Many gallbladder carcinomas are immunoreactive for TP53 {1907, 2125}

Histological variants of adenocarcinoma

Papillary adenocarcinoma. This malignant tumour is composed predominantly of papillary structures lined by cuboidal or columnar epithelial cells often containing variable amounts of mucin. Some tumours show intestinal differentiation with collections of goblet, endocrine, and Paneth cells. Papillary adenocarcinomas may fill the lumen before invading the wall. Papillary adenocarcinomas appear to be more frequent in the gallbladder than in the extrahepatic biliary tree {2150}. In addition, skip lesions may be observed in approximately 10% of cases {1989}.

Adenocarcinoma, intestinal type. This unusual variant of adenocarcinoma is composed of tubular glands or papillary structures lined predominantly by cells with an intestinal phenotype, namely goblet cells or colonic-type epithelium or both, with or without a variable number of endocrine and Paneth cells {41}.

Mucinous adenocarcinoma. Mucinous adenocarcinomas of the biliary tree are similar to those that arise in other anatomic sites. By definition, more than 50% of the tumour contains extracellular mucin {1774}. There are two histological variants of mucinous adenocarcinomas of the gallbladder and extrahepatic bile ducts: one variant is characterized by neoplastic glands distended with mucin and lined by columnar cells with mild to moderate nuclear atypia, and the second variant is characterized by small groups or clusters of cells surrounded by abundant mucin. Some tumours show both growth patterns. The abundant mucin makes the tumour appear hypocellular.

Cystadenocarcinoma refers to a unilocular or multilocular glandular tumour that may be the result of malignant transformation of a cystadenoma.

Clear cell adenocarcinoma. This rare malignant tumour is composed predominantly of glycogen-rich clear cells having well-defined cytoplasmic borders and hyperchromatic nuclei. In addition to clear cells, a variable number of cells contain eosinophilic granular cytoplasm. The clear cells line glands or are arranged in nests, sheets, cords, trabeculae or papillary structures {40, 145, 1856}. Foci of conventional adenocarci-

noma with focal mucin production are usually found and are useful in separating primary from metastatic clear cell carcinomas. In some clear cell adenocarcinomas of the biliary tree the columnar cells contain subnuclear and supranuclear vacuoles similar to those seen in secretory endometrium. Focal hepatoid differentiation with production of alpha-fetoprotein has been documented in clear cell carcinomas of the gallbladder {2000}.

Signet-ring cell carcinoma. Cells containing intracytoplasmic mucin displacing the nuclei toward the periphery predominate in this variant of adenocarcinoma. A variable amount of extracellular mucin is usually present. Lateral spread through the lamina propria is a common feature.



Fig. 9.09 Adenosquamous carcinoma of gallbladder.

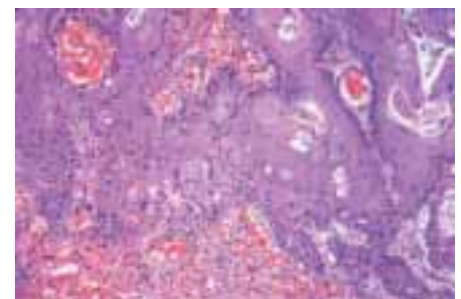


Fig. 9.10 Squamous cell carcinoma of gallbladder.

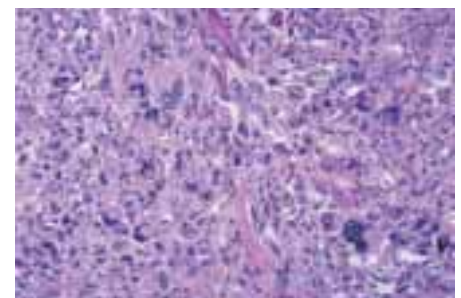


Fig. 9.11 Undifferentiated carcinoma of gallbladder, spindle and giant cell type. No glandular differentiation.

A diffusely infiltrating linear pattern resembling linitis plastica of the stomach is observed in some cases.

Adenosquamous carcinoma

This tumour consists of two malignant components, one glandular and the other squamous. The extent of differentiation of the two components varies, but in general they tend to be moderately differentiated {1357, 1867}. Keratin pearls are often present in the squamous component, and mucin is usually demonstrable in the neoplastic glands.

Squamous cell carcinoma

This malignant epithelial tumour is composed entirely of squamous cells. The extent of differentiation varies considerably. Keratinizing and non-keratinizing types exist. Spindle cells predominate in some poorly differentiated tumours, which may be confused with sarcomas. Immunostains for cytokeratin may clarify the diagnosis in these spindle cell cases. The tumour may arise from areas of squamous metaplasia. Intraepithelial neoplasia can be found in the metaplastic squamous mucosa {35}.

Small cell carcinoma

This lesion is covered in the chapter on endocrine tumours of the gallbladder and extrahepatic bile ducts.

Undifferentiated carcinoma

Undifferentiated carcinomas are more common in the gallbladder than in the extrahepatic bile ducts. Characteristically, glandular structures are absent in undifferentiated carcinomas. There are four histological variants {40, 411, 643, 1360}.

Undifferentiated carcinoma, spindle and giant cell type. The spindle and giant cell type is the most common and resem-

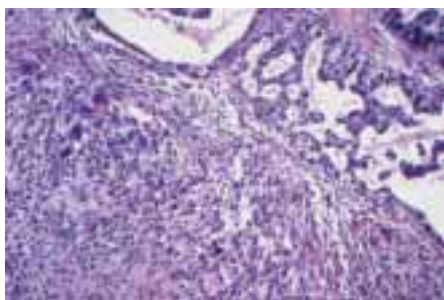


Fig. 9.12 Carcinosarcoma of gallbladder. The tumour shows malignant glandular elements and a sarcomatous component with osteoid formation.

