CHAPTER

14 Hepatobiliary and Pancreatic Tumors

LIVER CANCER

Anatomy

The liver is divided by the falciform ligament into right and left lobes by anatomists. However, it is the segmental anatomy of the liver based on the branches of blood supply which is practically important for the surgeon. The liver has a dual blood supply (the portal vein and hepatic artery) which divide in porta hepatis into right and left branches, hence, separating right and left hemilivers with a line of demarcation from the inferior vena cava above to the gall bladder. Each hemiliver is divided into 4 segments correspond ing to branches of vessels (Fig 14-1). In left hemi-liver, segment I corresponds to the caudate lobe, segments II and III to the left lobe and segment IV to the quadrate lobe. The remaining segments (V to VIII) comprise the right hemiliver.

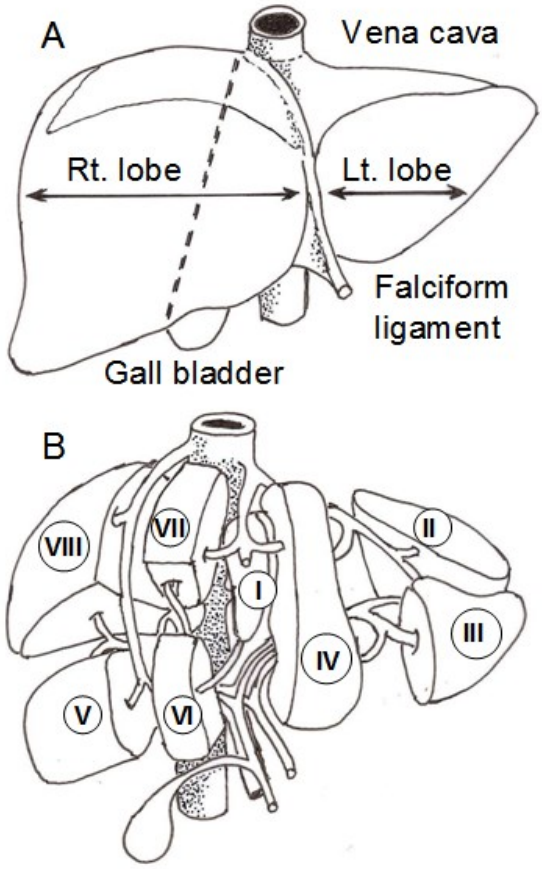

Fig 14-1 *Anatomy of liver A. Topographic anatomy, division into right and left lobes by falciform ligament B. Segmental surgical anatomy into 8 segments according to branches of hepatic artery and portal vein.*

Histology

The hepatic microarchitecture is based on two concepts, namely: the *hepatic lobule* (structural model) and the *hepatic acinus* (functional model). Liver lobules are hexagonal structures (1-2 mm) arranged around the central vein, whereas, in the acinar unit, liver tissue is related to the feeding blood vessels (branches of hepatic artery and portal vein) and divided into 3 zones from two adjacent lobules (Fig 14-2).

Hepatocytes are arranged in cords or columns (one cell thick), extending from portal areas to central vein, and separated by endothelium-lined sinusoids. Kupffer cells (phagocytic histiocytes) are attached to the luminal face of endothelial cells, whereas, bile canaliculi are located in between two adjacent hepatocytes. Blood flows through sinusoids from portal vessels to the central vein. Bile secreted by liver cells, passes in the opposite direction in canaliculi which drain into the terminal bile ducts in the portal tract.

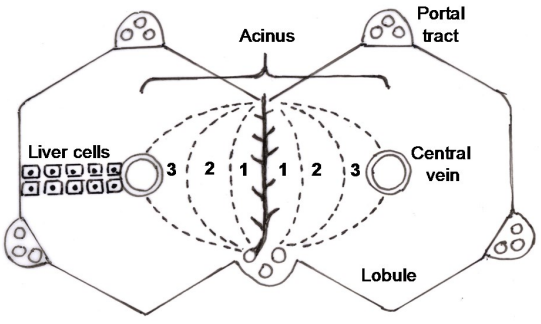

Fig 14-2 *Histology of liver. The lobular model is a structural arrangement of hepatocyte columns around the central vein, whereas, in the acinar functional model, hepatocytes are arranged in 3 zones around branches of the portal triads.*

Classification

A simplified classification of primary liver tumors is presented in (Table 14-1) modified from WHO scheme. As shown, the liver may be the seat of several differentiation lineage (epithelial, mesenchymal and mixed). Moreover, metastatic tumors of the liver are more common than primary ones.

HEPATOCELLULAR CARCINOMA (HCC)

Incidence

The highest incidence rate is in sub-Saharan tropical Africa and South-East Asia (China and Japan), with a rate of over 100 per 100, 000. The highest incidence in the world is in Mosambique where it constitutes two-thirds of male cancers and one-third of female cancers. HCC is uncommon in North America and Western Europe, where it contributes 0.5-2% of all cancers with an incidence rate of only 5 per 100, 000. The median age is 30 years in high incidence areas and 56 years in the West. Male predominance is 8:1 in high incidence areas and 3:1 in low incidence areas.

In Egypt, hepatocellular carcinoma contributes about 8% of all cancers (ranking the 2nd in males and the 6th in females) with a median age of 53 years and a male predominance of 5:1.

Etiology

1. Hepatotropic viruses, namely: hepatitis B virus (HBV) and hepatitis C virus (HCV). In Africa and China HBV is endemic, but in USA and Japan HCV predominates. The major routes of transmission are through blood transfusion or inoculations, but vertical transmission from mother to fetus is common in endemic areas.

2. Hepatocarcinogens: such as Aflatoxin (a product of the fungus Aspergillus flavus contaminating grains), anabolic steroids, contraceptive pills and estrogens.

3. Chronic liver disease: such as cirrhosis (viral or alcohol induced), genetic hemochromatosis and hereditary tyrosinemia.

