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Solid Tumour Section

Review

Digestive organs: Carcinoma of the gallbladder and extrahepatic bile ducts

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Identity

Other names: Biliary tract carcinoma, cholangiocarcinoma
Note: Defined as a malignant epithelial tumor arising in the gall bladder and extrahepatic bile ducts including ampulla of Vater.

Classification

Note: Tumor staging is separated by TNM classification (International Classification of Diseases, ICD).
TNM classifications for carcinomas of the gallbladder, extrahepatic bile ducts and the ampulla of Vater.
The histopathological classification of biliary tract carcinoma follows WHO classification:
- adenocarcinoma,
- adenosquamous carcinoma,
- squamous cell carcinoma,
- small cell carcinoma,
- adenoendocrine cell carcinoma,
- undifferentiated carcinoma, and
- carcinosarcoma.

Clinics and pathology

Disease

Carcinoma of the gallbladder and extrahepatic bile ducts is an aggressive malignancy with a poor prognosis.

Etiology

Carcinoma of the gallbladder and extrahepatic bile ducts is more common in Eastern Europe and Latin American countries, and in the yellow races. It occurs frequently in older age groups (6th to 7th decades of life). Statistical data in Japan and USA indicate that gallbladder carcinomas occur predominantly in female, whereas carcinoma of the extrahepatic bile duct occurs more frequently in males. Carcinoma of the extrahepatic bile duct is associated with primary sclerosing cholangitis, ulcerative colitis, abnormal choledochopancreatic junction, and parasitic infection (trematode). In gallbladder carcinomas, gallstones and abnormal choledochopancreatic junction are considered risk factors. Association with smoking and drinking is not established.

Epidemiology

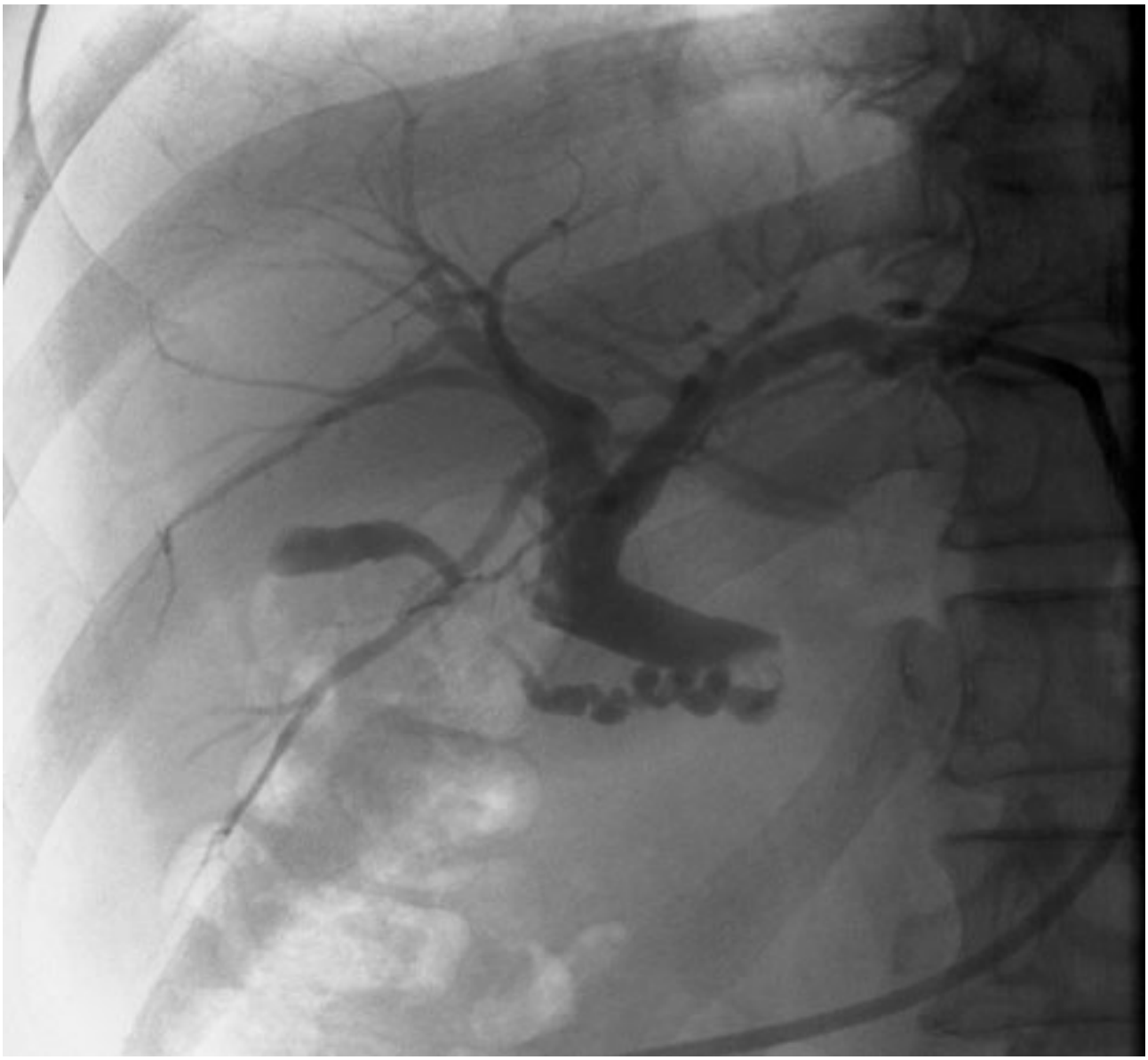
One of the common carcinomas worldwide.