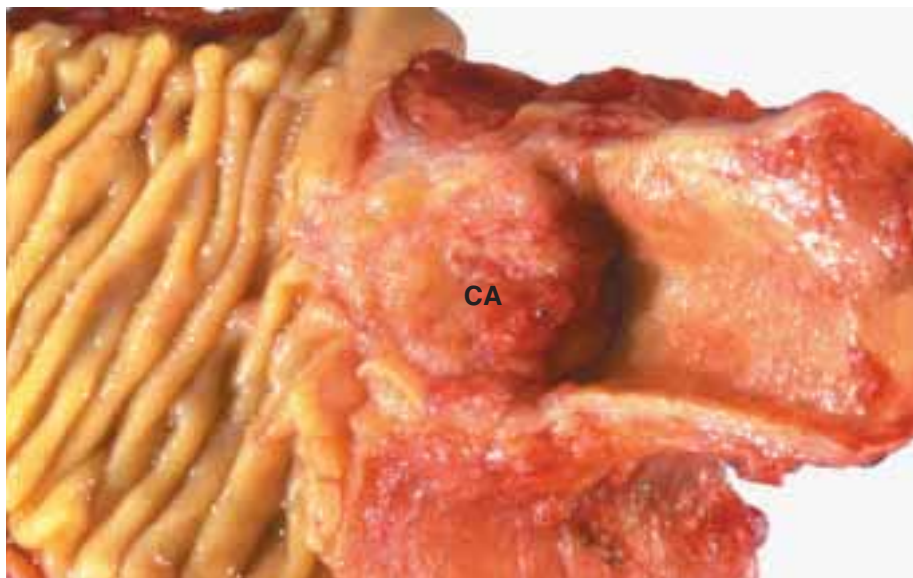


Fig. 9.13 Adenocarcinoma (CA) of the distal common bile duct, infiltrating the duodenal wall.

bles a sarcoma. These tumours have been referred to as pleomorphic spindle and giant cell adenocarcinomas or sarcomatoid carcinomas. They consist of variable proportions of spindle, giant and polygonal cells, but foci of well-differentiated neoplastic glands are usually found in some of these tumours after extensive sampling. Areas of squamoid differentiation may also be seen. Rarely, foci of osteoclast-like multinucleated giant cells are present. The presence of cytokeratin in the spindle cells may help to distinguish this tumour from carcinosarcoma.

Undifferentiated carcinoma with osteoclast-like giant cells. This variant contains mononuclear cells and numerous evenly spaced osteoclast-like giant cells resembling giant cell tumour of bone. The mononuclear cells show immunoreactivity for cytokeratin and epithelial membrane antigen while the osteoclast-like giant cells are positive for histiocytic markers such as CD68.

Undifferentiated carcinoma, small cell type. The tumour is composed of sheets of round cells with vesicular nuclei and prominent nucleoli that occasionally contain cytoplasmic mucin.

Undifferentiated carcinoma, nodular or lobular type. The fourth variant consists of well defined nodules or lobules of neoplastic cells superficially resembling breast carcinoma.

Carcinosarcoma

This malignant tumour consists of a mixture of two components: carcinomatous

and sarcomatous. The epithelial elements usually predominate in the form of glands but may be arranged in cords or sheets. Foci of malignant squamous cells are occasionally seen. The mesenchymal component includes foci of heterologous elements such as chondrosarcoma, osteosarcoma, and rhabdomyosarcoma. Cytokeratin and carcinoembryonic antigen are absent from the mesenchymal

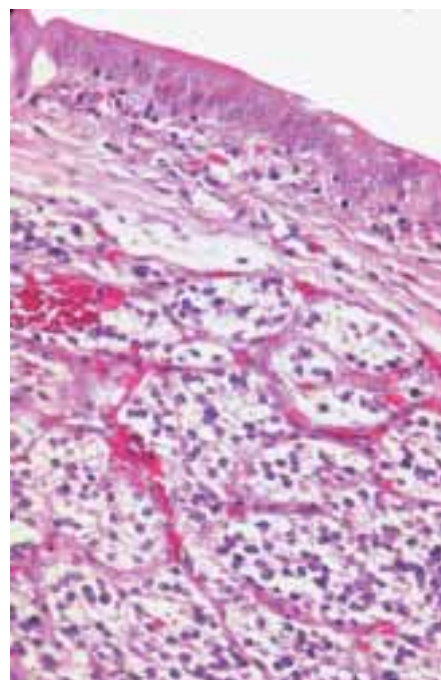


Fig. 9.14 Clear cell carcinoma of extrahepatic bile duct. The overlying biliary epithelium is non-neoplastic.

component, which helps to distinguish carcinosarcomas from spindle and giant cell carcinomas.

Grading

Adenocarcinomas can be divided into well, moderately, or poorly differentiated types. The diagnosis of well differentiated adenocarcinoma requires that 95% of the tumour contains glands. For moderately differentiated adenocarcinoma 40 to 94% of the tumour should be composed of glands and for poorly differentiated adenocarcinomas 5 to 39% of the tumour should contain glands. Undifferentiated carcinomas display less than 5% of glandular structures.

Precursor lesions

Adenoma

Adenomas are benign neoplasms of glandular epithelium (intraepithelial neoplasia) that are typically polypoid, single and well-demarcated. They are more common in women than in men [42]. There is a wide age range; although mostly a disease of adults rare gallbladder adenomas occur in children [1256, 2126]. They are more common in the gallbladder than in the extrahepatic bile ducts, and are found in 0.3-0.5% of gallbladders removed for cholelithiasis or chronic cholecystitis. A small proportion of adenomas progress to carcinoma [42, 909, 967].

Adenomas are often small, asymptomatic, and usually discovered incidentally during cholecystectomy, but they can be multiple, fill the lumen of the gallbladder and be symptomatic. Occasionally, adenomas of the gallbladder occur in

association with the Peutz-Jeghers syndrome [521] or with Gardner syndrome [1900, 2041]. Adenomas of the extrahepatic bile ducts are usually symptomatic and cause biliary obstruction. These benign tumours are not associated with lithiasis.

According to their pattern of growth, they are divided into three types: tubular, papillary, and tubulopapillary. Cytologically, they are classified as: pyloric gland type, intestinal type, and biliary type. Tubular adenomas of pyloric gland type are more common in the gallbladder while intestinal type adenomas are more common in the extrahepatic bile ducts [42].

Tubular adenoma, pyloric-gland type. A benign tumour composed of closely packed short tubular glands that are similar to pyloric glands. Early lesions appear as well demarcated nodules embedded in the lamina propria and covered with normal biliary epithelium. They are composed of lobules that contain closely packed pyloric-type glands, some of which may be cystically dilated. The epithelial cells are columnar or cuboidal with vesicular or hyperchromatic nuclei and small nucleoli and variable amounts of cytoplasmic mucin. Nodular aggregates of cytologically bland spindle cells with eosinophilic cytoplasm but without keratinization or intercellular bridges known as squamoid morules [984, 1361] are present in about 10% of the cases, whereas frank squamous metaplasia is exceedingly rare. Paneth cells and endocrine cells are often present. By immunohistochemistry, serotonin and a variety of peptide hormones

including somatostatin, pancreatic polypeptide, and gastrin have been detected in the cytoplasm of these cells. Smaller lesions show low-grade intraepithelial neoplasia, but larger adenomas may have high-grade changes or foci of invasive carcinoma. As they enlarge, most adenomas develop a pedicle and project into the lumen. Rarely, they extend into or arise from Rokitansky-Aschoff sinuses, a finding that should not be mistaken for carcinoma [42].