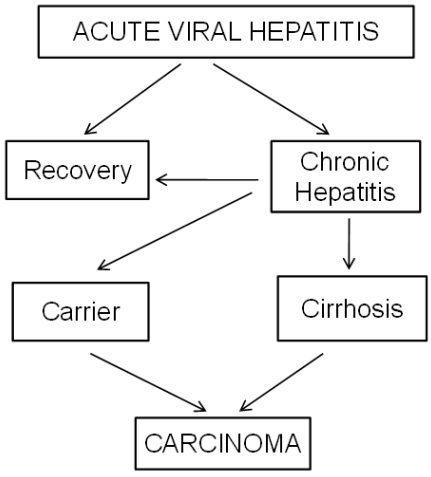

Fig 14-3 *Outcome of viral hepatitis.*

Table 14-1 Classification of Primary Tumors of the liver

Type	Benign	Malignant
Hepatocellular	Adenoma	Hepatocellular carcinoma (78%)
Biliary	Adenoma Papillomatosis Cystadenoma	Cholangiocarcinoma (8%) Cystadenocarcinoma
Mesenchymal	Angioma Infantile hemangio-endothelioma	Angiosarcoma Hemangioendothelioma
Mixed	Hamartoma	Cholangiohepatoma Hepatoblastoma

(Goodman, 2007)

The outcome of viral hepatitis is outlined in (Fig 14-3). Both chronic liver disease and malignancy are more frequent complications of HCV than HBV. Thus, the development of HCC after 15 years is 27% in HBV and 75% in HCV infections.

The role of the virus is probably indirect by producing liver necrosis, with subsequent regeneration and cirrhosis. Liver cell dysplasia, particularly the small cell type, is considered a precancerous lesion. The yearly incidence rate of malignancy in patients with cirrhosis is 3% both in Africa and the West. Recently, a direct role of the virus is considered possible. Thus, the virus genome after integration into DNA may encode a regulatory element (X-protein) that transactivates cellular proto-oncogenes. Another possible role of viral oncoprotein is to inactivate p53 protein product. Aflatoxin is a highly carcinogenic liver toxin. It can bind covalently with cellular DNA, and hence, cause mutations in proto-oncogenes or tumor suppressor genes. Aflatoxin and the virus may act synergistically, the former as an initiating agent and the latter as a promoting agent.

Molecular Oncogenesis

There is no unified molecular model for hepatocellular carcinogenesis in view of the extreme variability of gene alterations among the tumors. Hoshida and associates (2010) proposed a system of three groups according to the predominant cancer gene alteration, namely: (S1) characterized by TGF-β pathway activation, (S2) by MYC and ACT activation and (S3) by retained embryonic hepatocyte phenotype and frequent CINNBI (β-catenin) mutation. This classification may have valuable clinical application for targeted therapy.

LIVER NODULES AND PRECURSORS OF HCC

The classification of liver nodules is based upon: underlying etiology, clonality, size and histologic structure. Most nodules are monoclonal and associated with cirrhosis, but others (focal nodular hyperplasia) affect non-cirrhotic liver, and appears to be a polyclonal regenerative process due to vascular occlusion.

Nodules associated with cirrhosis need special attention since they are usually monoclonal and carry a potential risk of progression to malignancy. Cirrhosis is the end stage of many chronic liver diseases (viral, alcohol abuse, hemochromatosis). It is characterized by diffuse fibrosis of liver associated with regenerative nodules lacking lobular pattern and central veins (P 14-1 and P 14-2). Regenerative nodules may be micronodular (size <3 mm) or macronodular (3 mm to 2 cm in size) or mixed (P 14-3).

Cirrhosis itself is not precancerous, but it is the associated dysplastic or atypical changes in the regenerative nodules which are precursors of malignancy, especially small cell change. A list of precursor lesions, their recent terminology and diagnostic criteria is presented in (Table 14-2).

Table 14-2 Nomenclature of Putative Precursors of Hepatocellular Carcinoma in the Cirrhotic Liver

Terminology	Histology
Large cell dysplasia *	Large cells, low N/C ratio
Small cell dysplasia *	Small cells, high N/C ratio
Macroregenerative nodule (MRN)	3-8 mm size, plates 2-3 cell thick
Dysplastic nodule Low-grade High-grade	Macroscopic size (15 mm), plate 3 cells thick with dysplasia
Dysplastic focus	Microscopic, <1 mm
Nodule in a nodule	Dysplastic focus in a high-grade nodule

(Lefkowitch, 2010). * Recently called cell change rather than dysplasia

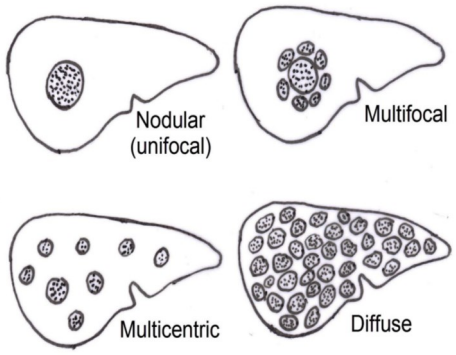

Fig 14-4 *The main gross patterns of hepatocellular carcinoma. An early cancer is <2 cm in diameter. A nodule in a nodule pattern may also be encountered and represent a dedifferentiation phenomenon in the original tumor (Bosman et al, 2010).*

Macroscopy

Grossly, malignant nodules of HCC appear paler in color than normal liver tissue (P 14-4 and P 14-5), yellowish green and extremely variable in size. Four gross patterns are recognized : nodular, multifocal, multiple and diffuse (Fig 14-4). Early small tumors (<2 cm), detected by imaging technique, may be encountered. A nodule in a nodule pattern is rarely seen and represent tumor dedifferentiation.

Histopathology

Three classic common patterns are observed: the trabecular, acinar and solid (P 14-6 to P 14-8). The best confirmatory markers are: HepPar-1, Moe-31 and p CEA. The latter will demonstrate bile canaliculi diagnostic of hepatocytic differentiation (P 14-6). Less common patterns of HCC are the fibrolamellar, clear cell and pleomorphic or giant cell patterns (P 14-9, P 14-10 and P 14-11). Fine needle aspiration cytology is a useful diagnostic method by revealing atypical trabecular malignant cell structures, associated with sinusoids (P 14-12).