Clinics

The clinical symptoms are affected by the complications such as gallstones and cholangitis. The most frequent symptom is right upper quadrant pain in gallbladder carcinomas and obstructive jaundice in extrahepatic bile duct carcinomas. Chills and fever appear when cholangitis develops. For early diagnosis, ultrasonography is useful; detection of biliary dilatation and tumor masses. For staging, computed tomography, magnetic resonance imaging, and endoscopic ultrasonography are effective. Percutaneous transhepatic cholangiography and endoscopic retrograde cholangiography are poorly available for qualitative diagnosis but performed in case of biliary drainage.

Cytology

Cytology of bile duct brushings is an important diagnostic tool for tumors of biliary ductal system presenting as duct strictures from which it can be difficult to obtain a histology biopsy. Bile duct brushings have been recognized as a technique



Extrahepatic bile duct carcinoma from the middle portion (percutaneous transhepatic cholangiography).

of moderate sensitivity and high specificity in identifying carcinoma. Reported diagnostic sensitivities for malignancy have ranged from 20 to 70% and specificity is almost 100%. Therefore, positive diagnoses of malignancy are of great clinical value but a negative result is relatively little clinical aid.

Treatment

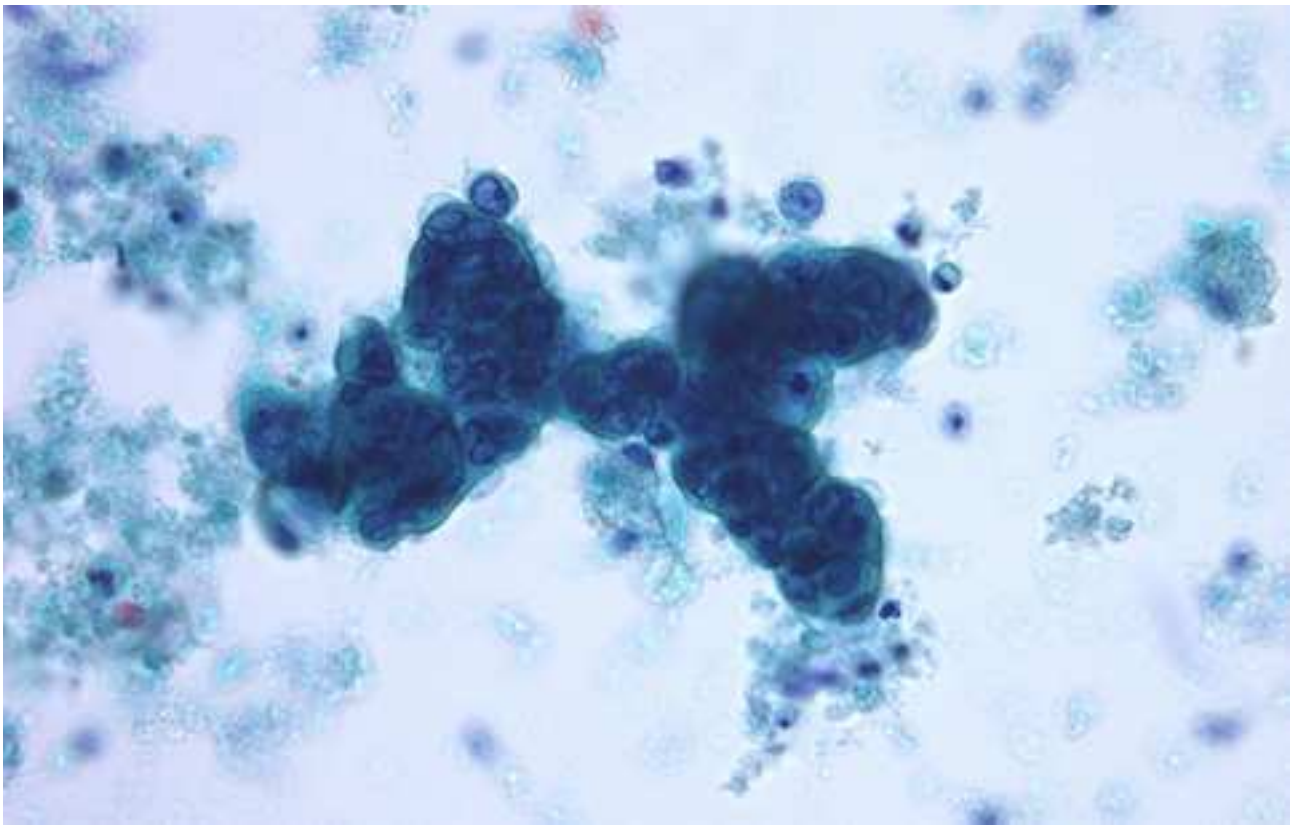
Surgical resection, chemotherapy, radiotherapy, immunotherapy.

Evolution

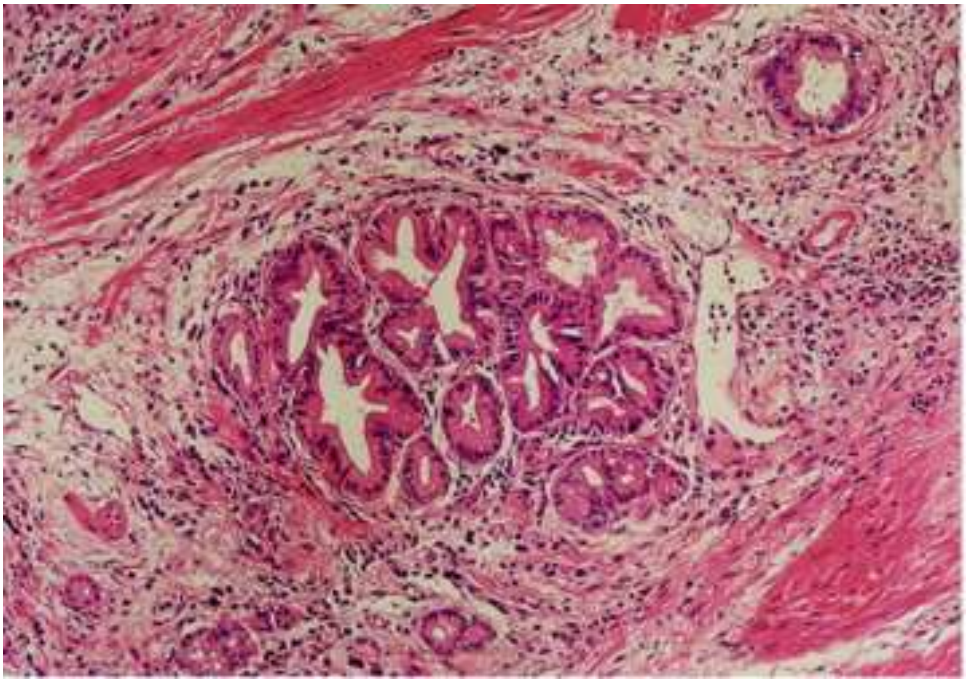
Recurrence should be given care to.