Tubular adenoma, intestinal type. This benign tumour is composed of tubular glands lined by cells with an intestinal phenotype, and closely resembles colonic adenomas. It consists of tubular glands lined by pseudostratified columnar cells with elongated hyperchromatic nuclei, and high-grade dysplastic changes are frequent. The glands lack invasive properties and focally are arranged in well defined lobules. The adenomatous epithelium may extend into the Rokitansky-Aschoff sinuses, a finding that should not be confused with stromal invasion. Clusters of goblet, Paneth, and endocrine cells are usually mixed with the columnar cells. Serotonin and, less frequently, peptide hormones have been identified in the endocrine cells by immunohistochemistry. Hyperplasia of metaplastic pyloric type glands is often seen at the base of the adenomas.

Papillary adenoma, intestinal type. This benign tumour consists predominantly of papillary structures lined by dysplastic cells with an intestinal phenotype. These adenomas, which usually arise in a background of pyloric gland metaplasia, may

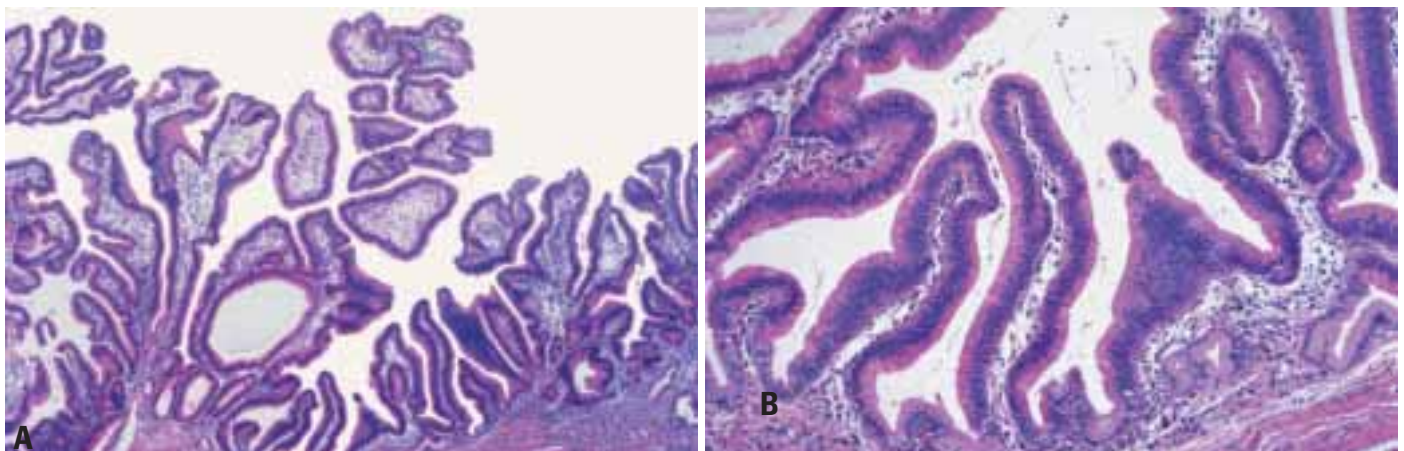


Fig. 9.15 Papillary adenoma of gallbladder, intestinal type. **A** Numerous papillary structures project into lumen. **B** Pseudostratified columnar cells with scattered goblet and Paneth cells.

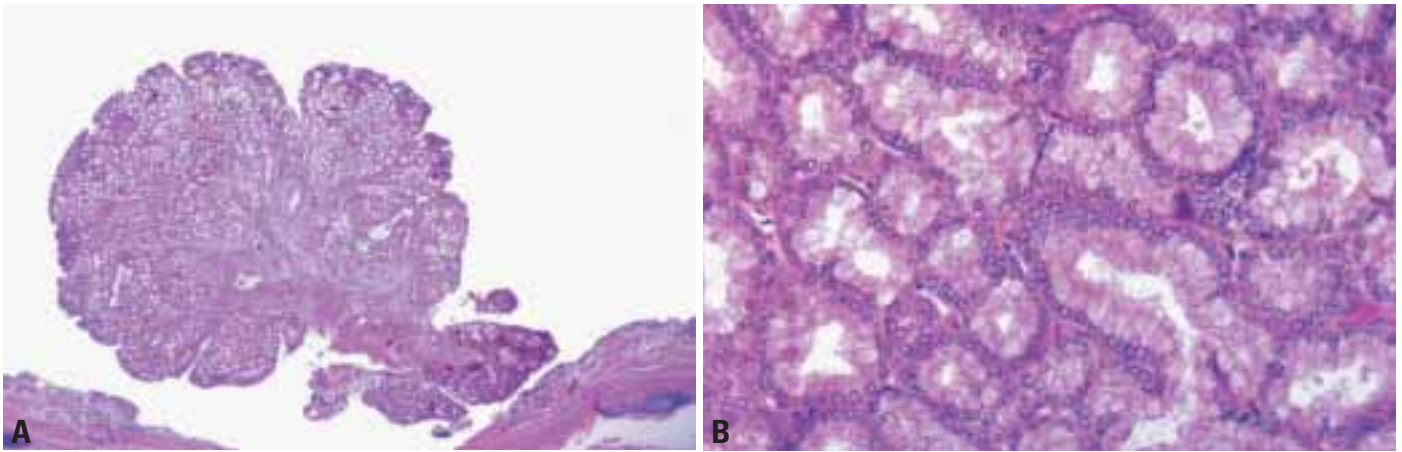


Fig. 9.16 A, B Tubular adenoma of gallbladder, pyloric gland type.

occur in the gallbladder or the extrahepatic bile ducts. In a series of five intestinal type papillary adenomas of the gallbladder, one progressed to invasive carcinoma [42]. The predominant cell is columnar with elongated hyperchromatic nuclei and little or no cytoplasmic mucin. The cells are pseudostratified, mitotically active, and indistinguishable from those of villous adenomas arising in the large intestine. Tubular glands lined by the same type of epithelium, but representing less than 20% of the tumour, may also be found. Dysplastic changes are more extensive than in pyloric-gland type adenomas. Also present are goblet, Paneth, and serotonin-containing cells. Some of the endocrine cells are immunoreactive for peptide hormones.

Papillary adenoma, biliary type. This lesion consists predominantly of papillary structures lined by cells with a biliary phenotype. It is well demarcated and consists of papillary structures lined by tall columnar cells, which except for the presence of more cytoplasmic mucin show minimal variation from normal gallbladder epithelium. Endocrine or Paneth cells are not found. Only mild dysplastic changes are noted. In situ or invasive carcinoma has not been reported in association with these adenomas. This is the rarest form of adenoma of the gallbladder; we have seen only one case. Most papillary lesions composed of normal-appearing gallbladder epithelium are examples of hyperplasia secondary to chronic cholecystitis.