Malignant hepatocytes have special characteristic morphologic features including: abundant eosinophilic cytoplasm, cytoplasmic or nuclear inclusions, secretion of bile and associated sinusoids.

Differential Diagnosis

1. Differentiation of a well-differentiated HCC from liver adenoma, dysplastic nodule and focal nodular hyperplasia (Table 14-3, P 14-13 and P 14-14).
2. Differentiation of HCC from intrahepatic cholangiocarcinoma (Table 14-4 and P 14-27).
3. Differentiation of a high grade HCC from hepatic metastases (Table 14-5).

Paraneoplastic Syndromes

Hepatocellular carcinoma may be associated with a variety of paraneoplastic syndromes, including: polycythemia, hyperglycemia and hypercalcemia, as a result of production of hormone-like factors by the tumor.

Table 14-3 Differential Diagnosis of Well-Differentiated Hepatocellular Carcinom (HCC) from Other Benign Nodules by Histologic Features

Feature	HCC	Hepatic Adenoma	Dysplastic Nodule	Focal nodular hyperplasia
Associated cirrhosis	80%	Absent	100%	Absent
Portal areas	Absent	Absent	Present	Present
Pattern	Trabecular acinar	Sheets	Trabecular Nodule in nodule	Lobular and scar
Anaplasia	Present	Absent	Absent	Absent
Nucleoli	Prominent	Absent	Absent	Absent
Mitosis	Present	Absent	Absent	Absent

(Bosman et al, 2010)

Table 14-4 Comparison of Histologic Features of Hepatocellular Carcinoma (HCC) and Cholangiocarcinoma (CC)

Feature	HCC	CC
Cytoplasm	Eosinophilic	Clear
Secretion	Bile	Mucin
Fatty change	Present (50%)	Absent
Mallory bodies	Present (20%	Absent
Squamous metaplasia	Absent	May be present
Canaliculi	Present	Absent
Pattern	Trabecular	Ductal
Sinusoids	Present	Absent
Desmoplasia	Absent *	Present
Association	Cirrhosis	Bile duct hyperplasia

(Bosman et al, 2010). *Except fibrolamellar HCC

Table 14-5 Differential Diagnosis of Poorly-Differentiated Hepatocellular Carcinoma from other Hepatic Malignancies by Immunohistochemistry

Marker	HCC	CC	Metastases adeno-carcinoma	Metastases Neuro-endocrine
Reliable				
HepPar-1	+	-	-	-
pCEA	Canalicular	Cytoplasmic	Cytoplasmic	-
mCEA	-	+	+	-
Moc-31	-	+	+	+
Chromogranin	-	-	-	+
Unreliable				
AFP	+ (50%)	-	-	-
CK7	±	+	±	-
CK20	±	+	±	-
PCK	+ (weak)	+ (strong)	+	±

(Goodman, 2007/Bosman et al, 2010)
Abbreviations: HCC hepatocellular carcinoma, cc intrahepatic cholangiocarcinoma, pCEA polyclonal carcinoembryonic antigen, mCEA monoclonal carcinoembryonic antigen, AFP alpha fetoprotein, PCK pancytokeratin, ± Variable result.

Spread

The carcinoma spreads *locally* by expansion or permeation. *Hematogenous* spread is more common than lymphatic spread and occurs through branches of portal veins to produce multiple liver metastases, or through hepatic veins (P 14-15) to produce pulmonary and bone metastases. *Lymphatic* spread may develop to the lymph nodes of porta hepatis.

Staging

The TNM staging system is generally adopted for HCC (Table 14-6). Abdominal CT is most helpful in precise staging of patients prior to surgery (P 14-15) by identifying multiplicity, angioinvasion and spread to adjacent organs. However, CT has limited sensitivity (55%) in detecting small tumors (<1 cm).

Prognosis

Liver transplantation is considered the only potentially curative treatment for HCC. In the experience of MD Anderson in orthotopic liver transplantation, the 5-year survival has improved from 25% in 1987 to 61% in 2001 (Kantarjian et al, 2011). A higher figure of 80% was reported in hepatoblastoma (Pizzo, 2006).

Table 14-6 TNM Staging of Hepatocellular Carcinoma

Stage	Criteria	5-year survival (%)
I	Solitary tumor, no Vascular invasion (T1) No metastases (N0M0)	55
II	Solitary tumor with vascular Invasion (T2) or multiple (<5 cm), no metastases	37
III	Multiple tumors (>5 cm) with: Invasion of: A. Portal or hepatic vein B. Adjacent organs C. Peritoneum, no metastases	15
IV	A. Any T with nodal or B. distant metastases	0.0

(Edge, 2010)

Conversely, the overall survival of unresectable HCC is very poor (median survival time only 8 months and no survivors in 3 years). Poor prognostic factors include: (1) advanced stages (III and IV) unresectability, (2) vascular invasion and (3) associated cirrhosis.

HEPATOBLASTOMA

Hepatoblastoma accounts for about 80% of malignant liver tumors in children. It occurs almost exclusively in infants during the first two years of life and is twice as frequent in males. The tumor arises from a multipotential blastoma, capable of both epithelial and mesenchymal differentiation. Some patients present with virilization as a result of ectopic sex hormone production. Serum level of alpha fetoprotein is often elevated.

Grossly, the tumors are more often solitary. *Histologically* 3 variants are recognized: (1) *fetal type:* consists of hepatocytes arranged in two cell thick laminae (P14-16), often associated with extramedullary hematopoiesis, (2) *embryonal type:* have more immature hepatoblasts with solid nontrabecular pattern, and (3) *mixed type* (25% of cases) showing both epithelial and mesenchymal elements with bone and cartilage formation. *Cytogenetically*, hepatoblastoma shows trisomy for 2q and 20. The molecular oncogenesis involves activation of β-catenin and Hedgehog pathways.

