Surgical Diseases of the Pancreas and Biliary Tree

Savio George Barreto
John A. Windsor
Editors

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Editors
Savio George Barreto
Gastrointestinal Surgery
Medanta – The Medicity
Gurgaon
Haryana
India

John A. Windsor
Professor of Surgery
HBP/Upper GI Surgeon
Auckland City Hospital
University of Auckland
Auckland
New Zealand

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Foreword

This multiauthored text is a valuable addition to the literature regarding pancreatobiliary surgery. The chapter authors and the editors are principally Asian and well recognized for their specific expertise. Their contributions are encyclopedic, extensively referenced, and up-to-date. The illustrations are pertinent to the text, of high quality, and many are in color. The overall tone of the book is clinical, with emphasis on preoperative and postoperative management. Areas of controversy are presented, and even-handed discussions offered. In a particularly useful feature, many of the contributors highlight areas necessitating future evidence-based data to resolve existing controversies.

The initial chapters on Anatomy and Physiology of the Pancreas and Biliary Tree are outstanding and can easily serve as authoritative references for house officers studying for in-service and qualifying examinations. While each of the 17 chapters comprising this book is informative and could stand alone as state-of-the-art reviews and contributions to surgical knowledge, they vary in value as guidelines for clinical management, a frequent complication of multiauthored texts. Particularly noteworthy from this clinician's standpoint were the excellent chapters on Choledochal Cysts, Mucinous Tumors of the Pancreas, Pancreatic Neuroendocrine Tumors, and Hilar Cholangiocarcinoma.

For each of the remaining chapters, any concerns that I had were minor, and truth be told, often reflected my personal biases or practice patterns. As an example, in Chap. 4, Table 4.1, statin drugs should probably be added to the list of pathogenic agents for gallstone formation. In the chapter covering External Biliary Fistula, I would have liked to have seen a discussion of the "Law of Fistulas," a useful concept for clinical management. The chapter on Portal Biliopathy was extremely interesting since it is rarely covered in texts, but the timing of surgical intervention was less clear. The chapter on Acute Pancreatitis was encyclopedic and quite current, but the emphasis on classification of severity provides me an opportunity to express one of my favorite biases. I believe that we have spent an inordinate amount of time and effort on classification systems for the severity of acute pancreatitis. The rationale has been to identify those patients that may require more intensive therapy. While determination of severity is intrinsically worthwhile, since we do not have a proven specific therapy for acute pancreatitis, other than enthusiastic fluid replacement and supportive monitoring in an intensive setting, the seemingly never-ending fine-tuning attempts to classify severity seem to be a largely wasted effort, as severe

acute pancreatitis is easily recognized by experienced clinicians. In my opinion, the efforts spent on the unnecessary polishing of severity classifications would be much better spent on the prevention or amelioration of the cytokine cascade of acute pancreatitis that is responsible for its severity. It is perhaps past time to return our efforts to the cause and prevention of severe acute pancreatitis, rather than to its classification.

Since benign biliary strictures are quite common in chronic pancreatitis, indications for intervention are important. Aside from the clear indication of jaundice due to benign intrapancreatic stricture, we have found that a persistent elevation of alkaline phosphatase predates the development of biliary cirrhosis and reliably indicates the need for biliary bypass.

Recently, Chey and co-workers have described a new functioning pancreatic islet cell tumor, a primary secretinoma, as an additional cause of the watery diarrhea syndrome, increasing the complexity and distribution of pancreatic neuroendocrine tumours (P-NETs).

Adding to the excellent chapter on Pancreatic Cancer, we have found that thoracoscopic splanchnicectomy is a valuable tool for controlling intractable pain from terminal pancreatic cancer. Although nerve interruption procedures are often subject to recurrence, perhaps due to central plasticity of the pain response, life expectancy for metastatic pancreatic adenocarcinoma is often less than the onset of post-neurectomy pain recurrence. Moreover, some patients desire mental clarity for their remaining time of life and wish to avoid narcotic obtundation.

The final chapter on ERAS (enhanced recovery after surgery) is a valuable concept, and not often applied to pancreatobiliary surgery. This seems to be a fruitful area for evidence-based study by future workers and students.

In summary, there is much to learn from this book, and the authors are to be congratulated for the value that they offer to readers.

4 April 2018

Edward L. Bradley III
Florida State University College of Medicine
Tallahassee, FL, USA

Preface

Diseases of the pancreas and biliary tree are amongst the most common abdominal conditions around the world, and they continue to fascinate and frustrate. Covering a wide range of inflammatory and neoplastic diseases they are responsible for considerable patient suffering. They also represent substantial work for generalists and specialists, including general surgeons, HBP surgeons, gastroenterologists, radiologists, intensivists, general practitioners, nursing staff and allied health workers.

The care of these patients is challenging and changing, not just because of the diseases themselves, but because of the need to remain current in the face of new knowledge, evidence and approaches to management. We have assembled an experienced team of authors who are here to help. All experts in their field, they have provided chapters that address these challenges with an erudite and evidence-based approach. The chapters are also practical, taking a step-by-step approach to real-world issues in patient care. All those providing care to patients with these diseases will find value in these pages.

We are sincerely grateful to the individual authors who have contributed to this book. They have been excellent to work with and responsive to the demands of both editors and publishers. And, as expected, we have gained new knowledge and perspectives, which has made this an enriching experience for us. This project would not have been possible without the sterling support of Dr. Naren Aggarwal and Mr. Kumar Athiappan from Springer through the entire process of bringing you this book.

The diseases of the pancreas and biliary tree continue to be our primary clinical and research interests and we hope you will be inspired to provide the very best of care for your patients, as you read and apply all that is contained here.

Gurgaon, India — Savio George Barreto
Auckland, New Zealand — John A. Windsor

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About the Editors

Savio George Barreto is a Gastrointestinal and Hepato-Pancreato-Biliary (GI & HPB) surgeon and researcher. He completed his undergraduate and postgraduate surgical degrees at Goa Medical College and Hospital, where he also trained in Internal Medicine and General Surgery. He completed his fellowship in GI & HPB Surgical Oncology at the Tata Memorial Hospital in Mumbai and his training in GI and Liver Transplant Surgery at Flinders Medical Centre and the Royal Adelaide Hospital, South Australia. After serving a year as the Chief Surgical Resident at Modbury Hospital, South Australia, Dr. Barreto returned to India. His career includes appointments as Consultant Surgical Oncologist at the Department of GI & HPB Surgical Oncology, Tata Memorial Centre, Mumbai, India, and as Consultant Surgeon at the Department of GI Surgery, GI Oncology and Bariatric Surgery, Medanta—The Medicity. He is currently a Senior Lecturer at the College of Medicine and Public Health, Flinders University, South Australia.

Barreto secured his Doctor of Philosophy degree from Flinders University for his work on the neuropeptide galanin and its antagonists, their effects on pancreatic exocrine secretion, and their role in acute pancreatitis. His interests focus on the basic science and surgical aspects of acute pancreatitis, pancreatic, gastric, and gallbladder cancer. He has published a carcinogenesis model in gallbladder cancer to aid in understanding the development of the cancer and to further therapy-directed research. He, along with Professor John Windsor, has proposed the first evidence-based definition of early gastric cancer. Dr. Barreto has authored more than 150 clinical and basic science research papers as well as book chapters on GI and HPB-related topics and has been invited to lecture on his work all over the world. He serves on the Indian Council of Medical Research Task Force groups for the development of guidelines for the management of gastric, pancreatic, and neuroendocrine cancers for India.

John A. Windsor grew up in the Indian Himalayas, completed his surgical training in Auckland and his specialist HBP training in Edinburgh. He is currently an HBP and Upper GI Surgeon at the Auckland City and Mercy Hospitals. He holds a personal chair in surgery, is Director of Surgical Research and Assistant Director of the national MedTech Centre of Research Excellence. For over 30 years he has been active in promoting research and education, especially in the training of surgeon

scientists. His surgical interests include the management of acute and chronic pancreatitis, pancreatic cancer, and gastro-esophageal reflux and cancer. His research interests include the pathophysiology of acute pancreatitis, the role of toxic mesenteric lymph in critical illness, and the mapping and modulation of gastric electrical activity. He has published over 380 peer-reviewed manuscripts and has an H-index of 60, over 200 invited lectures, and 8 visiting professorships to his credit. He has been Secretary General of the International Hepato-Pancreato-Biliary Association and Chair Section of Academic Surgery at the RACS. He has been awarded the Gluckman Medal for distinguished research contributions to the University of Auckland, the Sir Louis Barnett Medal for distinguished contributions to the RACS, and elected a Fellow of the American Surgical Association and the Royal Society of New Zealand.

Anatomy of the Pancreas and Biliary Tree

1

Constantinos P. Zambirinis and Peter J. Allen

1.1 Pancreas

The pancreas derives its name from the Greek words *παν* (*whole*) and *κρέας* (*flesh*), due to its fleshy consistency as well as the absence of bones or ligaments [1]. The pancreas has a complex microscopic structure and functions as both an exocrine and an endocrine organ. The exocrine component, which is responsible for the digestive functions of the pancreas, represents the bulk of the organ's mass (approximately 98%). The exocrine component is composed of an intricate network of blind sacs (acini) that produce an array of digestive enzymes and form small ductules that interconnect to form larger ducts of progressively increasing caliber, ultimately leading to the main pancreatic duct. This acinar network is supported by loose connective tissue that contains blood vessels, nerves, and pancreatic stellate cells. Interspersed within the exocrine gland are the pancreatic islets of Langerhans, which constitute the endocrine component of the pancreas. The islets of Langerhans are clusters of β, α, δ, PP, and ε cells (in decreasing order of abundance), which are responsible for the production of the hormones insulin, glucagon, somatostatin, pancreatic polypeptide, and ghrelin, respectively.

1.1.1 Embryology

The developmental biology of the pancreas has attracted the interest of the scientific community not only because of the complexity of the pancreatic structure but also because of the multiple diseases that result from developmental aberrations of this organ. Although significant progress has been made with the recent advances of

C. P. Zambirinis · P. J. Allen (✉)
Hepatopancreatobiliary Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: allenp@mskcc.org

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molecular biology that enable lineage tracing of the different cell types, many aspects of pancreatic development remain unclear.

The pancreas originates from the foregut as two separate primordia suspended in the mesentery. These separate components fuse to form the final organ that rests in the retroperitoneum (Fig. 1.1). Near the end of the fourth week of gestation, a mesenchymal condensation is formed dorsal to the primitive foregut, at the level of the future duodenum. This in turn induces the underlying foregut endodermal lining to form the dorsal pancreatic bud (Fig. 1.2). Specifically, mesenchymal fibroblast growth factor 2 (*FGF2*) and activin relieve the inhibition imposed on the foregut

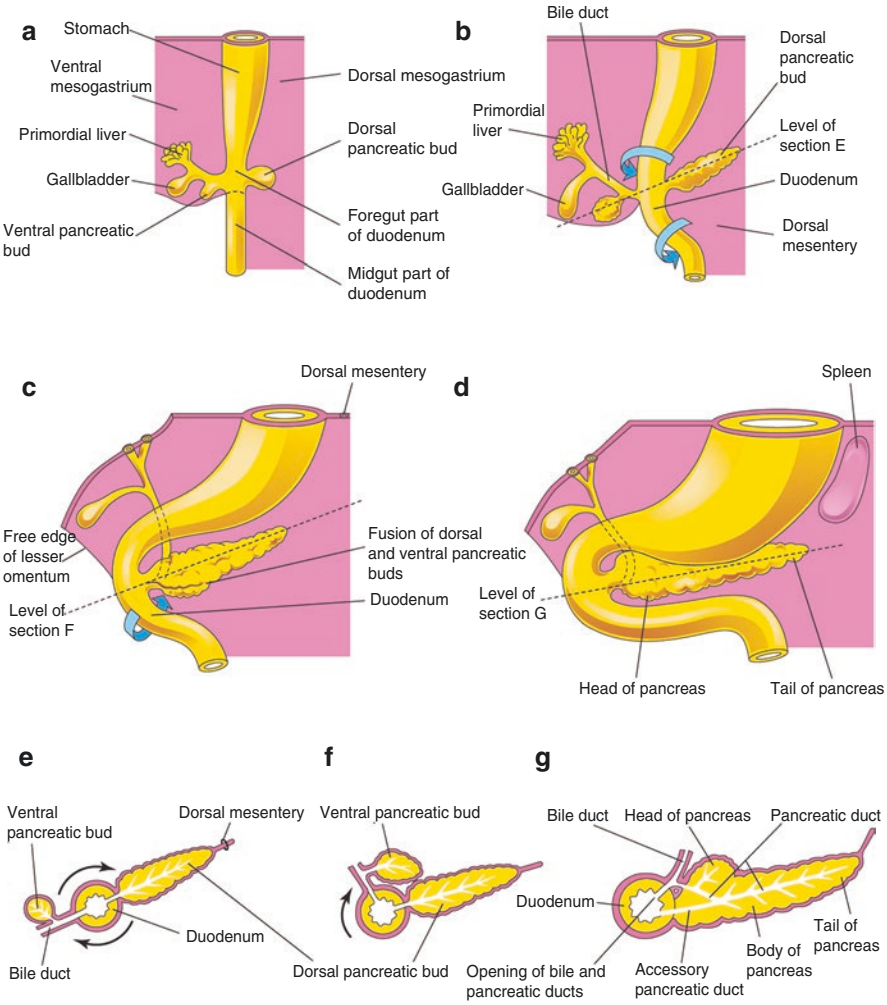


Fig. 1.1 Embryologic development of the pancreas. (**a–d**) Successive stages in the development of the pancreas from the fifth to eighth week. (**e–g**) Diagrammatic transverse sections through the duodenum and developing pancreas. Growth and rotation *(arrows)* of the duodenum bring the ventral pancreatic bud toward the dorsal bud, and the two buds subsequently fuse (Reproduced with permission from Moore et al., "*The developing human: Clinically oriented embryology*", 10th edition. Copyright Elsevier/Saunders 2015)

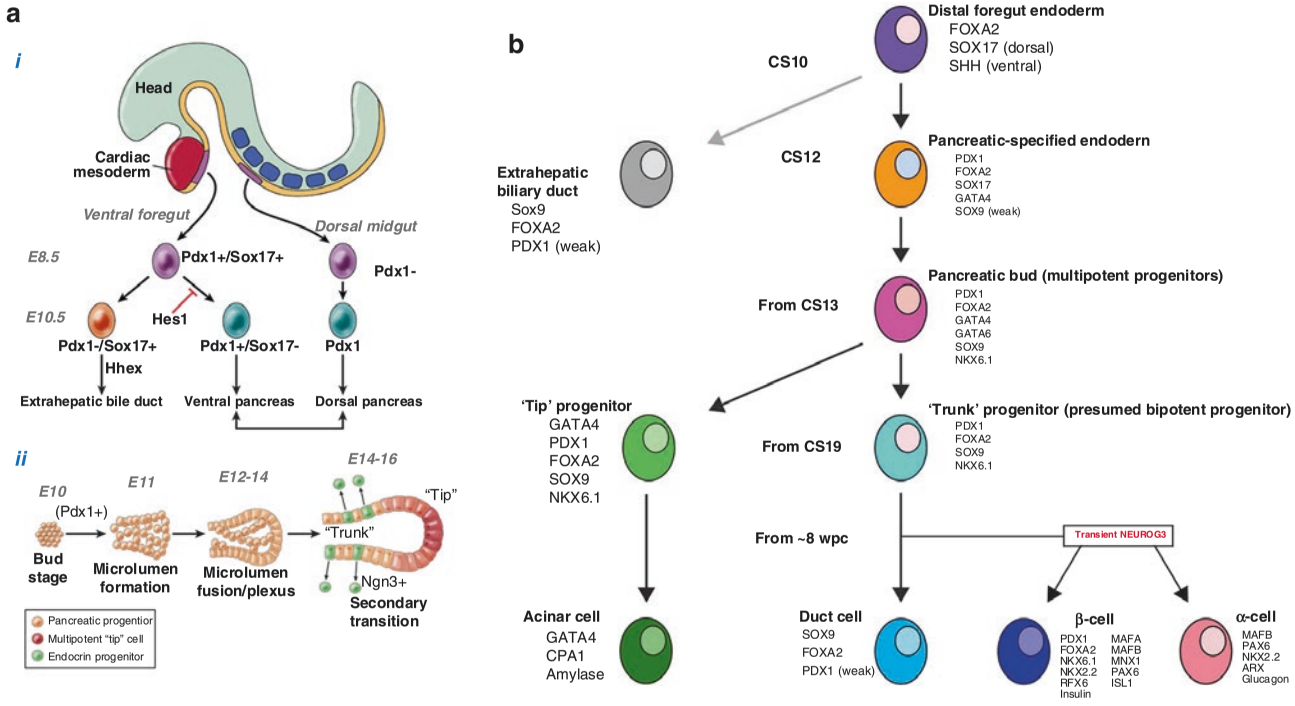


Fig. 1.2 Cellular and molecular interactions defining mammalian pancreas development. (**a**) Regulation of pancreas development in the mouse. Pancreatic specification begins with signals derived from the mesenchyme, with serial expression of different transcription factors (***i***). The "tip-trunk" model explains the intricate microarchitecture of the pancreas (***ii***). From [2]. (**b**) Transcription factors and other key markers that identify different cell types and stages during early pancreas specification and subsequent lineage commitment in humans (based on immunohistochemical studies). Only dorsal pancreas specification is shown for simplicity (markers for the extrahepatic biliary duct are in gray). CS, Carnegie stage; wpc, weeks postconception (Reproduced with permission from [16])

endoderm by sonic hedgehog (*SHH*) signaling, therefore enabling differentiation into the pancreatic primordium. The latter results from epithelial expression of the transcription factors pancreatic and duodenal homeobox 1 (*PDX1*) immediately followed by pancreas-specific transcription factor 1a (*PTF1A*) [2]. The importance of these transcription factors in pancreatic development is underscored by the fact that mutations in either gene lead to *pancreatic agenesis*. Both PDX1 and PTF1A have been exploited in various genetically engineered mouse models of pancreatic diseases, especially in mouse models of pancreatic cancer [3]. Furthermore, uncoordinated expression of pancreas-licensing signals can facilitate the development of *ectopic pancreatic tissue*—most commonly found in the mucosa of the stomach, duodenum, jejunum, or ileal diverticulum (of Meckel)—that may lead to atypical gastrointestinal symptoms (e.g., bleeding or even cancer).