Tubulo-papillary adenoma. When tubular glands and papillary structures each

comprise more than 20% of the tumour, the term tubulo-papillary adenoma is applied. Two subtypes are recognized: one is composed of tubular glands and papillary structures similar to those of tubulovillous intestinal adenomas; the other subtype consists of tubular glands similar to pyloric glands and papillary structures often lined by foveolar epithelium. Paneth and endocrine cells are present in some. Rarely, tubulo-papillary adenomas arise from the epithelial invaginations of adenomyomatous hyperplasia.

Other benign biliary lesions

Biliary cystadenoma. These lesions resemble their intrahepatic counterparts (see chapter on bile duct cystadenoma and cystadenocarcinoma). Cystadenomas are seen predominantly among adult females and are usually symptomatic. Some of the tumours may measure up to 20 cm in diameter leading to obstructive jaundice or cholecystitis-like symptoms. More common in the extrahepatic bile ducts than in the gallbladder, cystadenomas are multiloculated neoplasms that contain mucinous or serous fluid and are lined by columnar epithelium reminiscent of bile duct or foveolar gastric epithelium [404]. Occasionally endocrine cells are present. The cellular subepithelial stroma resembles ovarian stroma and shows immunoreactivity for estrogen and progesterone receptors [2029]. The stroma also shows variable fibrosis. Malignant transformation (cystadenocarcinoma) can occur [404].

Papillomatosis (adenomatosis). Papillomatosis is a clinicopathological condition

characterized by multiple recurring papillary adenomas, that may involve extensive areas of the extrahepatic bile ducts and even extend into the gallbladder and intrahepatic bile ducts. The disease affects both sexes equally. Most patients are adults between 50 and 60 years. Complete excision of the multicentric lesions is difficult and local recurrence is common. The lesion consists of numerous papillary structures as well as complex glandular formations. Because severe dysplasia is often present, papillomatosis is difficult to distinguish from papillary carcinoma. Some regard this lesion as a form of low-grade multicentric intraductal papillary carcinoma. Papillomatosis has a greater potential for malignant transformation than solitary adenomas.

Intraepithelial neoplasia (dysplasia)

If intraepithelial neoplasia is found, multiple sections should be taken to exclude invasive cancer. Cholecystectomy is a curative surgical procedure for patients with in situ carcinoma or with carcinoma extending into the lamina propria [35].

Epidemiology. The rate of intraepithelial neoplasia of the gallbladder reflects that of invasive carcinoma. In countries in which carcinoma of the gallbladder is endemic, the prevalence is higher than in countries in which this tumour is sporadic. Studies from different countries have shown that the incidence of high-grade dysplasia or carcinoma in situ in gallbladders with lithiasis has varied from 0.5-3% [35]. This variation in the incidence of intraepithelial neoplasia is also attributable to other factors such as lack of uniformity in morphological criteria and sampling methods.

Macroscopic features. Intraepithelial neoplasia is usually not recognized on macroscopic examination because it often occurs in association with chronic cholecystitis. The mucosa may appear granular, nodular, plaque-like, or trabeculated. The papillary type of intraepithelial neoplasia usually appears as a small, cauliflower-like excrescence that projects into the lumen and can be recognized on close inspection. However, in most cases, the gallbladder shows only a thickened and indurated wall, the result of chronic inflammation and fibrosis.

Microscopic features. Microscopically two types of intraepithelial neoplasia are recognized: papillary and flat, the latter being more common. The papillary type is characterized by short fibrovascular stalks that are covered by dysplastic or neoplastic cells.

Intraepithelial neoplasia usually begins on the surface epithelium and subsequently extends downward into the Rokitansky-Aschoff sinuses and into metaplastic pyloric glands. Columnar, cuboidal, and elongated cells with variable degrees of nuclear atypia, loss of polarity, and occasional mitotic figures are characteristic. The dysplastic cells are usually arranged in a single layer, but can be pseudostratified. Later, papillary structures covered by dysplastic epithelium may form. The large nuclei of dysplastic cells may be round, oval, or fusiform, with one or two nucleoli that are more prominent than those of normal cells.

The cytoplasm is usually eosinophilic and contains non-sulphated acid and neutral mucin. Goblet cells are found in one third of cases. An abrupt transition

between normal-appearing columnar cells and intraepithelial neoplasia is seen in nearly all cases. In general, the cell population of dysplasia is homogeneous, unlike the heterogeneous cell population of the epithelial atypia of repair. Widespread involvement of the mucosa by intraepithelial neoplasia often occurs. For this reason, we have suggested that some, if not most, invasive carcinomas of the gallbladder arise from a field change within the epithelium.

The cells of intraepithelial neoplasia are reactive for CEA and for the carbohydrate antigen CA19-9 [35]. Expression of p53 occurs in some lesions [2125].

Differential diagnosis. Reactive epithelial changes ('atypia of repair') differs from intraepithelial neoplasia in consisting of a heterogeneous cell population in which columnar mucus-secreting cells, low cuboidal cells, atrophic-appearing epithelium, and pencil-like cells are present. In addition, there is a gradual transition of the cellular abnormalities, in contrast with the abrupt transition seen in intraepithelial neoplasia. The extent of nuclear atypia is less pronounced in reactive changes and immunoreactivity for p53 protein is absent, while usually positive in intraepithelial neoplasia.

High-grade intraepithelial neoplasia and carcinoma in situ

In cases where the cells have all the cytological features of malignancy with frequent mitotic figures, nuclear crowding and prominent pseudostratification, the term carcinoma in situ may be used. Neoplastic cells first appear along the surface epithelium and later spread into the epithelial invaginations and antral-

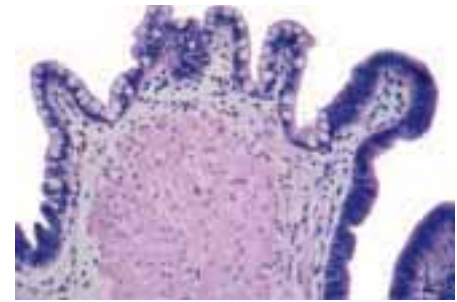


Fig. 9.18 High-grade intraepithelial neoplasia adjacent to intestinal metaplasia with numerous mature goblet cells.

type metaplastic glands. In the late stages of carcinoma in situ, the histological picture is that of back-to-back glands located in the lamina propria but often connected with the surface epithelium. However, not all in situ carcinomas exhibit this type of growth pattern. Some show distinctive papillary features with small fibrovascular stalks lined by neoplastic cells. Not infrequently, a combination of these growth patterns is seen.