ANGIOSARCOMA

This is a highly malignant vascular tumor of adults. An increased risk of hepatic angiosarcoma has been documented in the following four conditions: (1) vinyl chloride exposure, a chemical used in polyvinyl chloride (PVC) plastic industry. The average latent period is 17 years, (2) thorium dioxide exposure (Thorotrast) which was used in the past for radiography. The latent period is about 30 years, (3) arsenic exposure, and (4) cirrhosis, particularly the macronodular type.

The sarcoma is usually multicentric and hemorrhagic in appearance. Histologically, it is composed of vascular spaces lined by pleomorphic endothelial cells (P 14-17).

LIVER METASTASES

Secondary cancers in the liver are about 30 times more frequent than primary cancers, with an incidence rate of 39% of cancer patients in autopsy series. Carcinoma metastases are far more common than sarcomas. The most common origin of liver metastases are the common carcinomas of lung, breast and gastrointestinal tract. However, certain malignant tumors are well known of high metastatic tendency to the liver in over 50% of the affected patients (Table 14-7).

Grossly, liver metastases are commonly multiple (94%), of uniform size, peripheral in location and show umbilicated surface as a result of central necrosis. However, single metastasis may develop in patients with colonic carcinoma or hypernephroma. Resection of such solitary liver metastasis from colorectal carcinoma carries a 5-year survival of about 30%. Metastases are rare in the cirrhotic liver. This is explained by the fact that most of tumors occurring in cirrhotic livers are primary.

Table 14-7 Cancers with High Metastatic Potential to the Liver

Primary tumor	% liver metastasis
Gall bladder	78
Pancreas	70
Colon	65
Breast	53
Melanoma	50

GALL BLADDER CARCINOMA

Carcinoma of the gall bladder is more frequent in females (ratio 4:1) and about 90% of patients are over the age of 50 years. Conditions associated with increased risk include: cholelithiasis, biliary fistulas, adenomyomatosis, ulcerative colitis, polyposis coli and Gardner syndrome. In most cases, the invasive tumor arises from a sequence of intestinal metaplasia, dysplasia and carcinoma in situ. Grossly, the carcinoma may present as a diffusely-infiltrating tumor (70%) or a polypoid mass (30%). Histologically, adenocarcinoma and its variants are the most common (84%). Other histologic types include: adenosquamous carcinoma (10%), neuroendocrine tumors (5%) and rarely squamous carcinoma (1%).

Table 14-8 TNM staging of Gall Bladder and Extrahepatic Bile Duct Cancers

Stage	Criteria	5-year survival (%)
I	Invasion of lamina Propria and muscle (Confined to wall)	50
II	Perimuscular wall Invasion (subserosal)	30
III	Invasion of peritoneum, adjacent organs, main artery, node metastases (N1)	9
IV	Any T or N, distant metastases (M1)	2

(Edge, 2010)

Grossly, gall bladder carcinoma appears as a mass lesion (P 14-22) or a stenosing lesion at bladder neck (p 14-23). The *differential diagnosis* of adenocarcinoma (P 14-24) is from Rokitansky-Aschoff sinuses (P 14-25) and cholecystitis glandularis and cystica (P 14-26).

Gall bladder carcinoma has a great tendency to invade the liver directly, and to a lesser extent, the stomach and duodenum. It also metastasizes to the liver and the regional lymph nodes (cystic and pericholedochal or hilar nodes in hepatoduodenal ligament). Almost one half of patients already have metastatic disease at the time of presentation.

The stage of the tumor is the most important prognostic determinant (Table 14-8). Thus, the 5-year survival rate is over 50% for tumors confined to gall bladder (stage I) and below 10% in locally advanced and metastatic carcinomas (stages III and IV).

CANCER OF THE BILIARY TRACT

CHOLANGIOCARCINOMA (CC)

Incidence

Carcinoma of the biliary duct is a rare tumor, but is particularly common in Japan, Thailand and the American Indians, with an incidence rate of about 5 per 100,000. In the United States, the incidence is approximately one per 100,000. The median age is 60 years. Sexes are equally affected.

Table 14-9 Etiology of Cholangiocarcinoma, Risk Factors

Hepatolithiasis	(10%)
Chlonorchis sinensis	
Giardia Iamblia	
Choledochal cysts	
Papillary hyperplasia	
Sclerosing cholangitis	(40%)
Ulcerative colitis	(1.4%)
Thorotrast	
Dioxin	
Nitrosamines	
Isoniazid	
Oral contraceptives	

(DeVita, 1997)

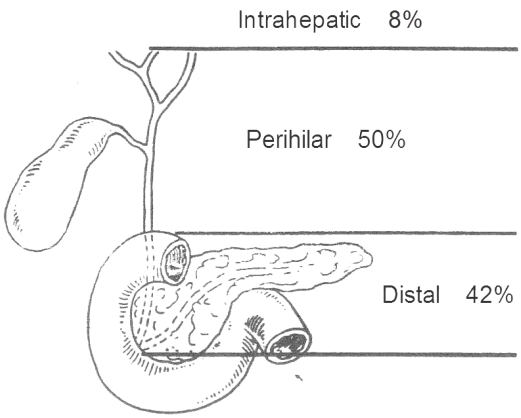

Fig 14-5 *Sites of cholangiocarcinoma and their relative frequency (564 patients, De Oliveira et al, 2007).*

Etiology

The risk factors that have been associated with increased risk of cholangiocarcinoma are presented in (Table 14-9). The pathologic precursors associated with the highest risk include: sclerosing cholangitis (40%) and hepatolithiasis (10%).