At the microscopic level, pancreatic development follows a process of branching morphogenesis. The inner cells of the growing pancreatic buds that lack contact with the surrounding tissues form microlumens (Fig. 1.2a). Adjacent microlumens subsequently fuse to form duct-like structures, while the epithelial lining is separated into proximal "trunk" and distal "tip" regions. The cells at the trunk regions will develop into cells with ductal and endocrine function. The cells of the tip region initially remain multipotent, but after progressive branching and elongation, the distal tip cells commit to the acinar lineage and will have exocrine function. Complex expression patterns of multiple transcription factors regulate the fate of each cell to give rise to the different lineages found in the adult pancreas (Fig. 1.2b).

Pancreatic parenchymal cells proliferate early in gestation resulting in an increase in the volume of the developing gland. The dorsal bud grows earlier than the ventral bud, taking a progressively oblong shape. The rotation of the stomach and duodenum influences the anatomy and orientation of the pancreatic primordia (Fig. 1.1). The ventral pancreatic bud follows the rotation of the duodenum, moving first to the right and then to its final dorsal position (Fig. 1.1). The two buds normally fuse in the retroperitoneum to form a single organ. The ventral bud eventually lies posterior to the superior mesenteric vessels, posterior and inferior to the dorsal pancreatic bud, giving rise to the bulk of the uncinate process and the inferior portion of the head of the pancreas. The rest of the head of the pancreas, the neck, body, and tail, are all derived from the dorsal bud.

Each of the two pancreatic buds has its own separate main duct (Fig. 1.1). The duct of the ventral bud lies in continuity with the main bile duct. The two ductal systems normally fuse to become one during the rotation of the duodenum and the pancreas (Figs. 1.1 and 1.3a). The ventral bud forms the proximal main pancreatic duct (of Wirsung), while the duct of the dorsal bud forms the rest of the main pancreatic duct spanning the neck, body, and tail of the gland. The proximal part of the duct of the dorsal bud usually persists as an accessory pancreatic duct (of Santorini) that opens in the minor duodenal papilla (Fig. 1.3a).

Abnormalities in the rotation and/or fusion of the two pancreatic buds may result in anatomical variants. The most common congenital anomaly of the pancreas is *pancreas divisum*. It is due to a failure of fusion of the ventral and dorsal duct system and can be subclassified depending on the extent of communication and the

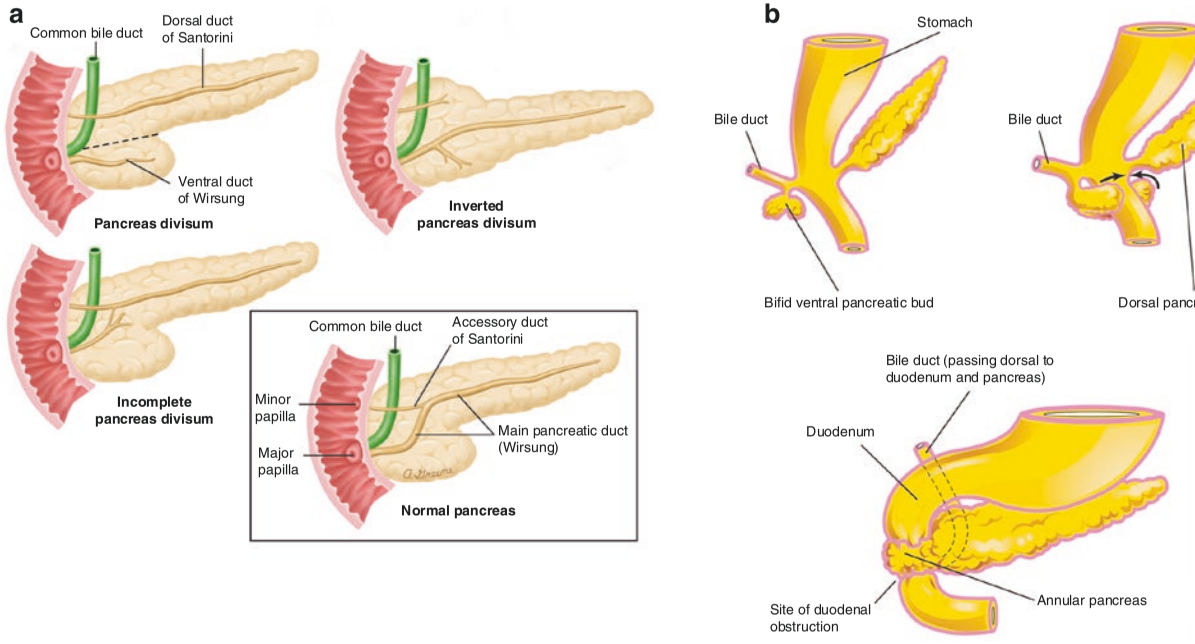


Fig. 1.3 Rotation of the pancreas primordia and its ductal system and related anomalies. (**a**) The rotation of the duodenum brings the two pancreatic buds together. Their ducts, initially separate, usually fuse to form the adult main pancreatic duct that drains into the duodenum. Failure of fusion results in pancreas divisum, whereby the two parts of the pancreas remain distinct to variable extent, each with its own duct [*Source*: UpToDate.com; Graphic 78,995 Version 3.0]. (**b**) Improper rotation of the pancreatic buds may lead to annular pancreas, in which the gland encircles the duodenum. This birth defect produces complete obstruction (atresia) or partial obstruction (stenosis) of the duodenum (Reproduced with permission from Moore et al., "*The developing human: Clinically oriented embryology*", 10th edition. Copyright Elsevier/Saunders 2015)

Table 1.1 Anatomic categorization of congenital pancreatic anomalies and variants

Ventral/dorsal ductal malfusion 1. Pancreas divisum 2. Incomplete pancreas divisum 3. Isolated dorsal segment
Rotation or migration problems 1. Annular pancreas 2. Ectopic pancreas 3. Ectopic papillae
Agenesis or hypoplasia
Ductal duplication
Atypical ductal configuration
Anomalous pancreatobiliary ductal junction
Cystic malformations

location of the two duct systems (Fig. 1.3a). Pancreas divisum is found in approximately 10% of individuals and is usually asymptomatic (in over 95% of individuals); it has been found to be a cause of recurrent acute and chronic pancreatitis. Another rare developmental anomaly is termed *annular pancreas*. In this case the ventral pancreatic bud has a bifid configuration, which leads to the encirclement of the duodenum and which can lead to narrowing of the duodenum (Fig. 1.3b). Approximately half of patients with annular pancreas also have pancreas divisum [4, 5]. Other congenital pancreatic anomalies are shown in Table 1.1.

1.1.2 Surgical Anatomy

In the healthy adult, the pancreas is a soft, retroperitoneal glandular organ, lying transversely and oblique and draped over the vertebral column at the level of L1–L2 vertebrae (Fig. 1.4). The bulk or volume of the pancreas varies and increases during the first 2–3 decades of life but progressively atrophies with aging.

The pancreas is divided into five parts: the head, neck, body, tail, and uncinate process (Fig. 1.4). The neck, head, and uncinate process are encompassed by the C-loop of the duodenum, to the anatomic right of the midline, and are in intimate relationship with the superior mesenteric vessels medially. The body extends laterally to the anatomic left, posterior to the stomach, with the tail terminating in the splenic hilum. The organ is surrounded by a thin capsule that is loosely attached to its surface. Most of the anterior surface of the pancreas is covered with peritoneum, except where it is crossed by the root of the transverse mesocolon, as well as where there is direct contact with the first part of the duodenum and the splenic hilum (Fig. 1.4).

The head of the pancreas is the thickest part of the gland. Anteriorly, it is related to the origin of the transverse mesocolon. Posteriorly, the head is related to the inferior vena cava (IVC), the right gonadal vein near its entrance into the vena cava, and the right crus of the diaphragm. The common bile duct runs either on the posterior surface of the pancreatic head or is embedded within the parenchyma of the gland.

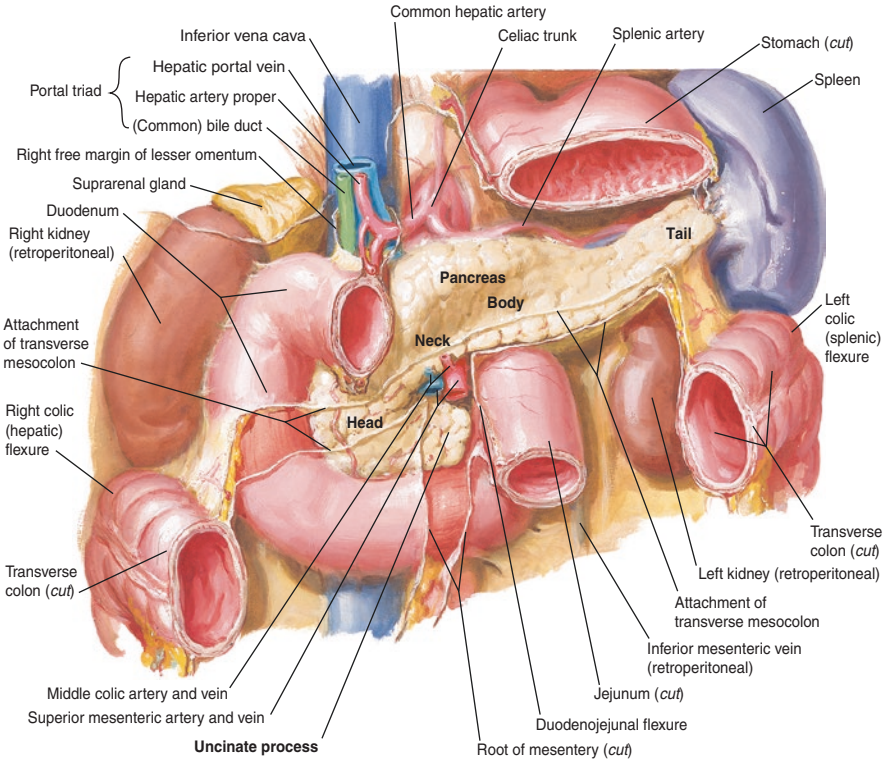


Fig. 1.4 The pancreas in situ [*Source*: Netter, F.H., Atlas of human anatomy. 6th ed. 2014: Saunders]

The transitional zone between the head and the body of the pancreas is termed the neck. It is defined by its anatomic location anterior to the formation of the portal vein (usually by the confluence of the superior mesenteric and splenic veins). It is approximately 2 cm wide and usually the most anteriorly located portion of the pancreas. Anteriorly the neck is covered by peritoneum and is related to the pylorus superiorly. Its posterior aspect is grooved by the superior mesenteric vein (SMV) and the portal vein (PV).

The anterior body of the pancreas is covered by the peritoneal layer that constitutes part of the posterior wall of the lesser sac (Fig. 1.5a). Toward the inferior border of the pancreas, the peritoneal layer is reflected anteroinferiorly to form the superior leaf of the transverse mesocolon (Fig. 1.5). The posterior surface of the body lies on the fusion fascia of Toldt in the retroperitoneum, the so-called bloodless plane of Treves. The posterior body is related to the abdominal aorta and the origin of the superior mesenteric artery (SMA), the left crus of the diaphragm, the left renal vein, the left kidney, and the left adrenal gland, from right to left (Figs. 1.4 and 1.5a).

The pancreas has important relationships to major blood vessels, of relevance to surgery of the pancreas. The splenic vein runs along the posterior surface of the

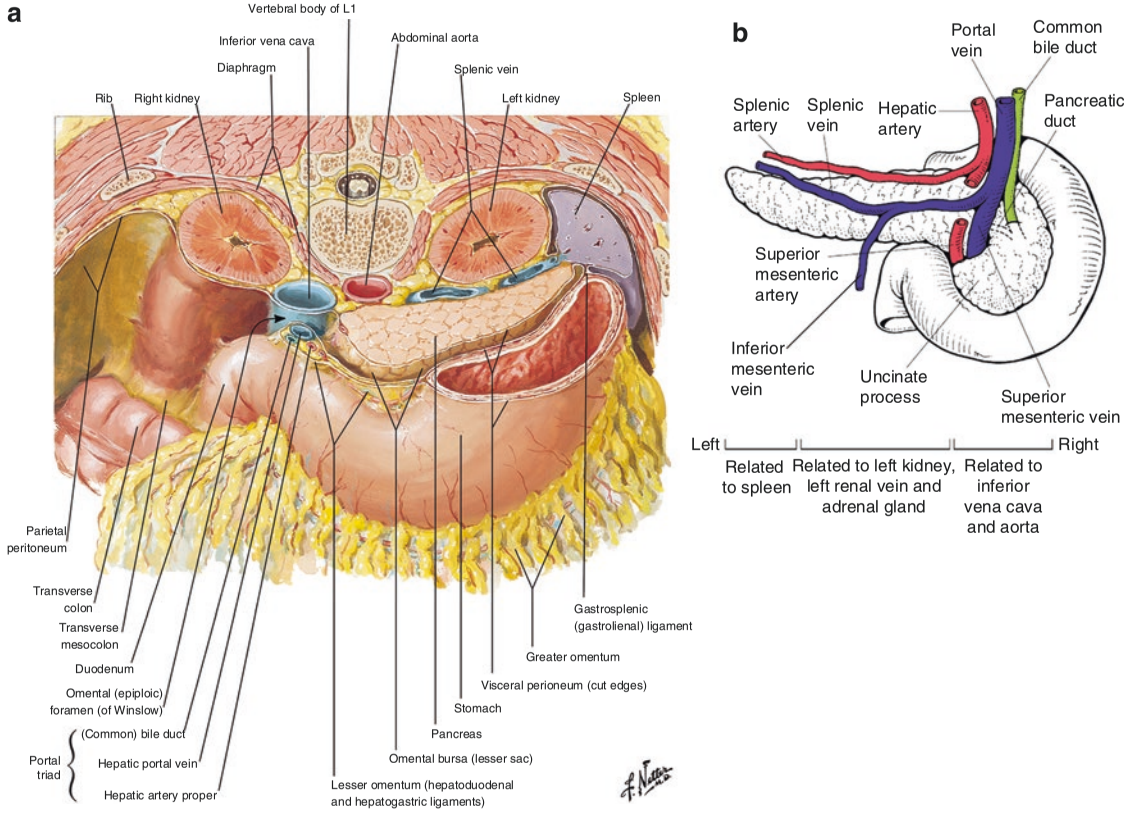


Fig. 1.5 Descriptive anatomy of the pancreas and its relationships to surrounding organs and vascular structures. (**a**) Axial cross-section at the level of L1 vertebral body. The omental bursa or lesser peritoneal sac is evident. Peripancreatic inflammation can lead to obliteration of this potential space by adhesions and complicate pancreatic dissection. (**b**) The posterior relationships of the duodenum and pancreas [*Sources*: Netter, F.H., Atlas of human anatomy. 6th ed. 2014: Saunders (**a**); Jarnagin, W.R., et al., Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th ed. 2012, Philadelphia, PA: Saunders (**b**)]

gland in a groove of variable depth, sometimes almost entirely embedded within the pancreatic parenchyma (Fig. 1.5). The celiac trunk and its branches emanate along the superior border of the body, with the common hepatic artery running to the right and the splenic artery to the left (Figs. 1.4 and 1.5b). The inferior border of the pancreas is crossed posteriorly by the inferior mesenteric vein (IMV), typically at its confluence with the splenic vein, and it serves as a useful landmark for identification of the former vessel on cross-sectional imaging (Fig. 1.5b).