The differential diagnosis between high-grade intraepithelial neoplasia (severe dysplasia) and carcinoma in situ is difficult and often impossible in many cases. This is not important because the two lesions, which vary only in degree histologically, are closely related biologically.

Histological variants of carcinoma in situ.

An in situ carcinoma composed of goblet cells, columnar cells, Paneth cells, and endocrine cells, has been described, which may represent an in situ phase of intestinal-type adenocarcinoma [35, 41]. Another type of in situ intestinal-type carcinoma is composed of cells closely resembling those of colonic carcinomas at the light and electron microscopic lev-

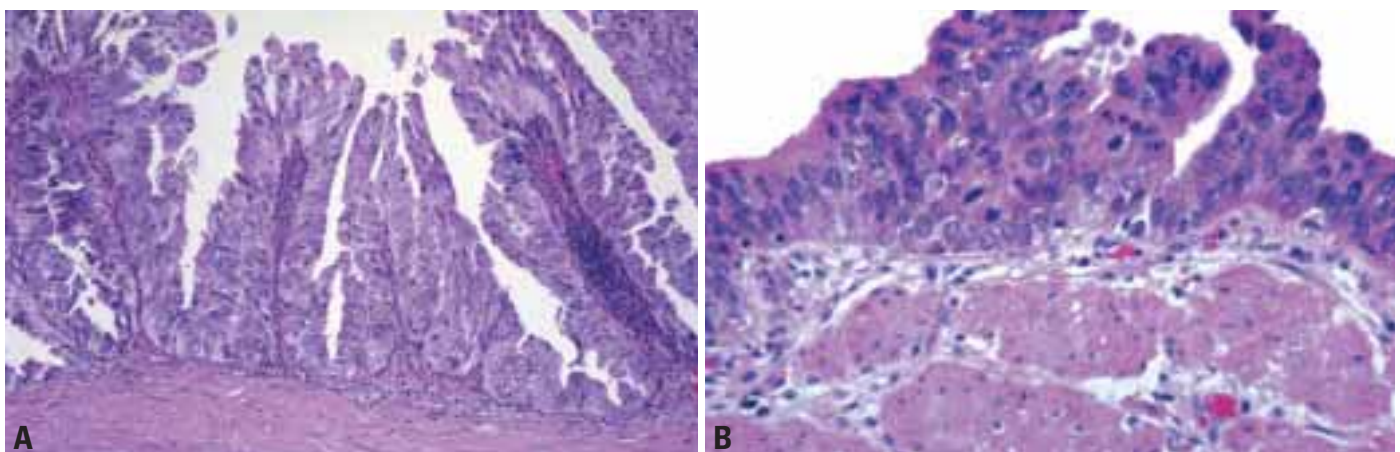


Fig. 9.17 High-grade intraepithelial neoplasia (carcinoma in situ) of gallbladder.

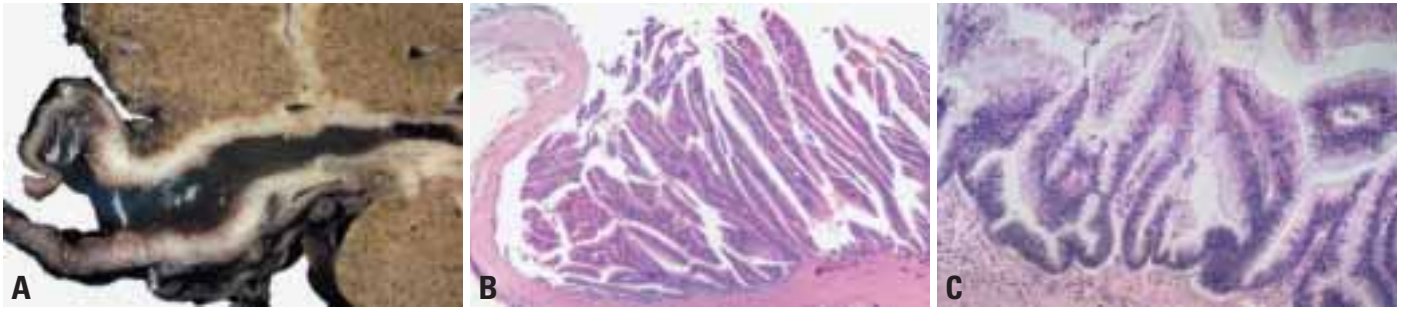


Fig. 9.19 Biliary papillomatosis. **A** Large, thickened intrahepatic and extrahepatic bile ducts. **B** Villous pattern. **C** There is no invasion by tumour cells.

els. The neoplastic columnar cells extend into the epithelial invaginations and the antral-type glands. Formation of cribriform structures in the lamina propria occurs. This tumour also has scattered endocrine cells, most of which are immunoreactive for serotonin.

Two examples of in situ signet-ring cell carcinoma confined to the surface epithelium and to the epithelial invaginations of the gallbladder have been reported {40}. These in situ signet ring cell carcinomas represented incidental findings in cholecystectomy specimens and were cytologically similar to those reported in the stomach. This unusual form of carcinoma in situ should be distinguished from epithelial cells which acquire signet-ring cell morphology when desquamated within the lumen of dilated metaplastic pyloric glands in cases of chronic cholecystitis and from mucin-containing histiocytes (muciphages).

The morphological type of in situ carcinoma does not always correspond with that of the invasive carcinoma. For example, we have seen conventional adenocarcinoma in situ in the mucosa adjacent to invasive squamous, small cell, and undifferentiated carcinomas.

The wall of the gallbladder with dysplasia or carcinoma in situ usually shows variable inflammatory changes, typically with a predominance of lymphocytes and plasma cells, although lymphoid follicles with germinal centers, xanthogranulomatous inflammation or an acute inflammatory reaction may be present.

Molecular pathology

Mutations of *TP53* are found in the vast majority of invasive gallbladder carcinomas {2124, 2127}. Loss of heterozygosity (LOH) at chromosomal loci 8p (44%), 9p (50%) and 18q (31%) are also frequently detected {2127}. These genetic

alterations are considered early events, while *RAS* mutations and LOH at 3p, *RB*, and 5q occur less frequently and are considered late events, probably related to tumour progression. Amplification of the *c-erbB-2* gene, that codes for a glycoprotein structurally similar to the epidermal growth factor receptor was detected in 30 of 43 invasive gallbladder carcinomas {1036}. However, no correlation between *c-erbB-2* gene amplification and prognosis was found.

In contrast to lesions of the gallbladder, the incidence of *TP53* mutations in extrahepatic bile duct carcinomas is lower and appears to be a late molecular event.