Macroscopy

Cholangiocarcinomas are best classified into three broad anatomic groups: intrahepatic, perihilar and distal (Fig 14-5). This classification system is a useful guide for therapy. Thus, intrahepatic tumors are usually managed as HCC with liver resection, and distal tumors are treated as pancreatic cancer with pancreaticoduodenectomy, whereas, perihilar tumors are commonly managed by nonoperative techniques such as stenting. The presence and location of these tumors are best shown by retrograde endoscopic cholangiography (REC) or percutaneous transhepatic cholangiography (PTC). Two gross types are observed: an exophytic papillary type projecting into the lumen, and a diffuse type infiltrating the wall with fibrosis.

The most common site of perihilar tumors is at the confluence of right and left hepatic ducts. A somewhat distinct variant is the sclerosing carcinoma (Klatiskin's tumor) which begins at the hepatic duct junction and spreads from there to long segments of the biliary tree. It is characterized by, a long clinical course, a well-differentiated histology and associated extensive fibrosis. The main differential diagnosis is sclerosing cholangitis.

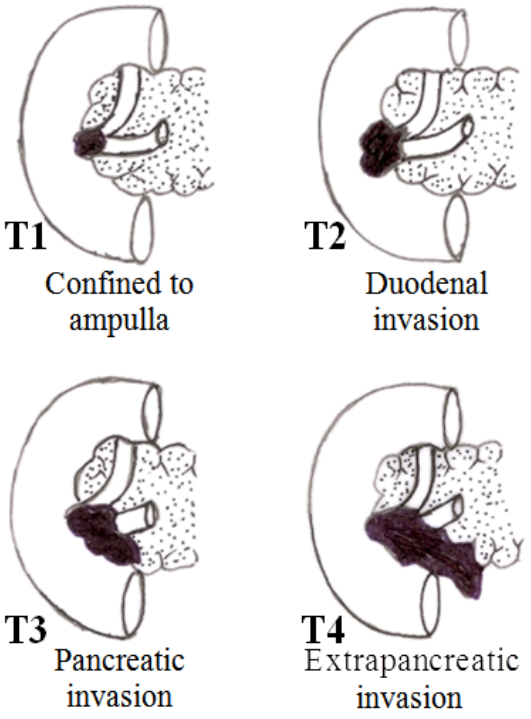

Fig 14-6 *The tumor (T) categories of ampullary carcinoma (Edge, 2010).*

Distal bile duct carcinomas are commonly located in the ampullary region (P 14-30 to P 14-32). At this site, tumors are classified anatomically into four main groups; according to the T categories of TNM system (Fig 14-6). This classification has important prognostic implications. The clinical manifestations of carcinoma of ampullary region are somewhat different from carcinoma of pancreas. Thus, the jaundice is often intermittent and may be associated with intestinal bleeding. The prognosis is also more favorable than pancreatic carcinoma (Table 14-10).

Histopathology

The large majority of bile duct malignancies are well-differentiated mucin secreting adenocarcinomas, often showing a papillary pattern and marked stromal fibrosis (desmoplasia) (P 14-27). Clusters of small acini, normally present in the wall of bile duct should not be interpreted as invasive carcinoma (P 14-28 and P 14-29). The differential diagnosis from hepatocellular carcinoma was previously outlined in (Table 14-4 and Table 14-5). Other differential diagnosis are presented in (P 14-33 to P 14-35).

The differential diagnosis of ampullary carcinoma is from papillary cystadenoma and ductal pancreatic adenocarcinoma invading the ampulla. Immunostains may help in the differential diagnosis. Ampullary carcinoma exhibit biliary ductal epithelial pattern (MUC-1 positive, CK20 negative), whereas, pancreatic carcinoma exhibit intestinal epithelium pattern (MUC-2, CK20 and CDX-2 positivity).

Spread

Direct spread to the liver is common in upper perihilar tumors. Lymph spread is more common than blood spread. The lymph nodes most commonly involved are the portal lymph nodes and posterior pancreaticoduodenal lymph nodes.

Prognosis

The overall 5-year survival is about 5% for intrahepatic carcinoma and 10-15% for hilar carcinomas. The prognosis of ampullary carcinoma is mainly dependent on stage (Table 14-10) lymph node metastases and pancreatic invasion are associated with unfavorable prognosis.

PANCREATIC CANCER

The present chapter describes carcinoma of the exocrine pancreas. Tumors of the endocrine pancreas are presented in (chapter 19, page 331).

Incidence

The incidence of pancreatic carcinoma in the West is about 10 per 100,000 and it constitutes 4% of all cancers. There is high incidence in Denmark, Finland and Scotland. It ranks the fourth cause of cancer mortality (5%). The mortality rate nearly approximates the incidence rate (overall survival is only 4%). The median age is 45 years and male predominance 1.5:1.

Table 14-10 TNM Staging of Ampullary Carcinoma

Stage	Criteria	5-year Survival (%)
I	Confined to ampulla (T1)	40
	Invading duodenal wall (T2)	42
II	Invasion of pancreas (T3)	33
	Positive lymph nodes	26
III	Invasion of peripancreatic tissue (T4)	16
IV	Any T or N, distant metastases (M1)	4

(Edge, 2010)

Etiology

Pancreatic carcinoma is related to the following etiologic factors: cigarette smoking (nitrosamine), high fat and meat diet, early onset diabetes, chronic pancreatitis, hereditary origin (3%), occupa -tional exposure (DDT), and partial gastrectomy.

Macroscopy

The carcinoma appears gray-yellowish in color (P 14-36), about 5 cm in diameter and multiple in 20% of cases. Tumors in the body and tail tend to be larger when diagnosed, probably due to delay in the production of symptoms. About 85% of carcinomas are located in the head of pancreas (Fig 14-7) and often produce obstruction of biliary and pancreatic ducts which appear dilated. The parenchymal changes distal to the tumor are characterized by pancreatitis and atrophy.