The tail of the pancreas is the relatively mobile, left-most part of the pancreas that is confined between the layers of the splenorenal ligament together with the splenic artery and the origin of the splenic vein (Figs. 1.4 and 1.5a). It is 1.5–3.5 cm long in adults and may extend variably to the hilum of the spleen in 50% of cases and may extend posterior to vessels in the hilum. This makes the tail of the pancreas vulnerable to injury during splenectomy and needs to be visualized prior to ligating the splenic vessels.

The uncinate process can be considered as a distinct part of the pancreas due to its different embryologic origin and its location extending posterior to the superior mesenteric vessels (Figs. 1.4 and 1.5). It extends in the plane between the superior mesenteric vessels anteriorly and the aorta posteriorly (Fig. 1.5b). Superiorly, it relates to the left renal vein. It lies immediately superior to the third part of the duodenum, such that tumors arising in the uncinate process can compress the former leading to duodenal obstruction (Figs. 1.4 and 1.5b).

The main pancreatic duct of Wirsung begins at the tail of the pancreas and runs through the body roughly midway between the superior and inferior border (Fig. 1.6a). It receives multiple small ductules throughout its course that drain the pancreatic parenchyma, thus increasing progressively in diameter from 1 mm in the tail to 3 mm in the head. It deviates inferiorly and posteriorly in the head as it

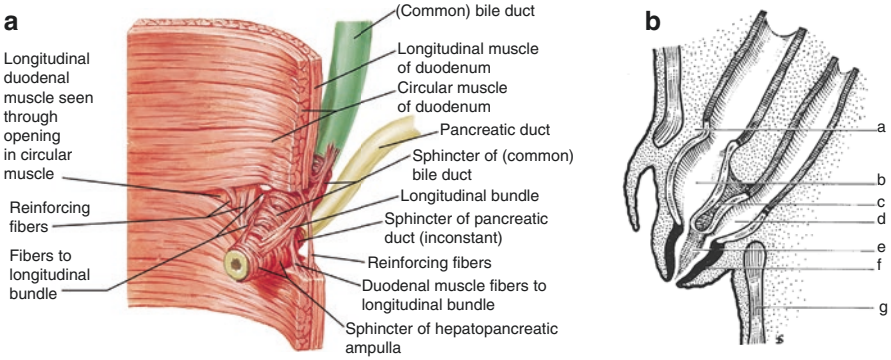


Fig. 1.6 Pancreatic duct and sphincter of Oddi. (**a**) Anatomy of the pancreatic duct at its junction with bile duct within the duodenal wall. (**b**) Schematic representation of the sphincter of Oddi: notch (a); biliary sphincter (b); transampullary septum (c); pancreatic sphincter (d); membranous septum of Boyden (e); common sphincter (f); smooth muscle of duodenal wall (g) [*Sources*: Netter, F.H., Atlas of human anatomy. 6th ed. 2014: Saunders (**a**); Jarnagin, W.R., et al., Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th ed. 2012, Philadelphia, PA: Saunders (**b**)]

courses toward the main ampulla. The pancreatic duct and bile duct are usually separated by the transampullary septum before joining in a "Y" configuration within the duodenal wall (Fig. 1.6c). The terminal part of the two ducts is surrounded by a complex circular arrangement of smooth muscle fibers known as the sphincter of Oddi (Fig. 1.6b, c). The sphincter of Oddi is anatomically distinct from the muscular layers of the duodenum, and it has a dual function: (a) to regulate flow of biliary and pancreatic secretions into the duodenal lumen and (b) to impede reflux of intestinal content into the pancreatobiliary ductal system.

The accessory duct of Santorini runs superior and parallel to the duct of Wirsung. It drains part of the head of the pancreas into the minor duodenal papilla, roughly 1–2 cm proximal to the ampulla of Vater. The pattern of fusion of the main and accessory ducts is variable and can be entirely separate (pancreas divisum) (see above).

1.1.2.1 Regional Blood Supply and Lymphatic Drainage

The celiac trunk emerges from the aorta immediately after it exits the aortic hiatus of the diaphragm, just superior to the upper border of the pancreatic neck (Fig. 1.4). It runs anteriorly for a very short distance and then typically trifurcates into the left gastric artery (LGA), the splenic artery, and the common hepatic artery (CHA; Figs. 1.4 and 1.7a). The LGA may occasionally arise directly off of the aorta as a separate branch (Fig. 1.4). The splenic artery, the largest of the three celiac branches, runs a tortuous course posterior to the superior border of the pancreas toward the splenic hilum (Fig. 1.4). The splenic artery provides blood supply to the stomach via multiple short gastric arteries as well as via the left gastroepiploic artery in addition to the pancreas and spleen. The CHA initially travels forward and then curves to the right just above the pancreas. It gives rise to the gastroduodenal artery (GDA) and the right gastric artery, after which it becomes the proper hepatic artery. The proper hepatic artery ascends in the hepatoduodenal ligament to the left of the CBD and anterior to the portal vein for a short distance (Fig. 1.5a) and usually divides into left hepatic (LH) and right hepatic (RH) artery (Fig. 1.7a). The LH artery rises vertically toward the base of the umbilical fissure of the liver, giving off one or more branches to the caudate lobe as well as a branch to the quadrate lobe (segment IV) known as the middle hepatic artery. The RH artery usually passes behind the common hepatic duct and enters the hepatocystic triangle on its way to the right liver. It gives off the cystic artery that supplies the gallbladder, as well as branches to the caudate lobe.

The SMA arises from the aorta in an acute angle at the level of L1, about 1 cm distal to the origin of the celiac trunk (Fig. 1.5b). It runs inferiorly, posterior to the neck of the pancreas, the PV, and SMV and anterior to the left renal vein, the uncinate process, and the third part of the duodenum, eventually continuing into the small bowel mesentery to branch off into colic, ileal, and jejunal arteries (Fig. 1.5b). Near its origin it is surrounded by fatty tissue containing lymphatics and nerves which is frequently invaded by pancreatic cancer, a critical determinant of resectability.

The classic anatomy of the arterial blood supply to the liver, biliary tree, and pancreas is found in only approximately 60% of cases. A great degree of variability

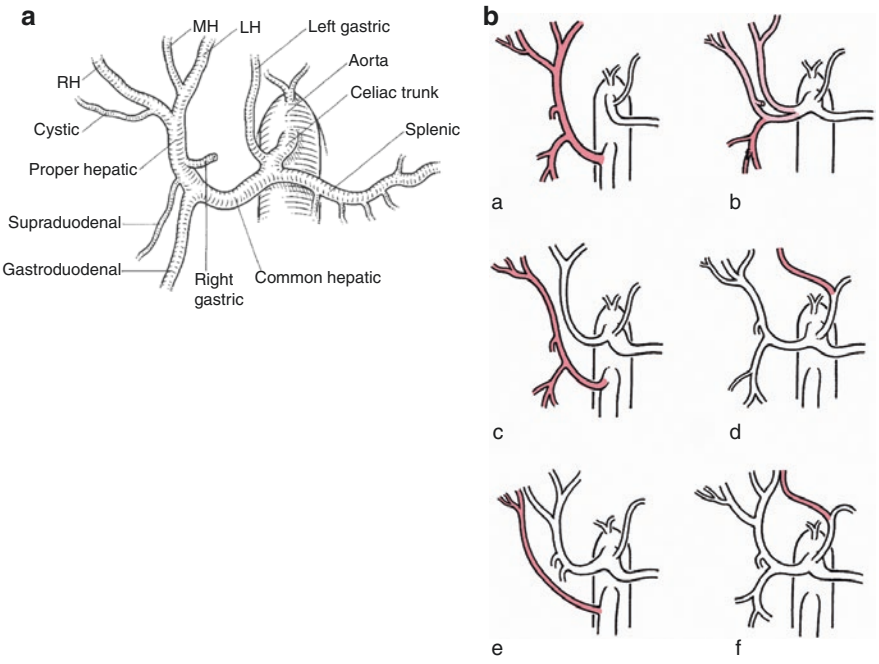


Fig. 1.7 Arterial inflow to the liver, biliary tree, and pancreas. (**a**) Usual anatomy of the celiac trunk. *LH* left hepatic artery, *MH* middle hepatic artery, *RH* right hepatic artery [*Source*: Jarnagin, W.R., et al., Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th ed. 2012, Philadelphia, PA: Saunders]. (**b**) Common anatomic variations of the branches of the celiac trunk

exists, and knowledge of these variations is very important for safe liver and pancreatic surgery (Fig. 1.7b). The CHA may arise from the SMA instead of the celiac trunk (Fig. 1.7b-a), coursing to the right of the portal vein and posterolateral to the CBD. This variation is important because it places the CHA at risk of operative injury during a pancreatoduodenectomy and should be identified preoperatively on imaging studies. The GDA may originate from the right hepatic artery (Fig. 1.7b-b) and may be duplicated. The RH artery arises from the SMA in up to 25% of cases (Fig. 1.7b-c, e) and may, or may not, anastomose with the LH artery. In a similar proportion of cases, the LH artery may be replaced by a branch arising from the left gastric artery (Fig. 1.7b-d) or duplicated (Fig. 1.7b-f). In rare occasions, either of the two hepatic arteries may be derived independently from the celiac trunk.

The pancreas is a richly vascularized organ. Consistent with its embryologic origin from the foregut-midgut junction, the pancreas receives its arterial inflow from branches of the celiac trunk as well as the SMA, which form multiple arcades within and around the gland (Fig. 1.8). The head and uncinate process along with the adjacent duodenum are supplied by two main arterial vessels: the superior pancreaticoduodenal artery (SPDA), a branch of the gastroduodenal artery, and the inferior pancreaticoduodenal artery (IPDA), a branch of the SMA (Fig. 1.8).

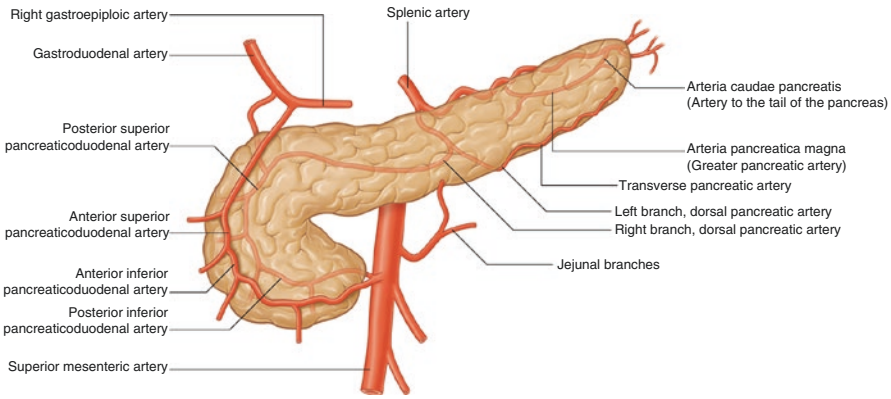


Fig. 1.8 The arteries supplying the pancreas form a rich anastomotic network around and within the gland [*Source*: Standring, S., Gray's Anatomy: the anatomical basis of clinical practice. 41st ed. 2016]

Each of these arteries divides into anterior and posterior branches. The anterior arteries unite to form the anterior (or ventral) pancreaticoduodenal arcade, and the posterior branches may unite in a posterior (dorsal) arcade (Fig. 1.8). The two arcades are connected by multiple small arteries that either run in the pancreaticoduodenal groove or traverse the pancreatic parenchyma. Usually a large branch known as the communicating artery (or middle pancreaticoduodenal arcade) runs between the main and accessory pancreatic ducts to connect the anterior arcade with the SPDA.

The body and tail of the pancreas are supplied by branches of the splenic artery (Fig. 1.8). These arteries enter the substance of the gland at its superior and inferior borders. During pancreatectomy, they should be ligated at the borders of the pancreas prior to transection, to prevent bleeding. Three large branches deserve special attention. The most prominent is the dorsal pancreatic artery, usually originating from the initial 2 cm of the CHA (Fig. 1.8). It supplies multiple small branches and divides into right and left terminal branches. The right runs toward the head to unite with the pancreaticoduodenal arcades, while the left branch courses toward the tail, eventually uniting with the transverse pancreatic artery. The other two named branches are the great pancreatic (*arteria pancreatica magna*) and the artery to the tail of the pancreas (*arteria caudae pancreatis*), both of which may join the transverse pancreatic artery running along the inferior border of the gland.

The pancreas drains into multiple peripancreatic lymph node stations via an extensive lymphatic network. Lymphatic vessels lying within the connective tissue septae of the gland unite to form larger branches that travel along the regional arteries. The lymphatic drainage of the body and tail of pancreas occurs into the nodes of the splenic artery and the inferior pancreatic and the splenic hilar nodes and from there to the celiac and preaortic nodes. The neck and head of the pancreas have a much wider drainage to the nodal stations of all the supplying arteries. Lymph node status is one of the most important prognostic factors of pancreatic cancer which

means that adequate lymphadenectomy and appropriate staging (including number of involved lymph nodes and presence of lymphatic invasion) are very important for appropriate management of these patients.

1.1.2.2 Innervation

The pancreas has a rich autonomic innervation that contributes to the regulation of both the exocrine and the endocrine functions of the gland. Parasympathetic nerve fibers distributed throughout the gland within the interlobular connective tissue transmit impulses to and from the vagus via its hepatic, gastric, and celiac branches. This is integrated with additional feedback from enteric neurons of the stomach and duodenum as well as sympathetic efferent neurons. In addition, sympathetic nerves innervate the intrapancreatic blood vessels and ducts, causing vasoconstriction and inhibiting exocrine secretion. Pain associated with pancreatic diseases is conveyed via visceral afferents of the celiac plexus and thoracic splanchnic nerves to the T6–T12 dorsal root ganglia, thus explaining its poor localization and ill-defined nature. However, in cases of extensive inflammatory or infiltrative processes involving the retroperitoneum, the regional somatic nerves may be involved leading to pain localized to the lower thoracic spine.

1.2 Biliary Tree

The biliary tree comprises of a series of epithelium-lined ductal structures which function as a conduit for bile from where it is produced in the liver to the duodenum. The biliary tree is divided into intrahepatic and extrahepatic portions, with the latter being further subdivided into the extrahepatic bile ducts and the accessory biliary apparatus (gallbladder and cystic duct). An in-depth understanding of the anatomy of the biliary tree and its associated vasculature constitutes an essential knowledge that must be possessed by every upper abdominal surgeon and general surgeon. Cholecystectomy is the most common abdominal procedure performed in developed countries, and biliary injury during this procedure continues to occur.

1.2.1 Embryology

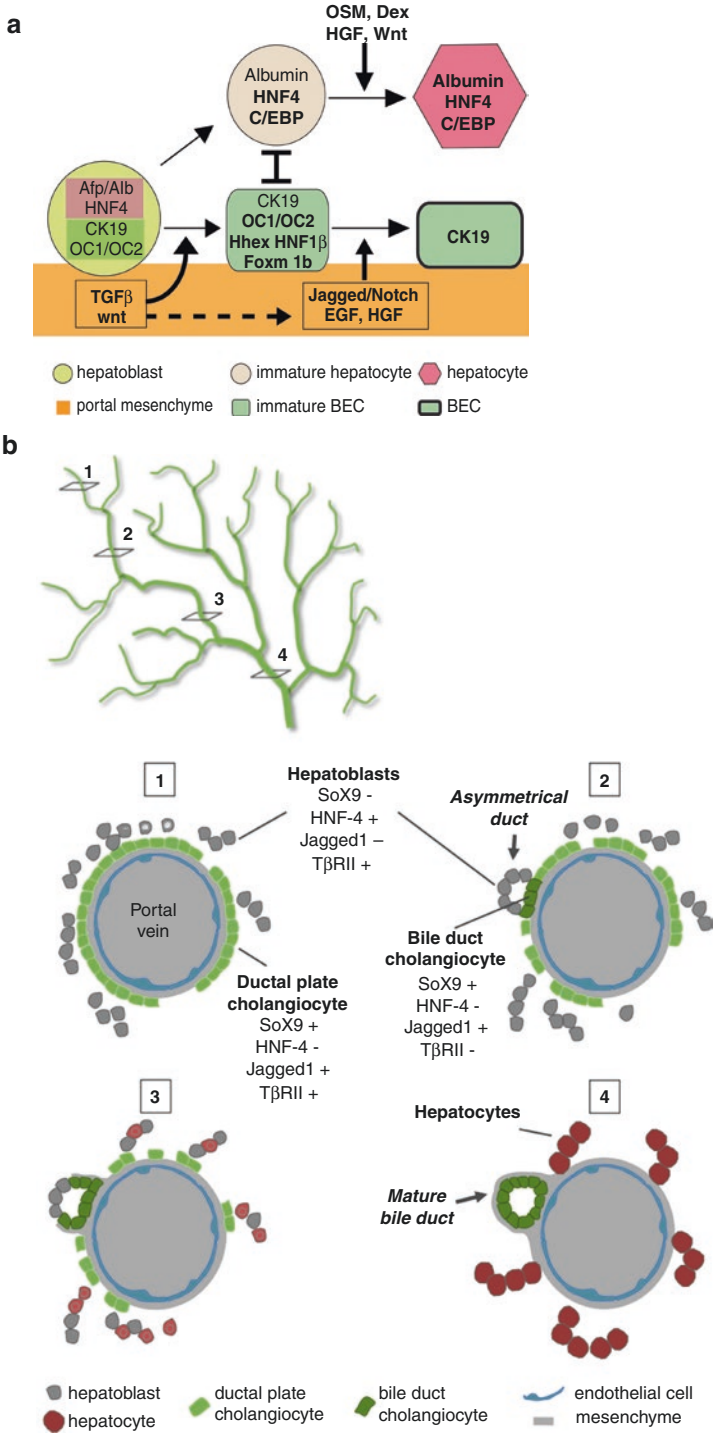
The events leading to the embryologic development of the liver and biliary tree have some similarity to the ones described above for the pancreas. The liver primordium appears in the middle of the third week of gestation as an outgrowth of the endodermal lining at the ventral aspect of the distal foregut. The hepatic progenitor cells, or hepatoblasts, proliferate rapidly and penetrate the basal lamina to expand into the septum transversum—a mesodermal plate separating the pericardial cavity and the future abdominal cavity. As this outgrowth (termed hepatic diverticulum or liver bud) continues to grow into the septum transversum, the connection to the distal foregut becomes progressively narrower, leading to the formation of the bile duct (Fig. 1.1). The part of the septum transversum lying between the liver and the

ventral abdominal wall eventually transforms into the falciform ligament, while the part of it between the liver primordium and the foregut forms the lesser omentum. An evagination at the ventral aspect of the developing bile duct gives rise to the gallbladder and cystic duct. Bile formation commences around the 12th week of gestation.

