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

<table>
<thead>
<tr>
<th>Benign Adenoma</th>
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<tbody>
<tr>
<td>Tubular</td>
<td>8211/0</td>
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<tr>
<td>Papillary</td>
<td>8260/0</td>
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<tr>
<td>Tubulopapillary</td>
<td>8263/0</td>
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<tr>
<td>Biliary cystadenoma</td>
<td>8161/0</td>
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<tr>
<td>Papillomatosis (adenomatosis)</td>
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Intraepithelial neoplasia (dysplasia and carcinoma in situ)

<table>
<thead>
<tr>
<th>Malignant Carcinoma</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
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<tr>
<td>Papillary adenocarcinoma</td>
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<tr>
<td>Adenocarcinoma, intestinal type</td>
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<td>Adenocarcinoma, gastric foveolar type</td>
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<td>Mucinous adenocarcinoma</td>
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<tr>
<td>Clear cell adenocarcinoma</td>
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<td>Signet-ring cell carcinoma</td>
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<td>Adenosquamous carcinoma</td>
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<td>Squamous cell carcinoma</td>
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Non-epithelial tumours

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<tr>
<td>Small cell carcinoma</td>
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<td>Large cell neuroendocrine carcinoma</td>
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<tr>
<td>Undifferentiated carcinoma</td>
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<tr>
<td>Biliary cystadenocarcinoma</td>
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</tbody>
</table>

Carcinoid tumour 8240/3
Goblet cell carcinoid 8243/3
Tubular carcinoid 8245/1
Mixed carcinoid-adenocarcinoma 8244/3
Others

TNM classification of tumours of the gallbladder

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 lamina propria or muscle layer |
| T1a Tumour invades lamina propria |
| T1b Tumour invades muscle layer |
| T2 Tumour invades perimuscular connective tissue, no extension beyond serosa or into liver |
| T3 Tumour perforates serosa (visceral peritoneum) or directly invades into one adjacent organ or both (extension 2 cm or less into liver) |
| 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) |

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 periampullary (head only), periduodenal, periporal, coeliac, and/or superior mesenteric 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 T3 N1 M0 |
| Stage IVA T4 N0, N1 M0 |
| Stage IVC Any T N2 M0 |

\(^1\) 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.

\(^2\) 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

<table>
<thead>
<tr>
<th>Stage Grouping</th>
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<td>Stage III</td>
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<td>N1, N2</td>
<td>M0</td>
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<tr>
<td>Stage IVB</td>
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### TNM classification of tumours of the Ampulla of Vater

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<td>T4</td>
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<td>Any T</td>
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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.

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1[1, 66]. The classification applies only to carcinomas.

2A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
Carcinoma of the gallbladder and extrahepatic bile ducts

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.

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.

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
Galstones. The incidence of gallbladder cancer is higher in patients with gallstones than in patients without stones 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. While some authors have reported a correlation between gallstone size and the risk of cancer, others have not found such a correlation.

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. 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-
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 choledocholpancreatic 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, scirrhoustric 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 scirrhoustric 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

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

**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.
Tumours of the gallbladder and extrahepatic bile ducts become calcified \(^{1465, 1606}\). About one-third of the well differentiated tumours show focal intestinal differentiation and contain 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 adenocarcinoma 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 supranuclear 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.
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 (39).

**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 resembles 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 component.
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

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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.
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 tubulovillos 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 asymptomatic. 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. Wide-spread 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-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-
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]. Depending 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 pancreatico-ciliary 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 events.

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

**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].

**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 associated with stones [34, 1524]. There is no available information on the aetiology of the very rare carcinoid tumours of the extrahepatic biliary tree.

**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 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, including 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 argyrophyllic 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.
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

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, granular 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 1b 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 biliary 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, haemangiomia, and lymphangiomia have been described. A benign stromal tumour of the gallbladder with interstitial cells of Cajal phenotype has been reported recently (35).
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). 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

**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 cholecystitis (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.