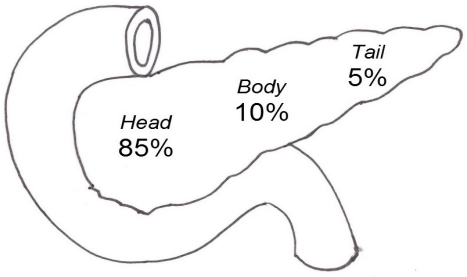

Fig 14-7 *Sites of exocrine pancreatic carcinoma and their relative frequency (Hruban and Fukushima, 2007).*

Molecular Oncogenesis

Like the adenoma-carcinoma sequence in colorectal carcinogenesis, current data suggest that there is a temporal sequence of molecular events in pancreatic cancer from hyperplasia, intra-epithelial neoplasia (IN) to invasive cancer (Fig 14 -8). Mutations of RAS (90%) and HER-2 (70%), as well as, telomere shortening are early events, whereas, CDKN2A or p16 (95%), p53 (60%) and DPCA and other additional mutations are late events. About 63 different genetic alterations were noted in a recent report (Jones et al, 2008). Among these genes are: wnt/notch and hedgehog (two important proliferation genes in embryonic cells), insulin growth factor (IGF), transcription factor NF-κB, cyclooxgenase 2 (cox-2) and vascular endothelial growth factor (VEGF). The high metastatic potential of pancreatic carcinoma is due to a RAS-mediated overexpresssion of VEGF.

Histopathology

Carcinoma of the pancreas displays a wide spectrum of tumor types, but ductal adeno-carcinoma predominates, constituting 95% of cases. Generally, the tumors may be classified into a large group of unfavorable types, and a rare group of favorable types (Table 14-11).

Unfavorable carcinomas

Ductal adenocarcinoma of the pancreas may histologically look well-differentiated and, hence, must be distinguished from normal and hyperplastic ducts. Eight histologic features are helpful to diagnose malignancy were proposed by Hruban and Fukushima (2007). These include:

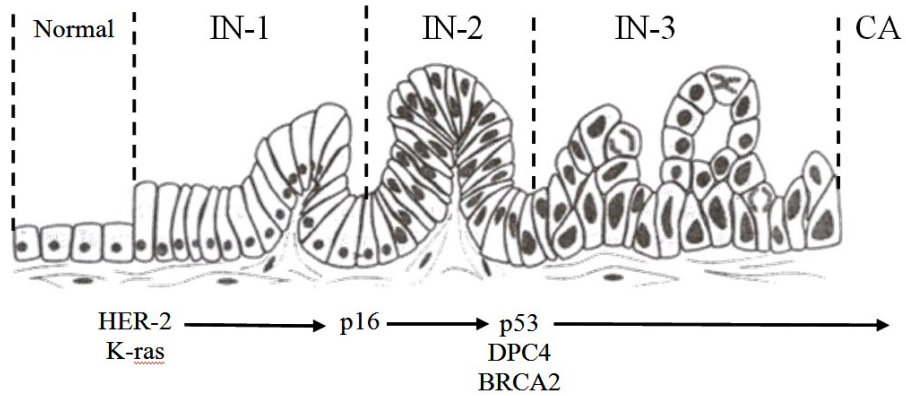

Fig 14-8 *The multistep molecular progression model of pancreatic carcinoma through 3 grades of intraepithelial neoplasia (IN). HER-2 and K-ras mutations are early events, whereas, other gene alterations are late events (Hruban et al, 2000/Bosman et al, 2010).*

Table 14-11 Histology of Pancreatic Cancer

MALIGNANT (UNFAVORABLE)
Ductal adenocarcinoma (95%)
Acinar adenocarcinoma
Mucinous noncystic carcinoma
Squamous cell carcinoma
Adenosquamous carcinoma
Small cell carcinoma
Serous microcystic carcinoma
Pancreatoblastoma
Sarcomas (rare)
LOW MALIGNANT POTENTIAL (FAVORABLE)
Serous cystadenoma and carcinoma
Intraduct papillary-mucinous neoplasm
Cystadenoma (mucinous or papillary)
Mucinous cystadenocarcinoma
Solid cystic (pseudopapillary) tumor

NB. 5-year survival <50% in unfavorable group, >50% in favorable group

haphazard growth pattern, glands adjacent to muscular vessels, perineural invasion, nuclear variation, intraluminal cell necrosis, small abortive glands and finally invasion of fat (P 14-37). Moreover, malignant glands are positive for CEA, but, normal glands are negative.

Grading of carcinoma is based on three criteria: (1) The degree of cellular anaplasia (2) mitotic activity / 10 high power field (<5 in grade 1, 6-10 in grade 2 and >10 in grade 3), and (3) extent of mucin reactivity in cytoplasm being lower in high-grade carcinoma.

Acinar adenocarcinoma of the pancreas is less common (2-5%) with distinctive histologic picture (P14-37C). It shows also different immunophenotype and genetic profile from ductal carcinoma (Table 14-12).

Favorable Carcinomas

1. Serous cystic neoplasms: are composed of glycogen-rich cuboidal epithelium that produce a watery fluid similar to serum. The majority are benign, but, few are of low malignant potential. Gross subtypes include: The microcystic cystadenoma (P 14-38), macrocystic and solid.

2. Intraduct papillary-mucinous neoplasm (IPMN): It presents as dilated ducts filled with mucin (P 14-39) and lined by atypical papillary mucin-secreting epithelium which is confined within the ducts (Yeh et al, 2010).

3. Mucinous cystic neoplasms are uncommon tumors with different clinicopathologic features from the conventional ductal adenocarcinoma (Klimstra, 2007). Thus, they are more common in females (5:1), present at a younger age, arise at tail and body of pancreas, attain a large size and are invariably cystic (P 14-40). Invasion of adjacent structures is uncommon and the prognosis is favorable. Histologically, the cysts are lined by mucin-secreting columnar cells with papillary projections into the lumen. Although, the epithelium appears malignant, there is lack of invasion of stroma or capsule. The stroma of the larger cystic spaces is usually densely cellular, resembling ovarian stroma.