Bidirectional communication of the endodermal liver primordium with the septum transversum mesenchyme and the overlying cardiac mesoderm is critical for liver specification. The entire gut endoderm has the potential to form liver tissue, but this is suppressed by the action of surrounding tissues, particularly the notochord. Bone morphogenetic proteins (BMPs) originating from the septum transversum enable the endoderm to respond to liver-inducing signals [6]—a phenomenon termed hepatic competence and mediated by expression of forkhead box proteins A (*FOXA*) transcription factors. Next, fibroblast growth factors (FGF) from the cardiac mesoderm disinhibit the liver specification program, which is tonically repressed, leading to liver induction. Vessel-forming endothelial cells also contribute to this process.

The proliferating hepatoblasts give rise to both mature hepatocytes and biliary epithelial cells, while the surrounding mesoderm of the septum transversum forms the stromal cells of the liver (primarily liver sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells) and its vasculature. Notably, at this stage of embryogenesis, the liver is an important site for hematopoiesis. Portal and hepatic vein radicals begin to form derived from the vitelline veins. The bipotential hepatoblasts initially express genes for adult hepatocytes (*ALB*, *HNF4A*) and biliary epithelial cells (*KRT19*). Subsequently, they downregulate either of the two and commit to the opposite lineage (Fig. 1.9a). This event appears to depend on the proximity of the cells to portal vein tributaries, possibly under the control of signals such as transforming growth factor-β (TGF-β) and Wnt originating in the periportal mesenchyme (Fig. 1.9).

Fig. 1.9 Embryologic development of the liver and biliary tree. (**a**) Model of hepatoblast differentiation into hepatocytes or biliary epithelial cells (BEC). Hepatoblasts are bipotential, which is reflected in expression of both hepatocytes (albumin) and BECs (CK19). Interaction with the periportal mesenchyme promotes differentiation to BECs by expression of BEC-promoting (OC1, OC2, HNF1β) and repression of mature hepatocyte (HNF4 and C/EBP) transcription factors. On the contrary, hepatoblasts not influenced by periportal mesenchyme signals (such as Wnt and TGF-β) undergo differentiation toward mature hepatocytes. Additional signals from the periportal mesenchyme (Notch, EGF, and HGF) facilitate ductal plate remodeling, while other factors (OSM, Dex, HGF, and Wnt) promote hepatocyte maturation (Reproduced with permission from Zorn, A.M., Liver development (October 31, 2008), StemBook, ed. The Stem Cell Research Community, StemBook, https://doi.org/10.3824/stembook.1.25.1, http://www.stembook.org. Copyright 2008 Aaron M. Zorn). (**b**) Formation of bile duct progresses from the hilum to the periphery of the liver. Sections at different stages of maturation are shown, with the least mature at the periphery (ductal plate; section 1) and mature bile ducts near the hilum (section 4). Part of the ductal plate cells form asymmetrical ducts that result in mature bile ducts, while the rest regress (Reproduced with permission from [7])


a
OSM, Dex
HGF, Wnt
Albumin
HNF4
C/EBP
Albumin
HNF4
C/EBP
Afp/Alb
HNF4
CK19
OC1/OC2
CK19
OC1/OC2
Hhex HNF1β
Foxm 1b
CK19
TGFβ
wnt
Jagged/Notch
EGF, HGF
hepatoblast
immature hepatocyte
hepatocyte
portal mesenchyme
immature BEC
BEC
b
1
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4
Hepatoblasts
SoX9 -
HNF-4 +
Jagged1 –
TβRII +
Asymmetrical
duct
Portal
vein
Bile duct
cholangiocyte
SoX9 +
HNF-4 -
Jagged1 +
TβRII -
Ductal plate
cholangiocyte
SoX9 +
HNF-4 -
Jagged1 +
TβRII +
Hepatocytes
Mature
bile duct
hepatoblast
hepatocyte
ductal plate
cholangiocyte
bile duct
cholangiocyte
endothelial cell
mesenchyme

A subpopulation of hepatoblasts encircles the portal veins to form a band of potential biliary epithelial cells. This band is termed the "ductal plate," and its constituent cells are called cholangiocytes (Fig. 1.9b). Soon this transforms into a bilayer with focal dilations. The latter give rise to the intrahepatic bile ducts in the portal triads. Remodeling of the ductal plates begins at the oldest ductal plates surrounding the larger portal veins near the hilum and progresses toward the periphery of the liver, following the portal vein system. The remaining ductal plate cells that were not incorporated into bile ducts then involute via apoptosis. The ductal plate is an important source of vascular endothelial growth factor (VEGF) that drives hepatic artery development [7]. The significance of the developmental relationship between the bile ducts, the portal vessels (hepatic artery, portal vein), and the portal mesenchyme is highlighted by *ductal plate malformations* that result from inappropriate interactions and ductal plate remodeling [8]. For example, *Alagille syndrome* is an autosomal dominant disease associated with mutations in *JAG1* and *NOTCH2* in which the bile ducts are absent from the portal tract, whereas there are increased numbers of hepatic arteries and fibrosis.

It is worth mentioning that ductal plate malformations are fundamentally different from biliary atresia. Biliary atresia begins with a normally developed biliary tree that is subsequently obliterated by inflammation and fibrosis due to perinatal environmental insults to the fetus (infectious and/or noninfectious). It involves predominantly the extrahepatic biliary tree and manifests as progressive neonatal jaundice that culminates in cirrhosis at a very young age, if left untreated. Although rare, it is critical that it is recognized as early as possible since portoenterostomy (Kasai operation and its variants) can have dramatically better outcomes if performed prior to 3 months of age and possibly spare the infant from a liver transplantation procedure.

1.2.2 Surgical Anatomy

The surgical anatomy of the biliary tree is integrated with the hepatic anatomy due to their common embryologic origin and their shared physiologic roles. Although multiple classifications of the hepatic structural anatomy have been proposed, the most surgically relevant is the one described by Couinaud [9]. The liver is subdivided into eight distinct segments—each with its own discrete biliary drainage, vascular inflow that enters the segment as a pedicle, and vascular outflow (Fig. 1.10a). The functional unit of the liver is the hepatic lobule, which consists of sheets of hepatocytes radiating outward from a central vein (Fig. 1.11). At the periphery of these polygonal units are multiple portal triads—each composed of a branch of the hepatic artery, a branch of the portal vein, and a bile duct, encased within trabeculae of connective tissue termed portal tracts. The hepatic artery and portal vein branches represent the vascular inflow to the hepatic lobule. The blood then circulates between the hepatocytes in spaces termed sinusoids in a centripetal manner, subsequently draining into the central vein (Fig. 1.11). The latter are tributaries of the hepatic veins and constitute the vascular outflow of the hepatic

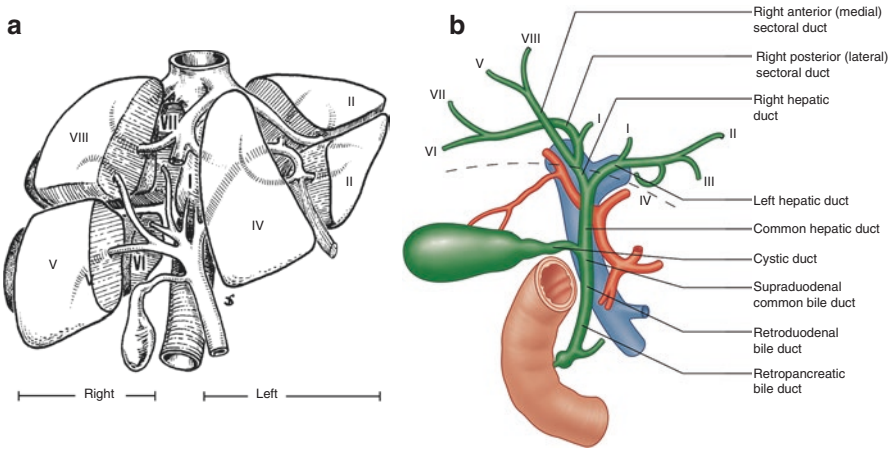

Fig. 1.10 Biliary drainage of the liver. (**a**) The functional division of the liver and its segments according to Couinaud's nomenclature, along with the biliary drainage of the two functional hemilivers, is shown [*Source*: Jarnagin, W.R., et al., Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th ed. 2012, Philadelphia, PA: Saunders]. (**b**) The overall arrangement of the intrahepatic and extrahepatic biliary tree. Note that segment I (caudate lobe) often drains via both right and left hepatic ducts. The dashed line represents the level of the liver parenchyma at the porta hepatis [*Source*: Standring, S., Gray's Anatomy: the anatomical basis of clinical practice. 41st ed. 2016]

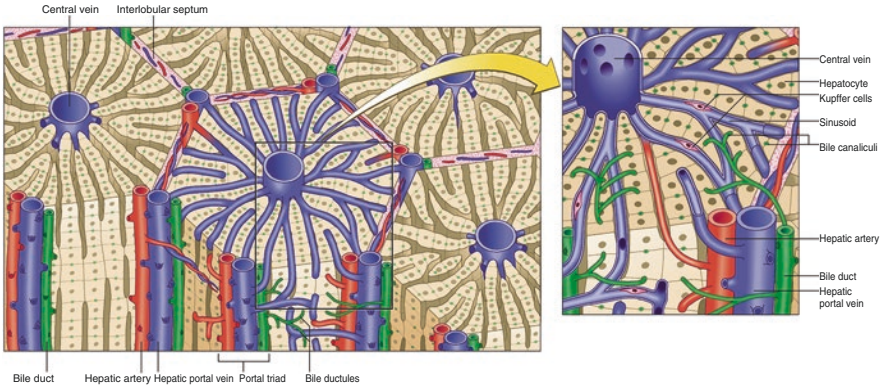

Fig. 1.11 Microarchitecture of the liver [*Source*: Standring, S., Gray's Anatomy: the anatomical basis of clinical practice. 41st ed. 2016]

lobule, ultimately draining into the IVC. As the hepatocytes carry out their metabolic functions, they secrete bile into canaliculi that terminate at the bile duct tributaries found within the portal triads. Bile duct tributaries from adjacent lobules merge to form bile ductules of progressively larger caliber, which eventually lead to the segmental bile ducts, each draining one of the eight liver segments (Fig. 1.10).

1.2.2.1 Intrahepatic Bile Duct Anatomy

The left liver (segments II, III, and IV) drains its bile into the left hepatic duct, and the right liver (segments V, VI, VII, and VIII) drains into the right hepatic duct (Fig. 1.10). Bile ducts generally course above the corresponding portal venous branches. Segmental branches join to form sectoral ducts, which derive their names from their location within the liver parenchyma (Fig. 1.10b). Thus, the bile ducts of segments II and III merge to form the left lateral sectoral duct, which is subsequently joined by the duct of segment IV to form the left hepatic duct. Similarly, the ducts of segments VI and VII form the right posterior (or lateral) sectoral duct, and the ducts of segments V and VIII form the right anterior (medial) sectoral duct. The right posterior sectoral duct runs a horizontal course and turns inferiorly to join the vertically coursing right anterior sectoral branch to form the right hepatic duct. The smaller caudate lobe (segment I) has a more variable biliary drainage such that in 78% of cases, it drains into both the right and left hepatic ducts, while in 15% and 7% of cases, it drains exclusively into the left or right hepatic duct system, respectively (Fig. 1.10b).

The biliary anatomy is subject to significant variation (Fig. 1.12) [9–11] and more so in women [12]. Up to 15% of individuals lack a defined right hepatic duct and instead have a "trifurcation pattern" where the common hepatic duct (CHD) is formed by the union of the right posterior and right anterior sectoral ducts with the left hepatic duct (Fig. 1.12). An equally common variant involves a right sectoral duct (more often the anterior) with a low insertion directly into the CHD. Less frequently a right sectoral duct (usually the posterior) may drain into the left hepatic duct. Variations involving ectopic drainage of individual segmental ducts may also occur [13]. Notably, a subvesical duct has been reported in 20–50% of cases, joining either the CHD or the right hepatic duct. It does not drain any specific liver territory and never communicates with the gallbladder, unlike the true ducts of Luschka [14], and is at risk of injury and postoperative biliary leak during cholecystectomy if dissection is not performed correctly and there is breach of the cystic plate. Anatomic variations of the left-sided ductal system are less common and usually involve either variations of the site of drainage of segment IV duct (most commonly joining the duct of segment III) or multiple segmental branches emerging from segment IV.

1.2.2.2 Extrahepatic Bile Duct Anatomy

The extrahepatic biliary tree can be divided into the extrahepatic bile ducts and the accessory biliary apparatus (Fig. 1.10b). The former comprises the extrahepatic segments of the right and left hepatic ducts, joining to form a single main bile duct that drains into the duodenum. The right hepatic duct is nearly vertical with a short extrahepatic course (0.5–2.0). The extrahepatic portion of the left hepatic duct runs a more horizontal course, posterior to the inferior border of the quadrate lobe (segment IV), and is longer (1.5–3.5 cm in adults). It is worth noting that ligation or stricture of an extrahepatic duct results in dilation of the duct and atrophy of the corresponding hepatic lobe with a high probability of subsequent cholangitis and even abscess formation. Therefore, any bile duct injury should be repaired when recognized and whenever it is feasible.