Although the frequency of *KRAS* mutations in gallbladder carcinomas has ranged from 0%-34% in different studies, most investigators have found these mutations to be significantly higher in extrahepatic bile duct tumours than in gallbladder carcinomas {2067}. Depend-

ing on the study, the incidence of *KRAS* mutations in extrahepatic bile duct carcinomas has varied from 0-100% {1586}, but most likely, the true incidence is around 56% {2067}. However, the incidence of *KRAS* mutations is greater in gallbladder carcinomas associated with an anomalous junction of the pancreaticobiliary duct than in carcinomas not associated with this congenital anomaly {661}. These molecular pathology findings support the concept that gallbladder carcinogenesis requires a number of genetic alterations involving activation of oncogenes or inactivation of tumour suppressor genes.

The molecular pathology of adenomas of the gallbladder differs from that of carcinomas. None of 16 adenomas showed *TP53* or p16 *Ink4/CDKN2a* gene mutations, which are common in carcinomas {2126}. Four adenomas had *KRAS* mutations (2 in codon 12 and 2 in codon 61) which are considered rare and late

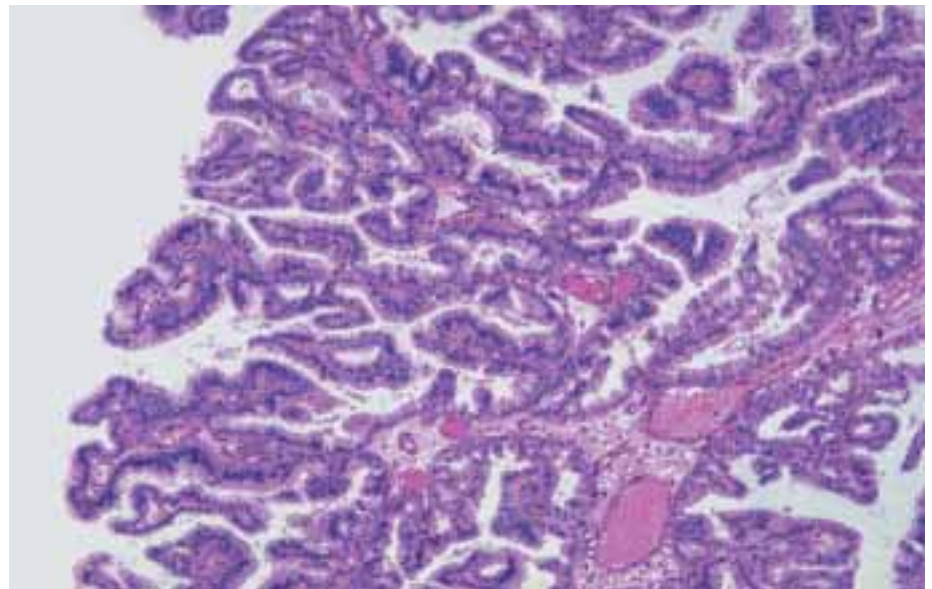


Fig. 9.20 Papillomatosis of extrahepatic bile duct.

events in the pathogenesis of carcinomas of the gallbladder. Only one adenoma of intestinal type showed loss of heterozygosity at 5q22 {2126}.

Intraepithelial neoplasia (both dysplasia and carcinoma in situ) shows a high incidence of loss of heterozygosity at the *TP53* gene locus. Other molecular abnormalities include loss of heterozygosity at 9p and 8p loci and the 18q gene. These abnormalities are also early events and

most likely contributing factors in the pathogenesis of gallbladder carcinoma. However, *KRAS* mutations were not detected in intraepithelial neoplasia {2125}.

Prognosis and predictive factors

The prognosis of tumours of the extrahepatic biliary tract depends primarily on the extent of disease and histological type {694, 695}. Polypoid tumours (which

histologically often prove to be papillary carcinomas) have the best prognosis. Non-invasive papillary carcinomas are associated with a better prognosis than other types of invasive carcinomas. Perineural invasion and lymphatic permeation are common in the extrahepatic bile duct carcinoma and are significant prognostic factors {2150, 376}.

Endocrine tumours of the gallbladder and extrahepatic bile ducts

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Definition

Tumours with endocrine differentiation arising from the extrahepatic bile ducts and gallbladder.

Epidemiology

In an analysis of 8305 cases of carcinoids of all sites, 19 cases of gallbladder and one case of biliary tract carcinoids were recorded, representing 0.2% and 0.01% of cases {1251}. The average age of presentation (60 years) is lower than the average age of presentation of non-carcinoid neoplasms (71 years). The reported male/female ratio is 1:1.2 {1251}. Small cell carcinomas of the gallbladder, like other carcinomas, are more common in females (M/F ratio: 1:1.8) {1359}. The reported average age of presentation is 65 years (range, 43-83 years) {1359}. Small cell carcinomas represent about 4% of all malignant tumours of the gallbladder {1359, 37}.

Aetiology

Small cell carcinomas are more common in females and are almost always associ-

ated with stones {34, 1524}. There is no available information on the aetiology of the very rare carcinoid tumours of the extrahepatic biliary tree.

Localization

All types of endocrine tumours are more often located in the gallbladder than in extrahepatic bile ducts {1251, 2157, 1639, 34}.

Clinical features

Gallbladder carcinoids can cause recurrent upper quadrant pain. Carcinoids of extrahepatic bile ducts typically produce the sudden onset of biliary colic and/or sometimes painless jaundice {1639}.

In the majority of cases of small cell carcinoma, the chief complaint is abdominal pain. Other clinical features include abdominal mass, jaundice, and ascites {1359}. A case of primary gastrinoma of the common hepatic duct with Zollinger-Ellison syndrome {1175}, and a patient with Cushing syndrome due to an ACTH-secreting small cell carcinoma have been reported {1801}.

Macroscopy

Carcinoids are usually small grey-white or yellow submucosal nodules or polyps, sometimes infiltrating the muscular wall, that may be located in any part of the gallbladder or the extrahepatic biliary tree {1639, 34}. Small cell carcinomas appear as a nodular mass or diffusely invade the gallbladder wall {1359}. A significant proportion of mixed endocrine-exocrine carcinomas have a polypoid or protruding aspect {2157, 2030}.

Histopathology

Carcinoid (well differentiated endocrine tumour)

The cells forming this tumour are uniform in size, with round or oval nuclei, inconspicuous nucleolus, and eosinophilic cytoplasm. Neoplastic cells are arranged in combined patterns with trabecular anastomosing structures, tubular structures and solid nests {1639, 299, 603, 177}. Tumour cells show positive staining for Grimelius silver {1639, 195, 115, 926, 1205}, chromogranin {1639, 57}, neuron-specific enolase {195, 115, 57}, and sev-

eral hormones including serotonin {115, 57}, gastrin {1175, 1156}, and somatostatin {603, 57}.