Prognosis

The prognosis of biliary carcinomas depends primarily on the extent of disease. In inoperable cases, one-year survival rates in gallbladder carcinomas and extrahepatic bile duct carcinomas are 10% or less and 20% or less, respectively.



Positive bile cytology specimen (Papanicolau stain). Isolated cells with increased nucleocytoplasmic ratio, marked anisocaryosis, loss of polarity, and prominent nucleoli.



Carcinoma of the gallbladder; well differentiated adenocarcinoma.

Cytogenetics

Note: Loss of heterozygosity at chromosomal loci 8p, 9p, and 18q are frequently detected.

Genes involved and Proteins

K-RAS

Location: 12p12.1

DNA/RNA

4 exons.

Protein

Proto-oncogene. GTP-GDP binding protein with GTPase activity. The K-ras proto-oncogene is thought to exert control over some of the mechanisms of cell growth and differentiation. This gene is converted to an active oncogene by point mutations significantly concentrated in codons 12, 13, or 61. The incidence of the mutations has variously been reported to be 17-59% of gallbladder carcinomas and 23-100% of bile duct carcinomas. K-ras mutations in biliary tract carcinomas with a background of pancreaticobiliary maljunction is significantly higher than in those without it, namely, 50-100% and 6-36%, respectively. Alteration of the K-ras oncogene may be very important in the early stages of carcinogenesis of biliary mucosa, especially in association with anomalous connections of the pancreatobiliary ducts. K-ras mutation is more frequently detected in carcinomatous and dysplastic lesions in gallbladder carcinoma cases with gall stones than in those without stones. There was a large difference in the incidence of K-ras mutations between distal (47-75%) and middle or proximal (0-8%) bile duct carcinoma. The distal portion may be to some extent influenced by pancreatic juice because of its anatomical location. K-ras mutations in biliary tract carcinomas are not statistically significantly correlated with tumor staging, histological type and age, sex, or survival of the patients.

p53

Location: 17p13

DNA/RNA

11 exons.

Protein

Tumor suppressor. Wild-type p53 plays an important role in the regulation of the cell cycle process, cell growth, and apoptosis in the event of DNA damage. The mutant proteins from the mutated genes disrupt critical growth-regulating mechanisms and may play a crucial role in the carcinogenesis. The reported incidence of p53 mutation is 31-92% in gallbladder carcinoma and 33-73% in bile duct carcinoma. In general, there is a tendency for higher grade carcinomas to express more p53 protein. p53 abnormalities may appear early during the transition from low-grade to higher-grade tumors and may play a role in the development of more malignant tumor phenotypes. A statistically significant difference is found for the incidence of p53 protein expression between extrahepatic bile duct carcinomas from the distal portion and those from the lower mid-region. This tendency is the same as that for K-ras mutations and the pancreaticobiliary maljunction may override the effect of p53 gene mutations.

p16 INK4A

Location: 9p21

DNA/RNA

3 exons.

Protein

Regulatory protein in the cell cycle and cyclin-dependent kinase (cdk4/cdk6) inhibitor. The tumor suppressor gene p16 is commonly inactivated in many neoplasms. Three distinct mechanisms of p16 inactivation have been reported in biliary neoplasms: deletion and point mutations of the p16 gene, and hypermethylation of 5' regulatory regions of p16. It has been reported that 60-80% of primary biliary tract carcinomas had point mutations in the p16 gene. Allelic loss at the p16 locus on chromosome 9p21 or p16 promoter hypermethylation occurred with sufficient frequency in extrahepatic bile duct carcinomas and in gallbladder carcinomas. Therefore, the p16 gene may possibly be crucial for biliary tract carcinogenesis and progression.

c-ERB-2

Location: 17q21.1

DNA/RNA

7 exons.

Protein

Proto-oncogene. Amplification and overexpression of c-erbB-2 are frequently shown in biliary tract carcinomas. It is suggested that c-erbB-2 expression may be associated with neoplastic progression in biliary tracts.

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