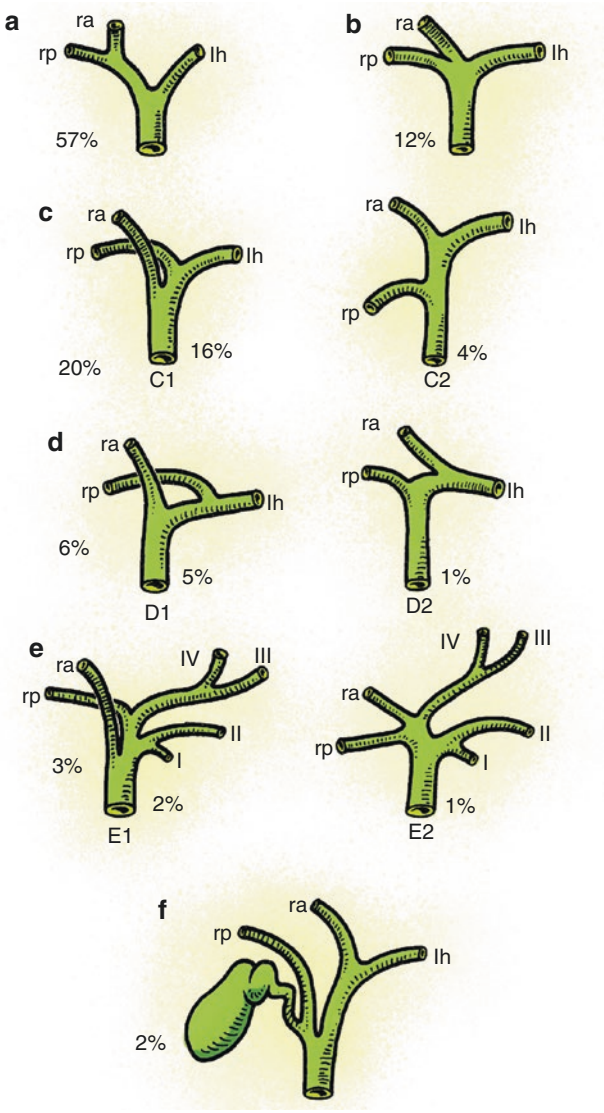

Fig. 1.12 Anatomic variations of the bile ducts. Main variations of the hepatic duct confluence [9]. (**a**) Typical anatomy of the confluence. (**b**) Triple confluence. (**c**) Ectopic drainage of a right sectoral duct into the common hepatic duct (c1, right anterior [ra] duct draining into the common hepatic duct; c2, right posterior [rp] duct draining into the common hepatic duct). (**d**) Ectopic drainage of a right sectoral duct into the left hepatic ductal system (d1, right posterior sectoral duct draining into the left hepatic [lh] ductal system; d2, right anterior sectoral duct draining into the left hepatic ductal system). (**e**) Absence of the hepatic duct confluence. (**f**) Absence of right hepatic duct and ectopic drainage of the right posterior duct into the cystic duct

The right and left hepatic ducts unite anterior to the portal venous bifurcation and the origin of the right branch of the portal vein (Fig. 1.10b). This confluence is situated to the right of the hepatic hilar fissure, immediately posterior to the quadrate lobe of the liver. The hepatic plate/sheath system is a fusion of the Glisson capsule and the connective tissue enclosing the biliary and vascular elements (Fig. 1.13). It consists of flat fibrous planes on the undersurface of the liver termed "plates" and tubular extensions termed "sheaths" that radiate into the liver parenchyma to transmit the portal bilo-vascular structures. Familiarity with the anatomy of the plate system is very important as it facilitates safe dissection of perihepatic structures due to its

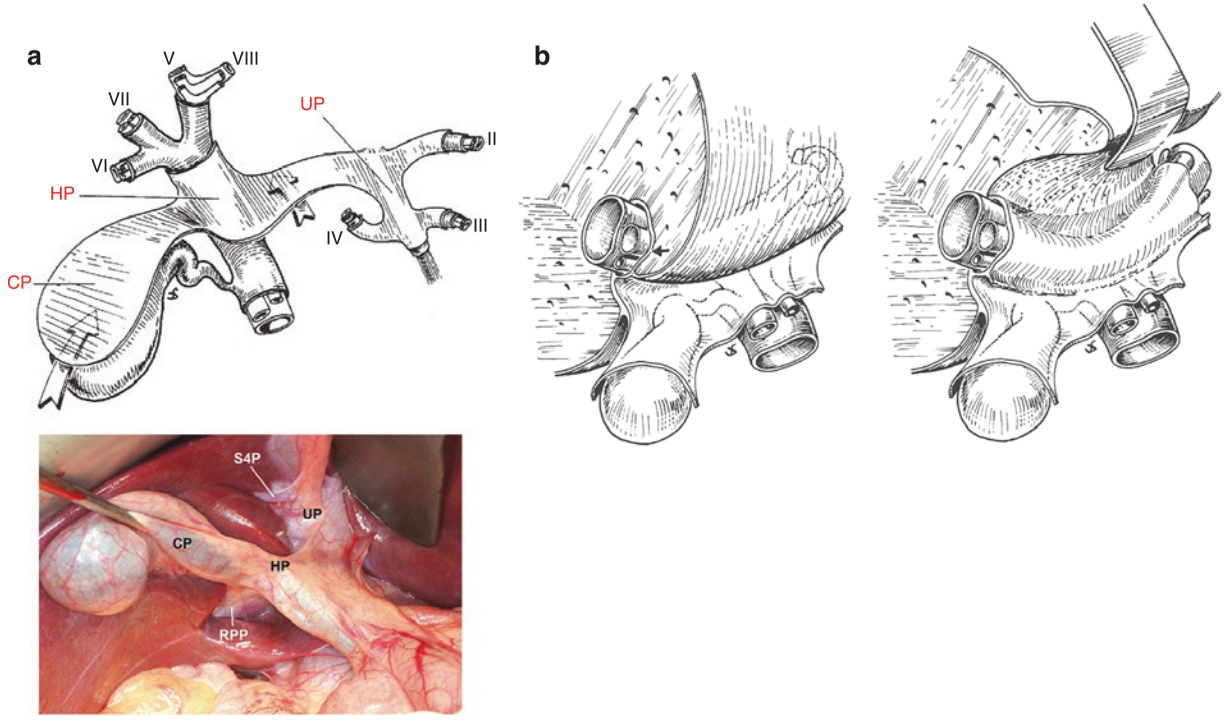

Fig. 1.13 The hepatic plate/sheath system. (**a**) Schematic representation (top) and in situ appearance (bottom) of the plate/sheath system, showing the cystic plate (CP) covered by the gallbladder, the hilar plate (HP), and the umbilical plate (UP). The large, curving arrows indicate the plane of dissection of the cystic plate during cholecystectomy and of the hilar plate during approaches to the left hepatic duct. S4P, segment 4 pedicle; RPP, right posterior pedicle. (**b**) The biliary confluence and left hepatic duct can be exposed by lifting the quadrate lobe upward after incision of the Glisson capsule at its base. This technique, "lowering of the hilar plate" [15], is generally used to display a dilated bile duct above an iatrogenic stricture or hilar cholangiocarcinoma [*Sources*: Photograph from Fischer, J.E., et al., Fischer's Mastery of Surgery. 6th ed. 2012, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; schematics from Jarnagin, W.R., et al., Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th ed. 2012, Philadelphia, PA: Saunders]

avascular nature. Thus, the hilar plate can be divided at the inferior border of the quadrate lobe and the latter elevated to facilitate access to the biliary confluence and left hepatic duct—a maneuver termed "lowering of the hilar plate" (Fig. 1.13) [15].

The main bile duct is divided into two portions by the entry of the cystic duct (CD) (Fig. 1.10b). The upper portion, the CHD, is approximately 2–3 cm long and has an average diameter less than 6 mm in adults. It descends in the free edge of the lesser omentum, situated anterior to the portal vein and to the left of the hepatic artery proper. The lower portion is the common bile duct (CBD). The CBD has a luminal diameter of less than 8 mm (based on radiological measurements) that may increase in people older than 60 years (Table 1.2). It is 6–8 cm long and can be subdivided into three parts according to its relations to the duodenum and pancreas (Fig. 1.10b). The supraduodenal part (3–4 cm long) descends posteroinferiorly anterior to the IVC, situated within the hepatoduodenal ligament anterolaterally to the PV and to the right of the hepatic artery (Fig. 1.5a). The retroduodenal part crosses behind the first part of the duodenum to the right of the GDA. The retropancreatic part runs through the parenchyma of the head of the pancreas (or occasionally behind it), anterior to the right renal vein and posterior to the SPDA. Its caudal end enters into the wall of the second portion of the duodenum together with the main pancreatic duct of Wirsung in a Y configuration. The two ducts unite within the duodenal wall forming a common channel, 2–10 mm long, that is focally dilated, and hence it is called the hepatopancreatic ampulla of Vater (Figs. 1.6 and 1.14).

1.2.2.3 Gallbladder and Cystic Duct

The accessory biliary apparatus is comprised of the gallbladder and CD (Fig. 1.14) and functions as a reservoir for bile during periods of fasting as well as a modifier of bile composition, mainly by concentrating it. The gallbladder is classically described as flask-shaped. It varies in size and its volume can reach up to 50 mL. It consists of a fundus, a body, and a neck. The neck lies close to the porta hepatis. It transitions into the body at an angle, forming the infundibulum (or Hartmann's pouch) which is more prominent in the presence of gallstone disease. The neck and body lie anterior to the second part of the duodenum (Fig. 1.14). The fundus is located more anterolaterally and may project beyond the liver edge in close proximity to the anterior abdominal wall at the level of the ninth costal cartilage. If elongated, the fundus may be highly mobile, and in rare occasions, it can result in folding back on the body. This variant termed "Phrygian cap" can be identified radiologically, is probably embryological in origin, and may be misinterpreted as a septum in an otherwise normal gallbladder or at times be confused for a malignancy.

Table 1.2 Size of common pancreatobiliary structures

Structure	Diameter (luminal)
Cystic duct	1–3 mm
Common hepatic duct	≤6 mm
Common bile duct	≤8 mm
Main pancreatic duct	≤3 mm

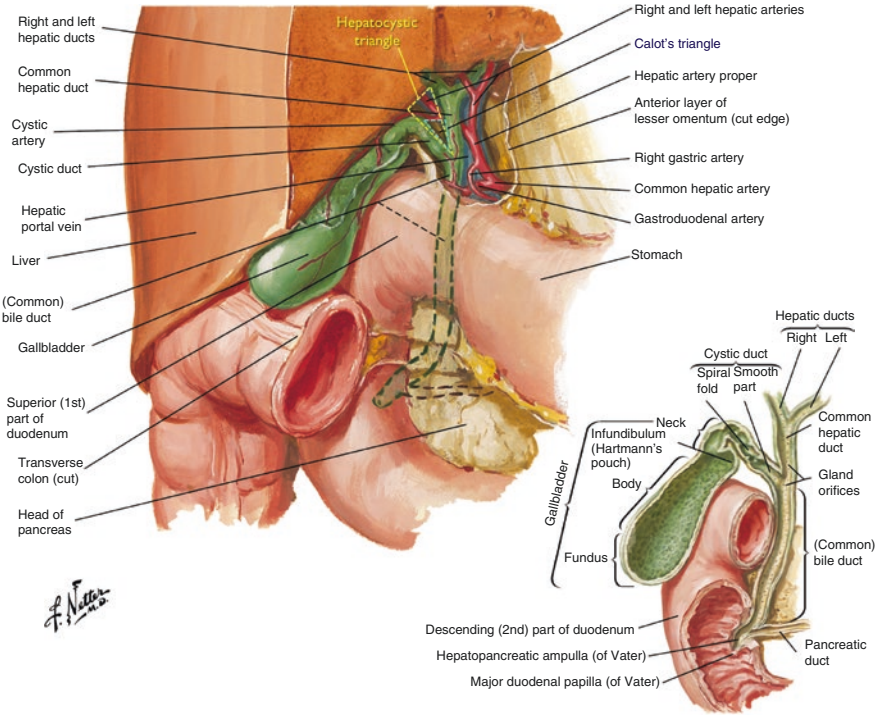

Fig. 1.14 Anatomy of the gallbladder and cystic duct. Note the *hepatocystic triangle*, limited by the common hepatic duct, right hepatic duct, cystic duct, and inferior liver edge. The *triangle of Calot* is limited by the common hepatic duct, the cystic duct, and the cystic artery [*Source*: Netter, F.H., Atlas of human anatomy. 6th ed. 2014: Saunders]

Various rare anomalies of the gallbladder anatomy have been described [11], including the absence of cystic duct, gallbladder agenesis, and dual gallbladder.

The gallbladder is situated within the cystic fossa on the undersurface of the liver and serves as the external sign of the division between the right and left liver (Cantlie's line) (Fig. 1.14). Its surface is covered by peritoneum except at the cystic fossa, where it is intimately associated with the liver. The neck almost always has a short peritoneal attachment to the liver (mesentery) that usually contains the cystic artery. Occasionally, the gallbladder may be completely surrounded by peritoneum and be suspended from the liver in its own mesentery, rendering the gallbladder susceptible to torsion. On the other hand, less frequently it might be situated deep into the hepatic parenchyma or even be completely buried within the liver (intrahepatic gallbladder). The latter case may be misinterpreted as gallbladder agenesis. Even more uncommon is the scenario where the gallbladder lies to the left of the round ligament.

The connective tissue between the gallbladder and the liver comprises the cystic plate (Fig. 1.13a). It is ovoid anteriorly and narrows posteriorly to join the sheath of the right portal pedicle and the hepatic plate. During cholecystectomy, the

dissection of the gallbladder off the liver proceeds along the avascular plane between the cystic plate and the gallbladder, which is filled with areolar tissue. Caution should be exercised in cases of chronic inflammation, in which case the cystic plate might be scarred and contracted, with obliteration of this avascular plane. This brings the bilio-vascular structures of the right pedicle in close proximity to the gallbladder and vulnerable to injury if dissection of the gallbladder enters the liver. In such cases, dissection of the gallbladder can be performed in a "top-down" or retrograde fashion to minimize the risk of injury to the right pedicle structures. And on some occasions, it is safer to leave the posterior gallbladder attached to the liver, removing the anterior gallbladder wall and obliterating the remaining gallbladder mucosa by cautery, as a subtotal cholecystectomy. Rarely, the cystic plate can be penetrated by submillimeter accessory bile ducts that drain directly into the gallbladder. These are termed "ducts of Luschka" and are important because if severed during cholecystectomy they can result in clinically significant bile leaks after the operation. Further, a subvesical duct from the right hemiliver may be deeply embedded in the cystic plate on its way to joining the right hepatic duct or the CHD, and it is at risk of injury if the cystic plate is not recognized and preserved at the time of cholecystectomy.

The CD arises from the neck of the gallbladder and descends in a posteromedial direction to join the CHD, marking the beginning of the CBD. It is lined by mucosa that has multiple crescentic intraluminal projections arranged in a spiral configuration, which are termed the "valves of Heister" (Fig. 1.14). The CD has a luminal diameter of 1–3 mm and is usually 2–4 cm long. Its length varies depending on the type of union with the extrahepatic bile duct system. In 75–80% of cases, the CD enters the main bile duct in a supraduodenal location; however this union may occur more caudally at the retroduodenal or even retropancreatic part of the CBD. Conversely, the CD may occasionally join the right hepatic duct or even a right hepatic sectoral duct. The orientation and mode of union may also vary. Most commonly, the CD joins the CHD from the right side in an angular fashion. However, the CD may merge in a parallel or even spiral fashion, at the anterior, posterior, or medial aspect of the main bile duct. This variation in the cystic duct increases the risk of misidentification and injury of the CBD during cholecystectomy.

1.2.2.4 Regional Blood Supply and Lymphatic Drainage

The main regional arteries supplying the hepatobiliary structures (celiac trunk, hepatic artery, SMA) and their variations have been described above. The right and left hepatic arteries branch off the hepatic artery proper and enter the liver enclosed in sheaths of connective tissue that are part of the plate/sheath system, forming the right and left portal triads. They bifurcate into smaller branches along with the portal vein and bile duct branches to form pedicles corresponding to individual segments. The right hepatic artery (RH) usually passes behind the CHD and enters the hepatocystic triangle of Calot (Fig. 1.14). However, in some cases it courses anterior to the bile duct, which is important in surgical exposure of the latter. The hepatocystic triangle is defined as the triangular space bordered by the common hepatic duct,

the cystic duct, and the inferior surface of the right lobe of the liver (Fig. 1.14). It is of critical importance during cholecystectomy, as it has to be dissected in order to confidently identify the cystic artery during cholecystectomy. The term "hepatocystic triangle" is nowadays used interchangeably with "Calot's triangle," although the original definition of the latter included the cystic artery instead of the inferior surface of the liver as the superior border. Notably, if there is a replaced or accessory common or right hepatic artery, it usually runs behind the cystic duct to enter the triangle of Calot.

The cystic artery usually arises from the RH artery and may cross the common hepatic duct anteriorly or posteriorly. It divides into anterior and posterior branches upon contact with the gallbladder. This division, however, may occur before the artery reaches the gallbladder wall, in which case one of the two branches may be unrecognized and divided without proper ligation during cholecystectomy, leading to hemorrhage. Multiple variations of the anatomy of the cystic artery exist; hence the surgeon should be vigilant and prepared to recognize them in order to avoid inadvertent hemorrhage or injury to biliary structures in an attempt to control the bleeding. The venous drainage of the gallbladder occurs via multiple small cystic veins that traverse the cystic plate to join segmental portal veins. Rarely, distinct cystic veins run parallel to the cystic artery to empty into the main portal vein.