Cases showing regional or distant metastases {177, 926, 1205, 57} or signs of local aggressive growth, including invasion of the entire wall {1205, 57} and neural invasion {1205}, should be considered as well differentiated endocrine carcinomas (malignant carcinoids).

Small cell carcinoma (poorly differentiated endocrine carcinoma)

The cell population and growth patterns of this tumour are similar to those of small cell carcinoma of the lung {38, 40, 1359}. Small cell carcinomas appear to be more common in the gallbladder than in the extrahepatic bile ducts. Some mimic carcinoid tumours.

Most tumours are composed of round or fusiform cells arranged in sheets, nests, cords, and festoons. Rosette-like structures and tubules are occasionally present. Extensive necrosis and subepithelial growth are constant features. In necrotic areas, intense basophilic staining of the blood vessels occurs. The tumour cells have round or ovoid hyperchromatic nuclei with inconspicuous nucleoli. A few tumour giant cells can be observed in some cases {1359, 34}. Occasionally, focal glandular configurations similar to

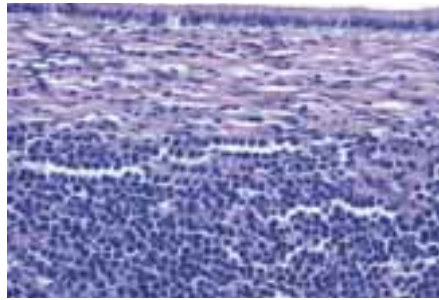


Fig. 9.22 Small cell carcinoma lying below normal gallbladder epithelium.

those of adenocarcinomas, and foci of squamous differentiation are seen {40, 774, 40, 1359}. Mitotic figures are frequently observed and they are reported to range from 15 to 206 (mean 75) per 10 high power fields {1359}.

Most small cell carcinomas show scattered Grimelius positive cells. In addition, tumour cells immunoexpress epithelial markers such as EMA, AE1/AE3 and CEA, and endocrine markers such as NSE, chromogranin A, Leu7, serotonin, somatostatin, and ACTH {1359, 34}. Ultrastructurally, a small number of dense core secretory granules can be found {34, 37}.

Mixed endocrine-exocrine carcinoma

A significant number of cases reported in the older literature as carcinoids, includ-

ing the cases reviewed by Yamamoto et al. {2157}, are in fact mixed endocrine-exocrine carcinomas. These are composite tumours in which areas of adenocarcinoma intermingle with areas of endocrine cell carcinoma formed by solid and/or trabecular structures with cells which are argyrophilic and immunoreactive for endocrine markers, including NSE, chromogranin, serotonin and gastrin {2157, 2030, 1405, 1575}. The adenocarcinoma component is usually tubular or papillary, formed by columnar cells, goblet cells and sometimes Paneth cells, but a case of a combined diffuse type tumour in which mucin-containing signet-ring cells were admixed with clear endocrine cells has also been reported {1455}.

These tumours behave as adenocarcinomas and, therefore, are clinically more aggressive than carcinoids. Adenocarcinoma with endocrine cells should not be included in this category.

Genetic susceptibility

Carcinoids of the gallbladder and extrahepatic bile ducts are infrequently associated with the Zollinger-Ellison, MEN I, or the carcinoid syndromes. One patient with von Hippel-Lindau syndrome and a carcinoid tumour of the extrahepatic bile ducts has been reported.

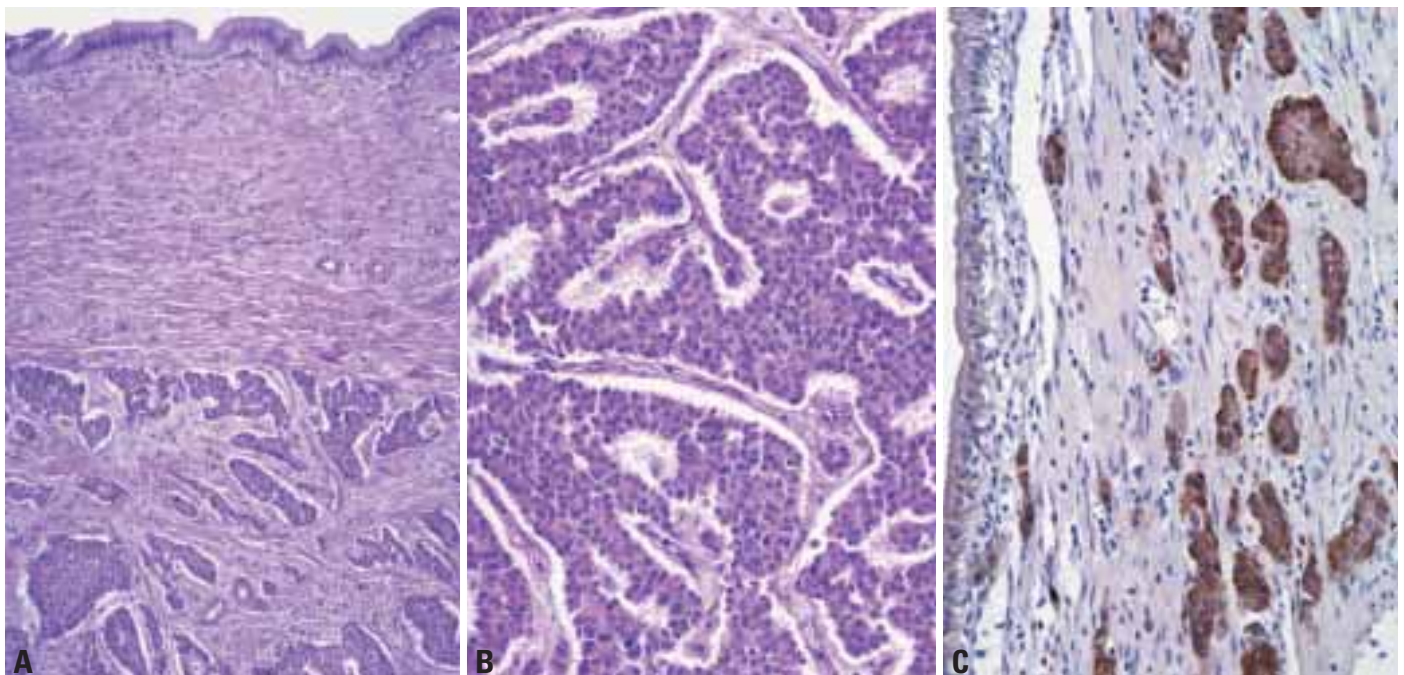


Fig. 9.21 Carcinoid tumour of common bile duct. **A** A band of fibrous tissue separates the tumour from normal bile duct epithelium. **B** Carcinoid cells with round nuclei and eosinophilic cytoplasm. **C** The tumour cells are immunoreactive for serotonin.