4. Solid cystic pseudopapillary tumor (Gruber-Frantz tumor): This low-grade tumor has distinctive pathologic features, but, uncertain line of differentiation. Necrosis of tumor cells with preservation of viable perivascular areas results in solid and cystic areas hence the name of the tumor (klimstra, 2007). The cells are polygonal to elongated and may show PAS positive cytoplasmic globules. The nuclei are uniform, oval, and folded with rare mitosis. The fibrovascular cores show prominent mucinous changes and exhibit a pseudopapillary pattern with the attached viable cells. The tumor cells are immunoreactive to keratin, vimentin, NSE, progesterone receptors, insulin and glucagon. This profile suggests that the tumor arises from a primitive pancreatic cell capable of both exocrine and endocrine differentiation.

Table 14-12 Pancreatic Ductal and Acinar Adenocarcinoma, Compared

Feature	Ductal	Acinar
Frequency	95%	5%
Pattern	Ductal	Acinar
Histochemistry	Mucin +	PAS +
Immunoreactivity	CK7, CEA, Muc-1, CA-19-9	CK7-ve, β-catenin, enzyme markers
Genetic	K-ras, p53, DPCCA, p16	APC/β-Catenin

(Bosman, et al, 2010)

A molecular model of oncogenesis of this tumor was proposed (Tang et al, 2007). Mutation of β-catenin, which is a constant feature of this neoplasm, causes instability of cell membrane adhesive molecules with loss of E-cadherin, and eventually dissociation of tumor cells resulting in the cystic and pseudopapillary pattern characteristic of this tumor.

Differential Diagnosis

Chronic pancreatitis produces a mass lesion which may be misdiagnosed as pancreatic carcinoma. The etiology is related to alcohol abuse, autoimmunity, genetic causes or idiopathic. In early lesions, the fibroinflammatory changes are limited to interlobular stroma, but in advanced cases pancreatic acini are replaced by fibrous tissue with only islet cells remaining (P 14-43). However, the regular focal distribution of ducts with cystic changes help to distinguish this disease from malignancy. Chronic pancreatitis commonly affects the head of pancreas and extensive fibrosis may obstruct the duct system.

Pathologic Effects

Carcinoma of the pancreas produces several effects and complications, including: (1) obstructive jaundice, occurs in 90% of cancer head, with dilated gall bladder (Courvoisier sign), (2) migrating thrombophlebitis (Trousseau syndrome) in 10% of cases, due to elaboration of platelet aggregating agents and procoagulants, (3) diabetes mellitus (10%) due to atrophy of islet cells, (4) invasion of celiac ganglion (pain), (5) splenic vein invasion (splenomegaly), and (6) portal vein invasion (hemorrhage from varices).

Spread

1. Local spread: to involve adjacent organs such as duodenum, stomach, spleen, colon, kidney or adrenal. Invasion of celiac axis or superior mesenteric vessels may occur and is a sign of inoperability (non resectable tumor).

2. Lymphatic spread: The regional peripancreatic lymph nodes are demonstrated in (Fig 14-9). The superior head (SH) group around the celiac axis and inferior head (IH) around the superior mesenteric vessels are most commonly affected by metastases. More distant lymph node groups may be involved including lateral aortic and supraclavicular: lymph node metastases are found in 75% of pancreatectomy specimens done for organ-confined tumors (T1 and T2). Moreover, residual malignancy is present in lymph nodes not removed by operation in 33% of cases and are important cause of recurrence. The rich lymphatics of the pancreas and lack of posterior peritoneal covering help the wide spread of tumor through retroperitoneal lymphatics.

3. Hematogenous spread: mainly to the liver, which is affected by metastases in 70% of patients.

4. Transperitoneal spread: to the mesentery or omentum.

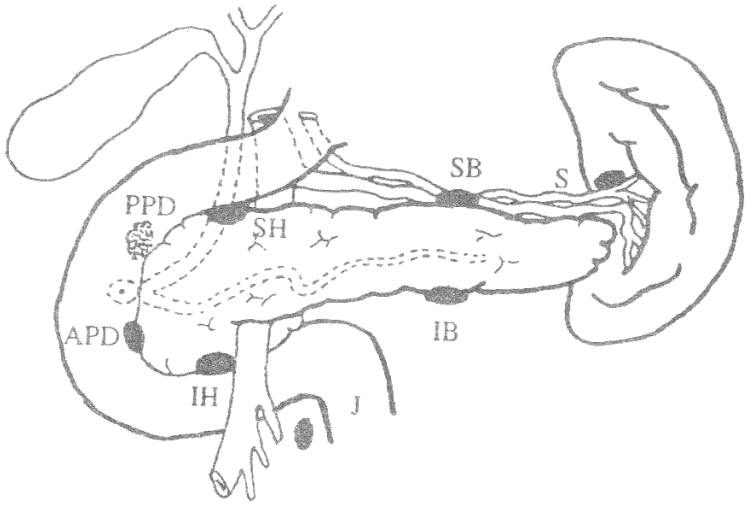

Fig 14-9 *Peripancreatic lymph nodes. SB superior body, IB inferior body, SH superior head, IH inferior head, PPD posterior pancreaticoduodenal, APD anterior pancreaticoduodenal, S splenic and J jejunal. The PPD and SH are the most common sites of metastases.*

Staging

The TNM staging system (Table 14-13) is useful in providing prognostic information and compare data. However, an alternative clinically-oriented staging system is more useful to guide surgical decisions (Fig 14-10 and Table 14-14). Two preoperative tests (CT and CA 19-9) may provide valuable information for staging. Thus, CT scan may identify invasion of superior mesenteric vessels prior to surgery (a serious indication of inoperability). Moreover, the serum tumor marker CA19-9. (which measures the moiety of the mucin MUC-1) is commonly elevated in pancreatic malignancy, and is highly suggestive of metastatic disease.

In resectable cases, evaluation of surgical margins is of utmost importance. Tissue must be taken from 4 sites: common bile duct, pancreatic neck, superior mesenteric area and posterior pancreatic retroperitoneal tissue.