The blood supply of the extrahepatic bile duct can be considered in relation to its three parts: hilar, supraduodenal, and retropancreatic. The supraduodenal duct is supplied by branches of the GDA, the superior pancreaticoduodenal artery, the retroduodenal artery, the RH, and the cystic artery (Fig. 1.15). These branches run in

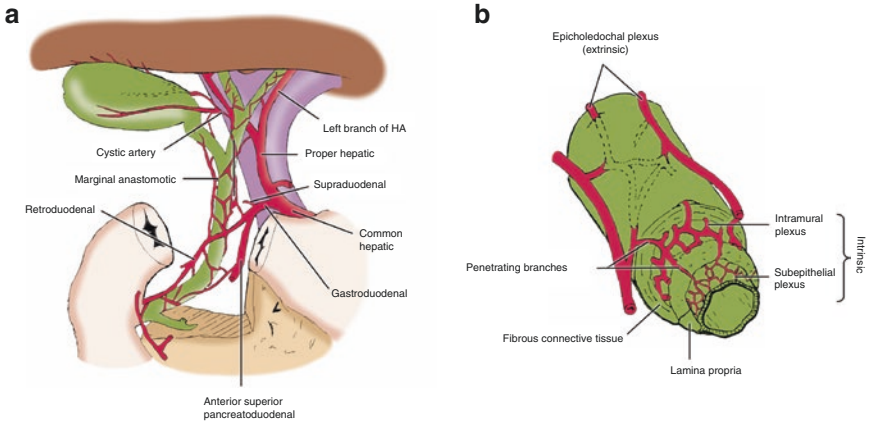

Fig. 1.15 (**a**, **b**) Arterial blood supply to the extrahepatic bile ducts showing the epicholedochal arterial plexus. *HA* hepatic artery [*Source*: Skandalakis, J. E. and G. L. Colborn, Skandalakis' Surgical anatomy: the embryologic and anatomic basis of modern surgery. 2004, Athens, Greece: Paschalidis Medical Publications, Ltd.; McGraw-Hill (distributor)]

an axial fashion at the 3 and 9 o'clock positions of the duct (Fig. 1.15a). They form a rich anastomotic network on the surface as well as within the wall of the duct (Fig. 1.15b). The hilar ducts receive ample blood supply from the neighboring arteries, in continuity with the epicholedochal plexus of the supraduodenal part (Fig. 1.15a). The retropancreatic part of the duct is mainly supplied by branches of the retroduodenal artery that run around the duct to contribute to its arterial plexus (Fig. 1.15a). The veins of the extrahepatic bile ducts follow the same course as the corresponding arteries coursing mainly at the 3 and 9 o'clock positions. They communicate with the venous outflow of the gallbladder and drain into the portal venous system indirectly, via the liver.

The lymphatic drainage of the gallbladder is mainly to the hepatoduodenal ligament lymph nodes (Fig. 1.16). This can occur via the cystic node, which lies in the hepatocystic triangle, via lymphatics that descend along the CBD, or via lymphatics of the hepatic aspect of the gallbladder that drain into intrahepatic lymph vessels first. Subsequently the lymph can drain into multiple peripancreatic nodal stations, ultimately reaching the celiac, superior mesenteric, and preaortic lymph nodes.

1.2.2.5 Innervation

The extrahepatic biliary tree and gallbladder are innervated by branches of the hepatic plexus. The hepatic plexus is an integrated network composed of sympathetic fibers from the celiac and superior mesenteric plexus, and parasympathetic fibers derived mainly from the anterior branch of the vagus. The latter provide motor stimulation to the bile ducts and gallbladder and inhibit the sphincter of Oddi. Sympathetic afferent fibers are the primary source of pain sensation, via the greater and lesser splanchnic nerves.

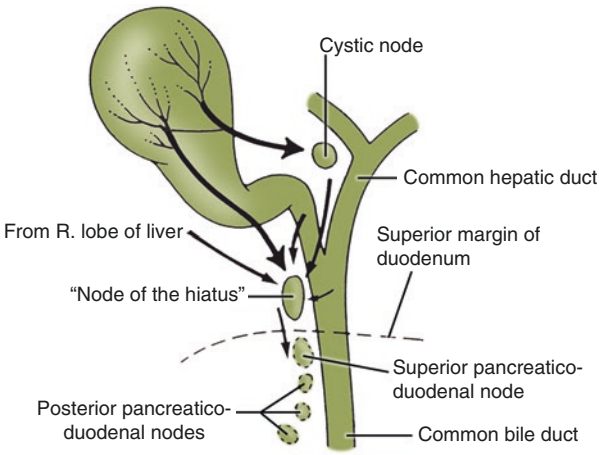

Fig. 1.16 Lymphatic drainage of gallbladder and biliary tract [*Source*: Skandalakis, J. E. and G. L. Colborn, Skandalakis' Surgical anatomy: the embryologic and anatomic basis of modern surgery. 2004, Athens, Greece: Paschalidis Medical Publications, Ltd.; McGraw-Hill (distributor)]

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Physiology of the Biliary Tree

2

Richard Hu, Robin Hu, and Stephen J. Pandol

2.1 Macro- and Microanatomy of the Biliary Tree

The bile duct system is comprised of an intrahepatic and extrahepatic portion. The intrahepatic system originates from the bile canaliculi radiating outward from of the hepatic acinus to the portal area. The bile ducts in the portal triads represent the major portion of the intrahepatic biliary system. The intrahepatic bile ducts drain into the left and right hepatic ducts. The human intrahepatic biliary ductal system is classified by size: hepatic ducts (>800 μm in diameter), segmental ducts (400–800 μm), area ducts (300–400 μm), septal bile ducts (100 μm), interlobular ducts (15–100 μm), and bile ductules (<15 μm) [1–3]. Three-dimensional reconstruction of the human biliary system has estimated the mean volume of the entire macroscopic duct system of human liver to be about 20.4 cm^3 and surface area of 398 cm^2. The internal surface of biliary ductal system is magnified more than fivefold by the microvilli located at the apical surface of the ductal epithelial cells. The system carries hepatocyte secretions and secretions from the bile duct cells (aka cholangiocytes) lining the system [4, 5]. The functional properties of bile duct cells are varied, and this is supported by the finding that larger but not small intrahepatic bile ducts are involved in secretin-regulated bile duct secretion and chloride-bicarbonate exchange [5]. Bile duct epithelial cells, also called cholangiocytes, have been morphologically and functionally categorized into small and large cholangiocytes, respectively, the cell volume of which correlates roughly with the diameter of the intrahepatic bile ducts. With

R. Hu (✉)
Division of Digestive Diseases, Olive View-UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
e-mail: RichardHu@mednet.ucla.edu

R. Hu · S. J. Pandol
Department of Biological Science and Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA
e-mail: Stephen.Pandol@cshs.org; stephen.pandol@med.va.gov

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regard to cellular structure, the small cholangiocytes are cuboidal, but the larger cholangiocytes in larger bile ducts are more columnar in shape. Moreover, small cholangiocytes are poorly specialized and have a high nucleus/cytoplasm ratio, whereas large cholangiocytes are supplied with plenty of organelles and a small nucleus/cytoplasm ratio. The large, but not the small, cholangiocytes have cilia, which act as chemo- and mechanosensors within the bile duct lumen [6].

Bile secretion starts at the level of the bile canaliculus which is bordered by the apical surfaces of the hepatocytes forming a hepatic acinus. The canaliculus carries secretions from the hepatocytes into the bile ductules [7]. The fluid of the bile canaliculus passes through small terminal channels of the canaliculus called the Canals of Hering, which have a histological component of basement membrane lined in part by hepatocytes and in part by cholangiocytes [8]. The Canals of Hering represent the transition from the bile canaliculi to the larger intrahepatic (perilobular or intralobular) ducts [8, 9]. The perisinusoidal space (or *space of Disse*) named after German anatomist Joseph Disse is located in the liver between a hepatocyte and a sinusoid. It carries the blood plasma allowing proteins and other plasma components from the sinusoids to be absorbed by the hepatocytes. Fenestrations and discontinuity of the vascular endothelium allow for ease of entry of blood plasma components into the space of Disse. This space may be altered or obliterated in acute and chronic liver diseases, leading to decreased uptake of nutrients and metabolites by hepatocytes. The perisinusoidal space also contains fat and fat-soluble vitamins storage cells named hepatic stellate cells (aka cells of Ito). A variety of cytokines and chemokines associated with inflammation can cause stellate cell transformation into myofibroblasts that mediates collagen production and fibrosis or cirrhosis [10]. Kupffer cells in the liver (aka stellate macrophages) are specialized macrophages lining the walls of the sinusoids and comprise part of the mononuclear phagocyte system of the liver [11] (Fig. 2.1).

The direction of bile flow is opposite to that of blood flow into the liver parenchyma, entering from the portal vein and hepatic arteriole in the portal area and flowing in the hepatic sinusoid toward the central vein which takes blood out of the liver and returns it to the central circulation (Fig. 2.1). Thus, blood enters from the portal area, and biliary secretions travel to the same portal area.

Interlobular bile ducts in the portal areas run with the portal vein and hepatic artery branches, and the flow in the bile ducts is in the opposite direction to the flow in these vessels [12, 13]. Interlobular bile ducts start at a diameter >30 μm and are lined by the cuboidal or columnar epithelium with microvilli on the luminal surface of the ductular cells [7]. The ductules increase in caliber and are gradually associated with smooth muscle cells. Eventually, the interlobular ducts emerge from the large intrahepatic ducts which are 1.0–1.5 mm and form the main hepatic ducts.

The confluence of the left and right hepatic duct takes place mostly outside the liver to form the common hepatic duct. The common hepatic duct extends from the confluence to the cystic duct insertion, which is highly variable. The common bile duct (CBD), distal to the insertion of the cystic duct, is approximately 7 cm long and in adults is normally between 0.4 and 0.8 cm in diameter [9]. The CBD runs in the free right margin of the lesser omentum within the porta hepatis alongside the

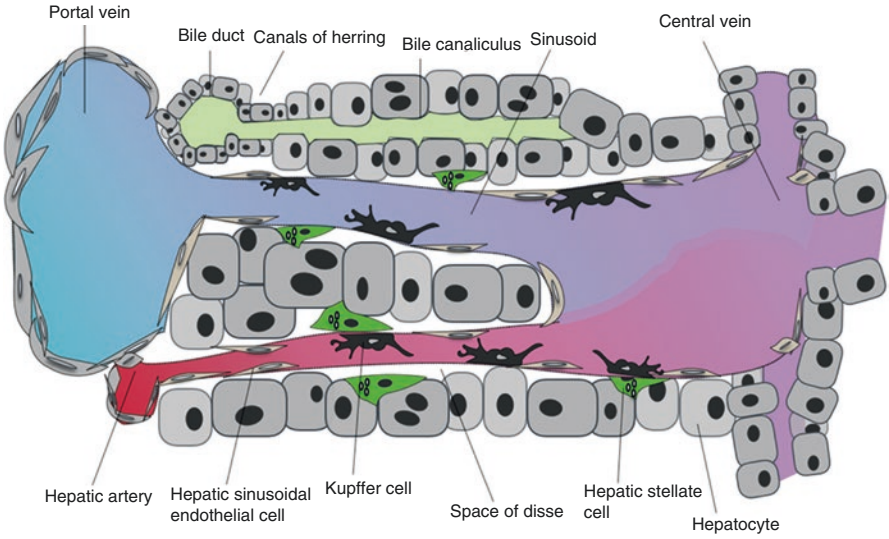

Fig. 2.1 Schematic representative of the bile duct structure and anatomic progression

hepatic artery and the portal vein [14]. In its distal portion, the CBD passes behind the first part of the duodenum and usually has an intrapancreatic course before tapering down and terminating at the ampulla of Vater situated in the medial wall of the second part of the duodenum [15]. Bile passively enters the gallbladder because of the pressure within the CBD generated by production of bile and the closure of the sphincter complex distally and is facilitated by the patent spiral valves of Heister in the cystic duct.

Passing through the duodenal wall, the bile and pancreatic ducts are invested by a thickening of both the longitudinal and circular layers of smooth muscles which constitute the sphincter of Oddi complex [13, 15, 16] which comprises several and variable components: (1) the sphincter of choledochus, (2) a pancreatic sphincter, (3) the fasciculi longitudinals, and (4) the sphincter of the ampulla of Vater.

The arterial blood supply to the bile ducts is from the right hepatic artery via the choledochal vessels that run along the wall of the CBD [9, 17]. Injury to the right hepatic artery can result in an ischemic biliary stricture.

2.2 Biliary Malformations

An *accessory bile duct* is an aberrant duct that drains individual segments of the liver directly into the gallbladder, cystic duct, left or right hepatic duct, or common hepatic duct [14, 18]. Complete duplication of the common bile duct is a rare condition with separate ducts draining the left and right lobes of the liver and each drain directly into the duodenum [14, 18]. Variations in the drainage and course of the cystic duct

are common [14]. Cystic duct absence associated with agenesis of the gallbladder can occur. Also, rarely the gallbladder empties directly into the common bile duct.

Choledochal cysts often present in childhood with right upper quadrant abdominal pain and jaundice, but they may be an incidental finding with imaging procedures. While choledochal cysts occur infrequently in Western population (1 in 100,000–150,000 individuals), they are more often seen in Asian countries (1 in 13,000 individuals) [19]. Choledochal cysts are classified into five types [20–22] (Fig. 2.2). Type I is the most commonly encountered in both adults and children (60–80%) in which there is cystic or fusiform dilation of the entire extrahepatic duct. Type II cysts (1–2%) are supraduodenal diverticula. Type III cysts (0.5–4%) are intraduodenal, often called choledochocele, and malignancy in Type III cysts is rare and lacks the female preponderance characteristic of other choledochal cysts. Type IV cysts are multiple extrahepatic or both intra-/extrahepatic dilation (15–30%); Type V cysts, also called Caroli's disease, involve only the intrahepatic duct. There is a risk of cholangiocarcinoma with choledochal cysts. Most recent studies reveal that 91% of choledochal cyst-associated malignancies occur in Type I and

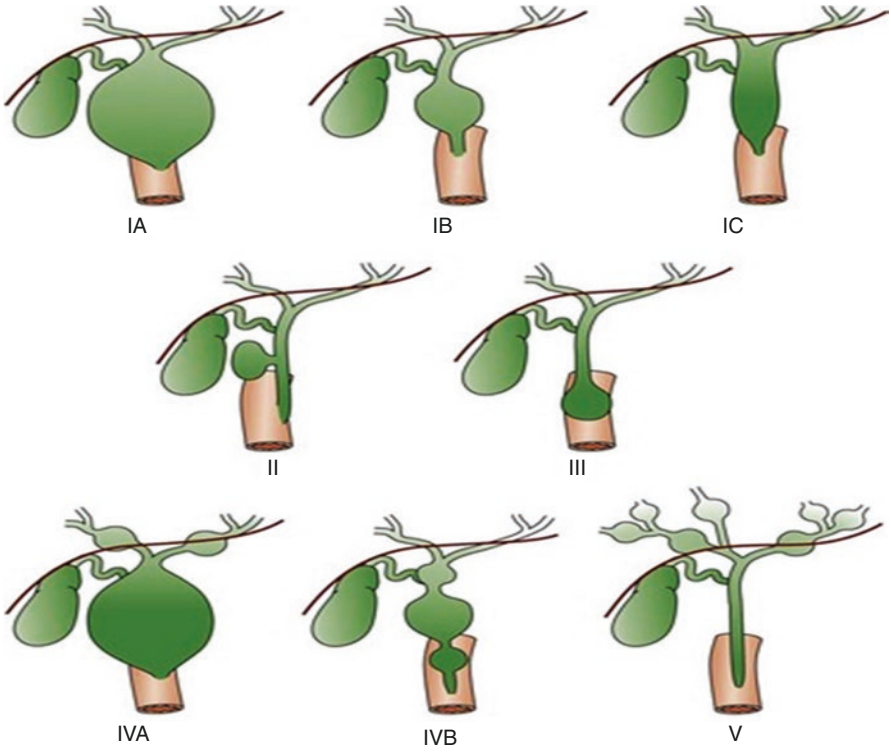

Fig. 2.2 Choledochal cyst classification. Type I cysts are either cystic (IA or IB) or fusiform (IC) dilation of the extrahepatic duct; Type II cysts are supraduodenal diverticulum; Type III cysts (choledochocele) are intraduodenal; Type IV cysts exist as multiple extrahepatic (IVB) or both intrahepatic and extrahepatic (IVA) dilation; Type V cysts involve only the intrahepatic ducts

Type IV cysts and are rare in Types II, III, and IV. Therefore, Type I and Type IV cysts should be surgically resected when identified [23, 24]. Although Type V cyst has much lower malignancy potential in comparison to Type I and Type IV, surgical treatments including lobectomy and liver transplantation based on the location of involvement are often necessary given its considerable potential for cholangitis and liver complications including biliary cirrhosis. A recent multicenter study to follow up the long-term results of surgical treatment for Type V cysts revealed that patients who underwent either hepatic resection (75%) or liver transplantation (19%) had excellent or good results achieved in 86%. Five-year overall survival was 97% after liver resection and 89% after liver transplantation [25]. (*Choledochal cysts will be dealt with in detail in Chapter 5*).

2.3 Bile Secretion and Enterohepatic Circulation

Bile production is initiated by hepatocytes which secrete their products into the canaliculus which is formed by the apical surfaces of hepatocytes forming an acinus. The secretion of bile salts (also called bile acids) across the canaliculus is the primary driving force of bile secretion. This is referred to as "bile salt-dependent flow (BSDF)" which comprises about one third of the bile flow. Another one third of bile flow is independent of bile salt secretion, which is referred to as "bile salt-independent flow (BSIF)," and the last third of bile flow comes from the bile duct epithelium. It is estimated that the daily bile production in an adult is about 750–1500 mL [26].