Genetics

Overexpression of *TP53* has been found in 64% of small cell carcinomas of the gallbladder {1359}, compared with a frequency of 44% in small cell carcinomas of the lung {773} and 75% in small cell carcinomas of the stomach {1589}.

Prognostic factors

The percentage of gallbladder carcinoids showing regional and distant

metastases has been estimated as approximately 44% and 11%, respectively {1251}. The 5-year survival rate was 41% in SEER data. Carcinoid tumours larger than 2 cm often extend into the liver or metastasize. Complete excision of small tumours is usually curative. The prognosis of small cell carcinoma of the gallbladder is poor, with only one of 18 patients {34} surviving 11 months following cholecystectomy, radiotherapy, and

chemotherapy. In one study, the survival rates differed significantly between stages I, II, III and stage IV {1359}. The survival of patients with small cell carcinoma of the gallbladder appears to be shorter than that of patients with papillary adenocarcinoma {1359}.

Neural and mesenchymal tumours

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Paraganglioma

This benign tumour is composed of chief cells and sustentacular cells arranged in a nesting or Zellballen pattern. The chief cells are argyrophilic and stain for neuron-specific enolase and chromogranin. The sustentacular cells are S-100 protein positive. The tumour is located in either the subserosa or muscular wall of the gallbladder and apparently arises from normal paraganglia. This rare and small tumour is usually an incidental finding in cholecystectomy specimens. Paragangliomas also occur in the extrahepatic bile ducts, where they may be symptomatic.

Granular cell tumour

Granular cell tumours are the most common benign non-epithelial tumours of the extrahepatic biliary tract. They are more common in the bile ducts than in the gallbladder. Although usually single, granu-

lar cell tumours may be multicentric or may coexist with one or more granular cell tumours in other sites, especially the skin.

Ganglioneuromatosis

Ganglioneuromatosis of the gallbladder is a component of the type IIb multiple endocrine neoplasia syndrome. The histological changes consist of Schwann cell and ganglion cell proliferation in the lamina propria as well as enlarged and distorted nerves in the muscle layer and subserosa. Neurofibromatosis is exceedingly rare in the gallbladder but has been reported in association with multiple neurofibromatosis.

Embryonal rhabdomyosarcoma ('sarcoma botryoides') is the most common malignant neoplasm of the biliary tract in childhood. It occurs more frequently in the bile ducts than in the gallbladder. *Kaposi sarcoma* of the extrahepatic bil-

iary tract is an incidental autopsy finding in the acquired immune deficiency syndrome. The haemorrhagic lesions are usually located in the subserosa or muscular wall of the gallbladder or in the periductal connective tissue of the bile ducts. Other malignant non-epithelial tumours are leiomyosarcoma, malignant fibrous histiocytoma and angiosarcoma. Leiomyoma, lipoma, haemangioma, and lymphangioma have been described. A benign stromal tumour of the gallbladder with interstitial cells of Cajal phenotype has been reported recently {35}.

Lymphoma of the gallbladder

A. Wotherspoon

In common with lymphoma elsewhere in the digestive system, primary lymphoma of the gallbladder is defined as an extranodal lymphoma arising in the gallbladder with the bulk of the disease localized to this site {796}. Contiguous lymph node involvement and distant spread may be seen but the primary clinical presentation is in the gallbladder with therapy directed at this site.

Primary lymphoma of the gallbladder is extremely rare, with only about 13 cases

reported {282, 1201, 94, 138}. Two cases of low-grade B-cell MALT lymphoma have been described {1201, 138}, while the majority of the remainder have been large B-cell lymphomas. MALT lymphomas may arise within acquired MALT that is frequently encountered within gallbladders associated with chronic cholecystitis {1943}. The morphology of primary MALT lymphoma of the gallbladder resembles that seen elsewhere in the digestive tract. Lymphoid follicles are

surrounded by an infiltrate of centrocyte-like (CCL) cells showing variable plasma cell differentiation. Infiltration of the epithelium with the formation of lymphoepithelial lesions is a typical feature. Characteristically, the CCL cells show expression of the pan-B-cell markers CD20 and CD79a, and there is frequent expression of bcl-2 protein. Tumour cells are usually negative for CD5 and CD10 but there may be expression of CD43.

Secondary tumours and melanoma

P. DeMatos
P.P. Anthony

Incidence and origins

Although rare in clinical practice, gallbladder and extrahepatic bile duct metastases were encountered in 15% and 6% of cases respectively in an autopsy study of melanoma patients {373}. Indeed, malignant melanoma accounts for more than 50% of all reported cases of gallbladder and intrabiliary metastases {100}. Other metastatic lesions include carcinomas of the kidney, lung, breast, ovary and oesophagus {35, 1674, 2085}; some examples result from transcoelomic spread in the setting of peritoneal carcinomatosis. The gallbladder and extrahepatic bile ducts may also be involved by direct extension from carcinomas of the pancreas, stomach, colon and liver.

Metastatic infiltration of the common bile duct by carcinoma of the breast, giving rise to obstructive jaundice, has been reported {471}. Certain types of non-

Hodgkin lymphoma (e.g. mantle cell lymphoma) may also involve the common bile duct.

Malignant melanoma

Primary malignant melanoma is exceedingly rare in the gallbladder. Junctional activity in the epithelium adjacent to the tumour, absence of a primary melanoma elsewhere in the body and long term survival are important features to distinguish primary from the more commonly occurring metastatic melanoma. However, junctional activity has been reported in metastatic melanoma in the gallbladder.

Clinical features

Involvement of the gallbladder by metastatic tumour rarely produces symptoms, which could explain the paucity of clinical reports published in the literature {373, 427}. When symptoms are present, they are usually those of acute cholecys-

titis {1433, 1013, 427}. Patients with bile duct metastases may present with obstructive jaundice {180}.

Ultrasound may be used to evaluate metastatic lesions within the gallbladder. Computed tomography is also helpful especially for assessing the extent of tumour when therapeutic intervention is contemplated {1013}. The common bile duct is best imaged through the use of ultrasound, endoscopic retrograde cholangiography, and percutaneous transhepatic cholangiography.

Macroscopy

Intraluminal metastases of melanoma tend to be polypoid whilst metastatic carcinoma of the breast and lymphoma produce diffuse infiltrates and strictures.

Histopathology

The features are similar to those observed in other organs.