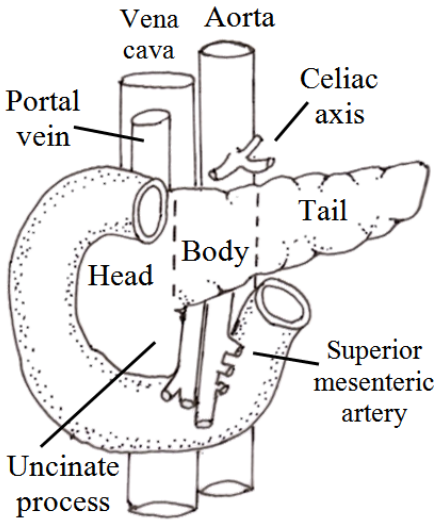

Fig 14-10 *Criteria of surgical resectability of pancreatic carcinoma. Cases with invasion of celiac axis or superior mesenteric artery are considered nonresectable, stage III (Edge et al, 2010).*

Prognosis

Duct carcinoma of the pancreas is among the most lethal human cancers, with an overall 5-year survival of only 4% and 18% for resectable cases (Table 14-14). This gloomy picture is due to the lack of a reliable screening method for early detection (90% of patients present with a late nonresectable stage). Moreover, 80% of resectable cases recur after operation, and so for, there is no effective chemotherapy or radiotherapy to save them. For *acinar adenocarcinoma*, the 5-year survival is more favorable, with reported figures of 25-50% depending on the stage (Bosman et al, 2010).

In regard to the survival of the favorable group of pancreatic neoplasms, the 5-year survival is highest (90%) for the solid cystic pseudo-papillary tumor, followed by the intraductal papillary tumor (83%) 5-year survival. Lower figures of about 50% survival was reported for mucinous cystic neoplasm and pancreatoblastoma (Bosman et al, 2010).

Table 14-13 TNM Staging of Pancreatic Adenocarcinoma

Stage	Criteria	5-year Survival (%)
I	Confined to pancreas, size <2 cm (T1)	31
	Confined to pancreas, size >2 cm (T2)	27
II	Extrapancreatic spread (but not invading celiac axis or superior mesenteric artery	16
	Lymph node metastases	8
III	Invasion of celiac axis or superior mesenteric artery (nonresectable)	7
IV	Any T or N with distant metastases (M1)	3

(Edge et al, 2010).

Table 14-14 Surgical Staging System for Pancreatic Carcinoma

Stage	Frequency (%)	5-year Survival (%)
I. Organ confined, resectable	10	18
II. Locally-advanced	30	6
III. Metastatic	60	1

(Abraham et al, 2010/Bosman et al, 2010)

The most important prognostic factor after operation is the adequacy of surgical margin. Histologic subtype of the tumor also influence prognosis.

Detection

The majority of patients with pancreatic carcinoma present at an advanced stage. Only 10% of patients present at stage I with the disease clinically confined to pancreas. Most of these, apparently early cases, develop local recurrence and liver metastases after resection. Early detection remains a major problem, but the following techniques may be helpful: (1) CT scan, MRI, (2) endoscopic retrograde cholangiopancreatography (ERCP) and (3) Serum tests of potential detection value are S Pan-1 and CA 19-9.

REFERENCES

Adsay NV: Cystic lesions of pancreas. Mod Pathol, 20:71-93, 2007.

Bosman FT, Carneiro F, Hruban RH and theise ND: WHO Classification of Tumors of the Digestive System. IARC, Lyon, 2010.

Clavien P and Breitenstein S: Malignant Liver Tumors. 3rd edition, Wiley-Blackwell, Oxford, UK, 2010.

De Oliveria ML and Cunningham JL: cholangiocarcinoma, 31 year experience with 564 patient at a single Institution. Ann surg, 245-754, 2007.

Dooley JS, LOK AF, Burroughs AK and Heathcote EJ: Sherlock's Diseases of the Liver and Biliary System. 12th edition, wiley-Blackwell, Oxford, Uk, 2011.

Edge SB: AJCC Cancer Staging Hand Book, 7th edition, Springer, 2010.

Feig BW and ching CD: The MD Anderson Surgical Oncology, 5th edition, Lippincott Williams and Wilkins, Philadelphia, 2012.

Hoshida Y, Toffanin S, and Lachenmauer A: Molecular classification and novel targets in hepatocellular carcinoma. Semin liver Dis, 30: 35-51, 2010.

Hruban RH, Goggins M and Parsons J: Progression model for pancreatic cancer. Clin Can Res, 6: 2969-2972, 2000.

Goodman ZD: Neoplasms of the liver. Mod Pathol, 20: 49-60, 2007.

Hruban RH and Fukushima N: Pancreatic adenocarcinoma, update on the surgical pathology of carcinomas of dutal origin and pan INS, Mod Pathol, 20: 61-70, 2007.

Kantarjian HM, Wolff RA and Koller CA: the MD Anderson Manual of Medical Oncology, 2 nd edition, McGraw Hill, NY, 2011.

Katz MH and Hwang R: TNM staging of pancreatic adenocarcinoma. CA, 58: 111-125, 2008.

Klimstra DS: Nonductal neoplasms of the pancreas. Mod Pathol, 20: 94-112, 2007.

Kloppel G: Chronic pancreatitis, pseudotumors and other tumor-like lesions. Mod pathol, 20: 113-131, 2007.

Lefkowitch JH: scheuer's Liver Biopsy Interpretation, 8th edition, Saunders Elsevier Philadelphia, 2010.

Lawy AM, Leash SD and Philip PA: Pancreatic Cancer. Springer Science, New York, 2008.

Tong WW, Stelter AA and French S: Loss of cell-adhesion molecule complexes in solid pseudopapillary tumor of pancreas. Mod Pathol, 20: 509-513, 2007.

Washington MK and Silverberg SG: Tumors of the Liver. Pathol case Rev, 14: 1-49, 2009.

Yeh MM, Morohoshi T and Silverberg SG: Pathology of Pancreatic neoplasms and lesions, an update. Pathol Case Rev, 15: 183-224, 2010.