The principal components of bile are bile acids, phospholipid, cholesterol, bilirubin, and protein. The primary bile salts in humans are cholic acid (CA) and chenodeoxycholic acid, which account for 60% and 25% of total bile salts, respectively [27, 28] (Fig. 2.3). Bile acids are synthesized by the liver from cholesterol in pericentral hepatocytes of the hepatic acini. In humans, the newly synthesized bile acids are cholic acid (CA) (60% of the total bile salts) and chenodeoxycholic acid (CDCA) (25%). Hepatic bile acid synthesis is believed to involve two major pathways which are described as the "classic neutral" and "alternative acidic" pathways. The classic pathway maintains CA biosynthesis, while the alternative pathway favors CDCA biosynthesis. The bile acid biosynthesis is a complex process, mediated by 17 different enzymes divided into two groups with functions of performing modifications to the sterol ring structure and modifying the sterol side chain, respectively [29]. The neutral pathway is believed to be quantitatively more important in humans [30]. The neutral pathway is quantitatively more important in adult humans as a mutation of CYP7A1, a key enzyme in this pathway, results in inhibition of 90% of bile acid synthesis [30, 31]. On the other hand, the acidic pathway is predominant in neonates as CYP7A1 is not expressed at early age [32, 33].

Both CA and CDCA are conjugated via their carboxyl group to the amino group of taurine and glycine in hepatocytes and then secreted into the bile canaliculus (Figs. 2.4 and 2.5). Conjugation enhances hydrophilicity of the bile acid. The conjugation to glycine or taurine decreases the passive diffusion of bile acids across cell membranes during their transit through the biliary tree and small intestine.

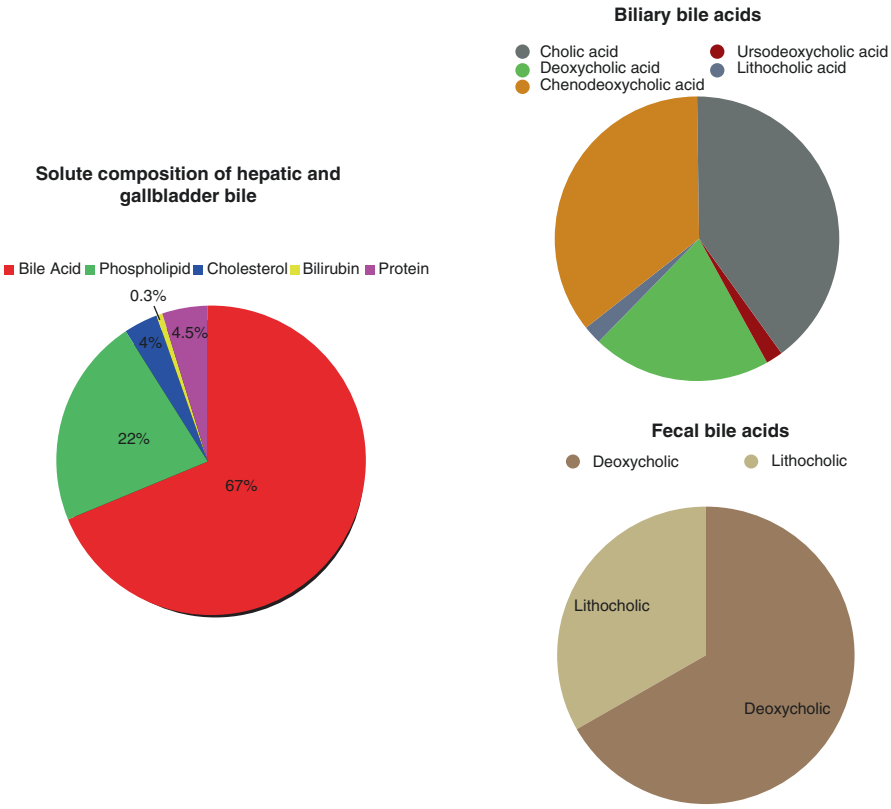

Fig. 2.3 Solute composition of bile

The ultimate effect of conjugation is to maintain a high intraluminal concentrations of bile acids to facilitate fat digestion and absorption. The significance of bile acid conjugation process is evidenced by the finding that failed bile acid conjugation due to inherited defects contributes to fat-soluble vitamin malabsorption and steatorrhea [34, 35]. The conjugated bile acids are taken up by specific transporters in the ileum [36] and are then carried back to the liver by way of the portal vein where they are recycled. This pathway is known as the "enterohepatic circulation" (Fig. 2.6). In adult humans, a bile acid pool was estimated to be 50–60 umol/kg body weight, corresponding to 2–4 g, and it is maintained through the enterohepatic circulation. Although a small amount of bile acid is lost in the feces, the enterohepatic circulation conserves over 90% of the total bile salt pool.

Once secreted, bile flows through the canaliculus to the periphery of the hepatic acinus, enters the bile ductal system within the portal triad, and flows to the gallbladder where it is mainly stored between meals. During digestion, the bile acids secreted by the liver bypass the gallbladder and pass directly into the duodenum. During this phase of bile secretion, the bile acid concentration in the small intestine is less than 10 mmol/l. Between meals the sphincter of Oddi contracts and the

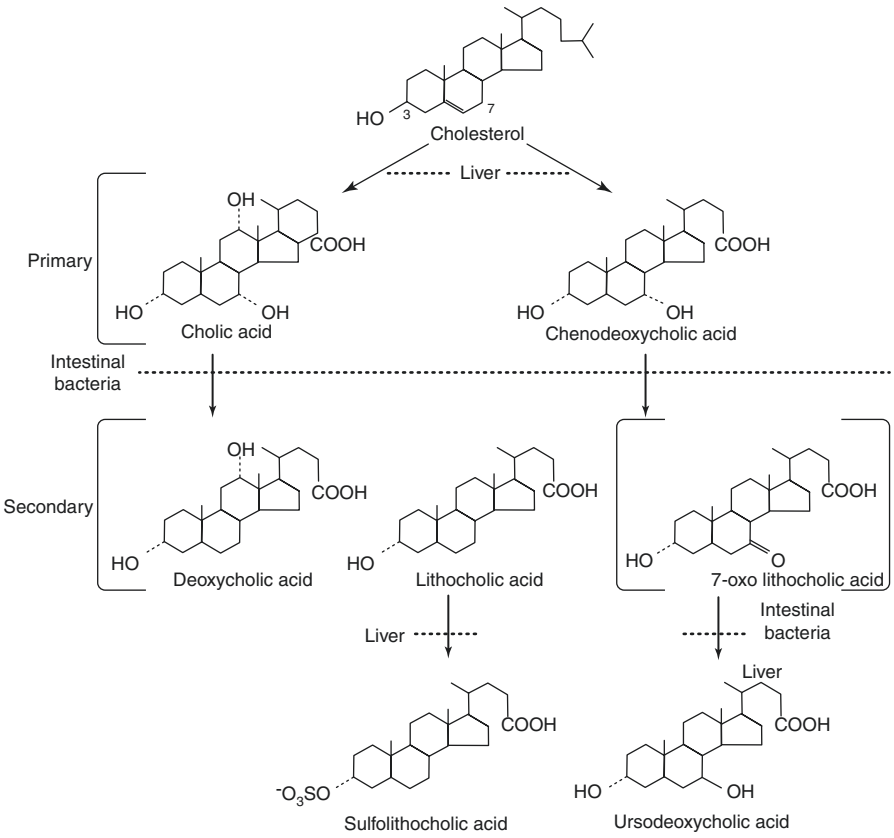

Fig. 2.4 Major primary and secondary bile acids and their sites of synthesis and metabolism. Intestinal flora converts the primary bile acids into secondary bile acids through the 7α-dehydroxylation and deconjugation, subsequently becoming tertiary bile acids after sulfation by the liver and kidney and hepatic reduction of the 7-oxo derivative of chenodeoxycholic acid by the liver

gallbladder relaxes, resulting in a larger fraction of the secreted bile acid to enter the gallbladder for storage. Therefore, the enterohepatic cycling of bile acids increases during digestion and decreases between meals and during fasting. This rhythm of bile acid secretion is maintained even after cholecystectomy.

Gallbladder emptying of bile is mediated by hormonal and neural pathways that cause contraction of the gallbladder and relaxation of the sphincter of Oddi at the same time. The main hormone is cholecystokinin (CCK) which is secreted by intestinal I cells located at the second portion of duodenum. These I cells respond to nutrients entering the duodenum. The end result is that bile is secreted into the lumen of the gut in response to the food that requires digestion and absorption. Bile salts are an important component of bile acting as detergents to solubilize lipids and participate with pancreatic lipases in the digestion and absorption of fat in the meal.

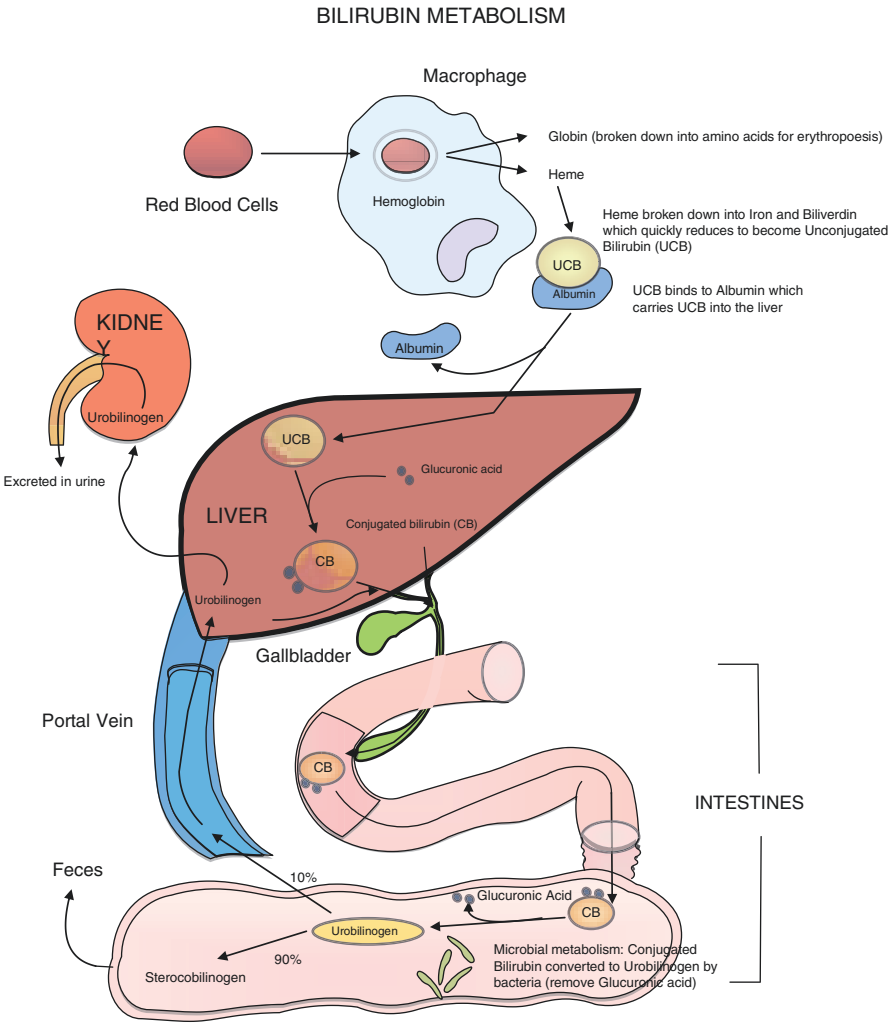

Fig. 2.5 Schematic representative of bilirubin metabolism

Bile salts form micelles, circular or cylindrical structures, which surround cholesterol and other lipids to greatly enhance their solubility. The bile salts also prevent the precipitation of cholesterol secreted into the biliary system by the liver so that formation of cholesterol gallstones within the bile ducts and the gallbladder is attenuated in addition to enhancing the lipid digestion and absorption. In the intestine, conjugated bile salts are absorbed predominantly by an active transport system restricted to the terminal ileum and to a lesser extent, by passive absorption down

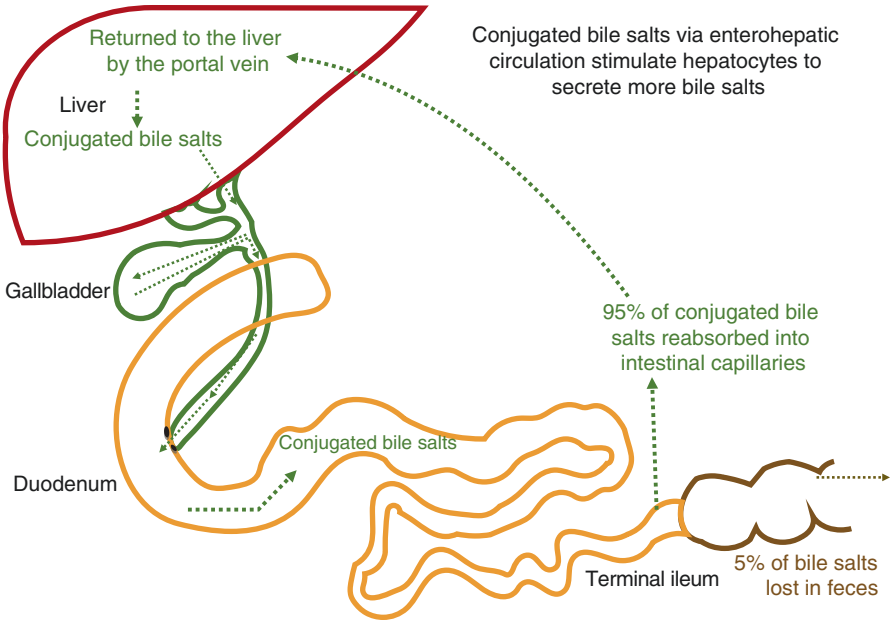

Fig. 2.6 Enterohepatic circulation. The anatomic components of the enterohepatic circulation of bile acids are the liver, biliary tract, small intestine, portal venous circulation, and, to a lesser extent, colon systemic circulation. Majority of bile acids are reabsorbed into systemic circulation through enterohepatic circulation

the length of the small intestine. The bile salt pool cycles 2–3 times each meal. Therefore, there are about 6–10 cycles per day, and the intestine reabsorbs most of the bile salt pool. Less than 1.0 g of bile salts escape the enterohepatic circulation and are eliminated in the feces daily. Hepatocytes convert cholesterol into bile salts, and this process balances fecal excretion, which is an important route for elimination of cholesterol from the body. Bile salts enhance the absorption of fat-soluble vitamins, divalent cations, and large fatty acids through a similar physicochemical mechanism.

Intestinal bacteria modify bile acids by converting the primary bile salts to the secondary bile acids, deoxycholic acid, and lithocholic acid, which make up approximately 15% of total bile salts, and they can de-conjugate conjugated bile acids. Unconjugated bile acids are reabsorbed passively, circulated back to the liver where they are re-conjugated, mixed with newly synthesized bile acids, and resecreted into the bile. This process of intestinal deconjugation and hepatic reconjugation is a normal part of bile acid metabolism.

An additional bacterial modification is epimerization of the C-7 hydroxy group of CDCA to form the 3α,7β-dihydroxy bile acid ursodeoxycholic acid (UDCA).

UDCA is conjugated in the liver, circulates within the pool of primary bile acids, and normally constitutes a very small portion of biliary bile acids (<5%). UDCA is used clinically as a therapeutic agent in cholestatic liver diseases to reduce pruritus. When UDCA is administered in a therapeutic dose, the proportion of UDCA in bile may rise up to 40% of the total.

Factors which impair the enterohepatic bile salt circulation lead to a decline in the size of the bile acid pool and an increase in the synthesis of more primary bile salts from cholesterol. This leads to a lowering of serum cholesterol. As an example, bile salt-binding resins are still utilized as second-line treatment for hypercholesterolemia in patients who cannot take statins or where statins are not fully effective. A reduction in bile salt reabsorption within the ileum also causes increased utilization of cholesterol produced in the liver along with a failure of bile acid reabsorption. Also, in this case the bile acids pass into the colon where they are de-conjugated by bacteria so that the resulting high concentrations of free bile salts can cause a secretory diarrhea in the colon.

2.4 Common Surgical Conditions that Alter Bile Salt Physiology

Given the importance of the ileum for bile salt absorption, conditions affecting this portion of the small bowel are most important and result in decreased absorption. The most common conditions are an ileal resection and ileal diseases [37–39], such as Crohn's disease, ileal bypass, and radiation enteritis. Diarrhea in such patients is termed Type I bile acid malabsorption. Type III bile acid malabsorption is also common and is associated with conditions such as cholecystectomy, peptic ulcer surgery, chronic pancreatitis, celiac sprue, cystic fibrosis, and medication-induced intestinal ulcerations, such as nonsteroidal anti-inflammatory drugs. Type II bile acid malabsorption is extremely rare and is caused by inherited mutations in the apical sodium-dependent bile acid transporter (ASBT) gene [40]. If the resection of the ileum is limited, the impact on liver bile acid metabolism is minimal as compensatory biosynthesis in the liver balances the increased bile acid loss from feces. With significant resections but less than 100 cm, hepatic bile acid synthesis rises more dramatically to compensate for the increased loss and results in increased bile salts entering the colon where they cannot be absorbed. In the colon the bile salts cause diarrhea. This condition can be treated with bile salt-binding agents such as cholestyramine. However, with larger loss of function of the ileum due to larger resection of the terminal ileum (e.g., >100 cm), there is less recirculation of bile salts back to the liver, and there is decreased bile salt stores that in turn can result in formation of cholesterol stones in the gallbladder and biliary tree. Severe depletion of bile salts that can occur with a combination of loss of ileal function and treatment with cholestyramine can lead to severe fat maldigestion and malabsorption. The bile acid pool becomes progressively depleted, and the fat malabsorption appears because of the lack of micelles and the significant loss of absorption surface. The increased dihydroxy bile acid and fatty acid flux through the colon cause water and electrolyte

secretion resulting in severe diarrhea. In this situation, fat can be supplied in the diet with medium-chain triglycerides (MCTs) that do not require bile acids for solubilization and absorption.

Bile salt malabsorption following pancreatic resection may be attributed to concurrent cholecystectomy or the binding of bile salts to maldigested protein, carbohydrates, and fiber. Precipitation of bile salts may occur due to the change in pH in the small bowel as a result of reduced bicarbonate secretion secondary to diminished pancreatic volume [41]. The presence of a blind loop of bowel within the reconstruction following pancreaticoduodenectomy (PD) predisposes the patient to bacterial overgrowth, which has been documented in 65% of patients with pancreatic exocrine insufficiency (PEI), with an increased incidence following resection compared to those with pancreatic disease alone [42]. In addition to contributing to gastrointestinal symptoms, this may precipitate further bile salt malabsorption.

Recent research from both humans and preclinical animal models suggests that changes in the concentrations of plasma bile acids might contribute to the metabolic changes after the weight reduction surgeries such as Roux-en-Y gastric bypass (RYGB), adjustable gastric band (AGB), and sleeve gastrectomy (SG) [43–46]. Almost all of the studies of RYGB indicate that serum bile acids remain elevated to up to 15 months [44, 45, 47–50]. The changes in serum bile acid concentration might contribute to the metabolic changes after surgery [51], and a systematic review concludes that the changes in circulating bile acids after surgery may play a major role through a combination of the activation of the farnesoid X receptor A (FXRA), the fibroblast growth factor 19 (FGF 19), and the G-protein-coupled bile acid receptor (TGR5). Bile acids can regulate glucose metabolism through the expression of TGR5 receptor in L cells, resulting in a release of glucagon-like peptide 1 (GLP-1) [52]. It is interesting to note that emerging evidence suggest alterations of gut microbiota after bariatric surgery are also linked to weight loss [53–56].

2.5 Bile Duct Function

The main function of the bile duct is to carry biliary secretions. To maintain this process, liver parenchymal cells must transport bile acids efficiently from the portal blood into bile using Na^+-dependent transport systems at the sinusoidal and canalicular plasma membrane [57]. Hepatocytes function differently during different phases of digestion as a function of their location. In the fasting state, bile acids are taken up predominantly by the periportal hepatocytes. In contrast during the fed state, more hepatocytes in the liver acinus participate in bile acid uptake. Bile acid synthesis takes place predominantly in perivenous hepatocytes. Therefore, periportal hepatocytes primarily absorb and secrete recirculating bile acids, while perivenous cells predominantly secrete newly synthesized bile acids. The transport of circulating bile acids through periportal hepatocytes drives the majority of bile flow [58].

Bile duct epithelial cells, the cholangiocytes, play an active role in the secretion and absorption of biliary constituents. Transporters involved with this process include a bile salt transporter as well as glucose transporters responsible for the uptake of bile

acids and glucose from the lumen. The cholangiocytes have secretin receptors, as well as aquaporin-1 water channels, involved in mediating ion and water secretion that help transport biliary constituents into the intestine during a meal. The secretin-mediated responses involve activation of the cystic fibrosis transmembrane regulator (CFTR). Thus, in cystic fibrosis, there is a decrease in bile flow leading to liver injury and fibrosis [59–65]. There are additional ion channels that can also mediate ion and water channels that can partially compensate for a lack of CFTR function.

In small duct cholangiocytes, on the other hand, Ca^{2+}-activated signaling pathways seem predominant. Indeed, the activation of purinergic receptors in small and large duct cholangiocytes induces Ca^{2+}-dependent Cl^- secretion via transmembrane member 16A (TMEM16A), providing an alternative route to the secretin-stimulated cAMP-dependent ductal fluid secretion [60, 61]. Functionally, large duct cAMP-dependent cholangiocytes are more susceptible to damage, whereas small duct cholangiocytes are more resistant to injury [62–65]. During damage of large duct cholangiocytes, small duct cholangiocytes replenish the biliary epithelium.

2.6 Gallbladder Physiology

The gallbladder is a pear-shaped organ lying on the inferior surface of the liver in a fossa between the right and quadrate lobes. The gallbladder is about 3 cm wide and 7 cm long with a capacity of 30–50 mL [16, 66]. The gallbladder is mainly a storage reservoir that allows bile acids to be delivered in a high-concentration, timely, and controlled manner to the duodenum to solubilize and promote digestion and absorption of dietary lipid [13]. The gallbladder also absorbs water and ions, and its absorption surface is increased by numerous folds [12]. The posterior aspects of the fundus and body are anatomically adjacent to the transverse colon and duodenum, respectively. This relationship is relevant in severe acute pancreatitis as gallstones erode through to form a fistula, and its content is drained [66]. The Hartmann's pouch of the gallbladder is formed due to the bulging of the inferior surface of the infundibulum that lies close to the neck of gallbladder. If gallstones get impacted in the Hartmann's pouch, which they are prone to do, they can cause obstruction of the cystic duct contributing to the development of acute cholecystitis [66]. Extreme inflammation associated with the Hartmann's pouch can lead to extrinsic compression of the adjacent common hepatic duct causing cholestasis (Mirizzi's syndrome Type I). If the stone erodes into the common bile duct through development of a cholecystocholedochal fistula, choledocholithiasis results with advanced biliary obstruction (Mirizzi's syndrome Type II).

The cystic duct measures approximately 4 cm long connecting the gallbladder neck to the common bile duct. The mucosal membrane of the gallbladder neck forms the spiral valves of Heister to keep it constantly open; thus, bile can pass upward into the gallbladder when the bile duct at its distal end is closed. Cystic duct is a common site of impaction of gallstones.

The gallbladder is supplied by the cystic artery, a branch of the right hepatic artery and an end artery. This is relevant because inflammation of the gallbladder

can result in thrombosis of the cystic artery, resulting in ischemia, gangrene/necrosis, and perforation of the gallbladder [66].

The sympathetic innervation of the gallbladder is via the celiac axis and travels with branches of the hepatic artery and portal vein [67]. Visceral pain, frequently referred to the right subcostal, right scapular, and epigastric regions, is conducted through sympathetic fibers. Parasympathetic innervation through the vagi regulates the gallbladder motility [66]. The gallbladder mucosa is lined by columnar epithelial cells. In the gallbladder neck, there are tubuloalveolar glands which are responsible for the production of mucus [66]. The Rokitansky-Aschoff sinuses are invagination of the surface epithelium that may extend through the muscularis. These structures can be a source of inflammation, due to bacterial stasis and proliferation within the sinuses. The ducts of Luschka may be observed along the hepatic surface of the gallbladder fossa. They drain the gallbladder cavity into the intrahepatic bile ducts in segment 5 of the liver [13, 66]. These ducts are important as they will be divided at the time of cholecystectomy and, if not recognized, are responsible for a bile leak into the peritoneum [68].

2.7 Congenital Malformations of the Gallbladder

A number of gallbladder anomalies have been described. Most of these do not have clinical significance including agenesis and hypoplasia of gallbladder and a double gallbladder. Occasionally the abnormalities of the gallbladder may predispose to bile stasis, formation of gallstones, and inflammation such as gallbladder diverticula and septation of the gallbladder. In addition, various gallbladder malpositions have been described which may result in abnormal mobility making the gallbladder susceptible to torsion. Gallbladder has been also found in an extremely uncommon location such as the abdominal wall, falciform ligament, or even retroperitoneum [18, 69].

Biliary atresia (BA) is a rare, complex disorder. Two different forms are described. Syndromic BA (aka the embryonic type), which accounts for about 10–20% of cases, is associated with other congenital anomalies such as an interrupted IVC (inferior vena cava), intestinal malrotation, preduodenal portal vein, situs inversus, cardiac defects, and polysplenia. This type of BA is likely due to an insult during organ development occurring during differentiation of the hepatic diverticulum from the foregut of the embryo and is associated with a poorer outcome [70]. Nonsyndromic BA (aka the perinatal type) may have its origins later in gestation and runs a different clinical course. The prognosis of BA is improved significantly by early detection. BA must always be excluded in any infant who has conjugated hyperbilirubinemia after 14 days of age. A combination of timely expert surgery (Kasai portoenterostomy) and liver transplantation has yielded a good long-term survival in more than 90% of affected patients. Although laparoscopic Kasai portoenterostomy has drawn great attention, a recent study has shown that outcomes in terms of native liver survival rates and actuarial survival rates were less favorable compared with more conventional surgery [71].

Conclusion

The biliary system provides bile important for digestion and absorption of meals and elimination of bilirubin and cholesterol. As indicated in this chapter, congenital abnormalities, disorders of the biliary system and components of the enterohepatic circulation, and surgical procedures can alter the biliary system in predictable ways based on the physiologic pathways and anatomy described in this chapter. An appreciation of the functioning of the biliary system as well as the enterohepatic circulation will help clinicians better understand and manage the alterations that occur to this system as a result of disease, or surgical procedures.

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Physiology of the Pancreas

3

Richard Hu, Robin Hu, and Stephen J. Pandol

3.1 Macro- and Microanatomy of the Pancreas

The pancreas plays a central role in digestion and metabolism of nutrients. Major functions of the pancreas include secretion of digestive enzymes into the duodenum for the breakdown of complex proteins, lipids, carbohydrates, and nucleic acids, secretion of bicarbonate into the duodenum in order to neutralize the acidic chyme exiting the stomach, and secretion of islet cell hormones into the circulation to control systemic metabolism of nutrients after absorption.

In the adult the pancreas is a retroperitoneal organ that is obliquely orientated. The head of the pancreas is clasped by the duodenum on the right. The tail of the pancreas extends to the splenic hilum to the left. The pancreatic body is ventral from the 2nd to the 4th lumbar spine, making it susceptible to injury with blunt trauma to the abdomen.

The blood supply to the pancreas is highly variable, but originates from branches of the gastroduodenal, superior mesenteric, and splenic arteries. These form anterior and posterior arcades which supply the pancreatic head, while the body and tail are supplied predominately by branches of the splenic artery which courses superior to the body of the pancreas.

Venous drainage of the pancreas is predominantly through the splenic vein and into the portal vein. The portal and superior mesenteric vein passes medial to the uncinate process and deep to the pancreatic neck. The splenic vein enters the portal vein having coursed posterior to the pancreatic tail and body. The splenic vein is

R. Hu (✉)
Division of Digestive Diseases, Olive View-UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
e-mail: RichardHu@mednet.ucla.edu

R. Hu · S. J. Pandol
Department of Biological Science and Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

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prone to thrombosis during episodes of severe acute pancreatitis, and this causes segmental venous hypertension, and blood drains from the blood via the short gastric veins, and this can give rise to gastric varices. An effective treatment of bleeding from these varices is a splenectomy.

Innervation of the pancreas comes from the sympathetic and parasympathetic nervous system. Sympathetic nerves arrive through the greater and lesser splanchnic nerve trunks which arise from the 5th to the 9th thoracic spine level. Sensory nerves travel with the parasympathetic fibers through the vagal nerve. Both systems travel through the celiac plexus although some sympathetic fibers may travel through the superior mesenteric ganglion. The sympathetic nerves and enteropancreatic interneurons are inhibitory, while the parasympathetic nerves are stimulatory to pancreatic responses. There are also interneurons that travel from the myenteric plexus of the stomach and duodenum to innervate the pancreas. The pancreas has an extensive array of intrapancreatic ganglion and postganglionic fibers that innervate ductal cells, acinar cells, and islet cells. Pain fibers travel with the sympathetic system [1, 2]. Typical pancreatic pain is felt in the epigastrium and when severe radiates to the mid-back. This is the feature of acute, chronic pancreatitis and locally advanced pancreatic cancer.

The exocrine pancreas utilizes an elaborate duct system linking every acinar cell to the intestine. In most patients there is a main pancreatic duct which is derived from fusion of two ducts—duct of Wirsung from the embryological ventral bud and duct of Santorini from the embryological dorsal bud. The main pancreatic duct usually has a common channel with the bile duct, and together they project into the duodenum at the major papilla (ampulla of Vater), which is surrounded by the sphincter of Oddi.

The functional unit of the exocrine pancreas is the acinus and its draining ductules. The acinar cells of the acinus form the terminal end of the ductular system. This terminal end is referred to as the lumen of the acinus. The acinar cells are oriented so that the zymogen granules (containing digestive proenzymes) empty into the lumen. Each acinus is supported by a rich blood and nerve supply. The most proximal (intercalated) duct cells in relation to the acinus secrete bicarbonate-rich fluid.

3.2 Pancreas Development and Malformations

The pancreas develops from two outpouchings from the duodenum during the 5th week of life (Fig. 3.1). The ventral and dorsal buds rotate and merge forming the body of the pancreas during the 7th week of gestation. The dorsal bud forms the body and tail of the pancreas, whereas the ventral bud forms the pancreatic head. Malformations are usually from errors in rotation or fusion.

The ductal systems coming from the ventral and dorsal buds usually merge and join the common bile duct and empty into the duodenum through the ampulla of Vater (major papilla) (Fig. 3.2). The following are malformations resulting from alterations in this usual process.

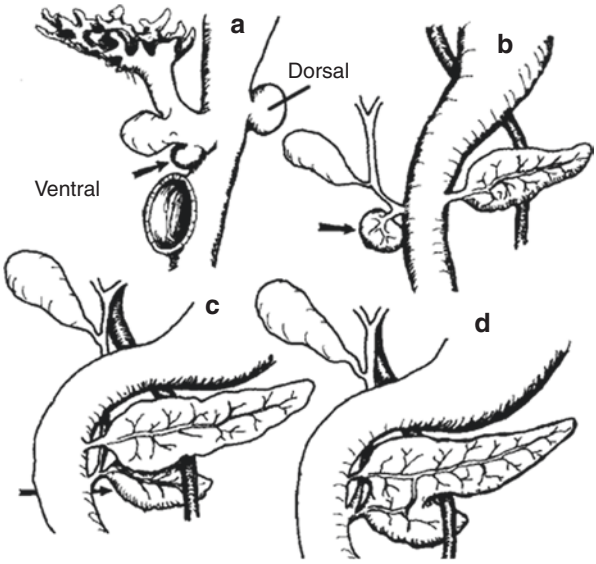

Fig. 3.1 The development of the pancreas. The arrow follows the ventral pancreas as it migrates behind the duodenum. The superior mesenteric-portal vein which is enveloped by the migrating pancreas. Malformations are usually from errors in rotation or fusion

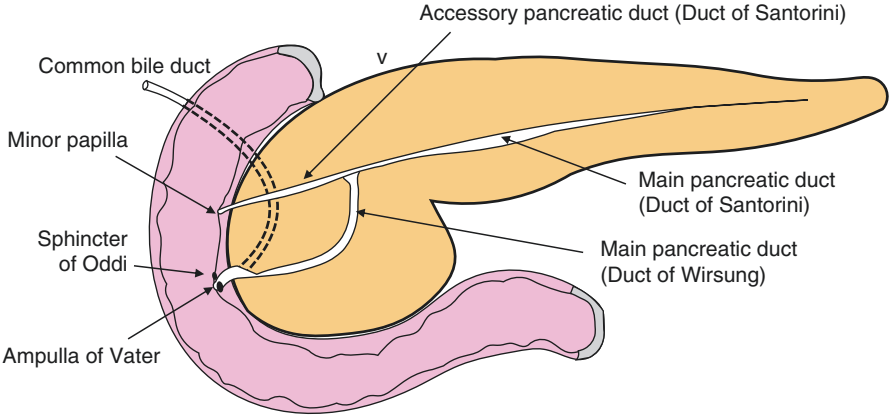

Fig. 3.2 Normal pancreatic duct system

Pancreas Divisum In 5–10% of patients [3–5], the two original ducts do not fuse so that they both drain directly and separately into the duodenum (Fig. 3.3). In this case the dorsal duct of Santorini drains into the duodenum independent through the minor papilla, which is also in the duodenal wall, proximal to the major papilla by 1–2 cm. Failure of the two pancreatic duct systems to fuse results in pancreas divisum. This condition can be associated with acute or recurrent acute pancreatitis [6–8], but more often the pancreas divisum is incidental and not related to the pancreatitis. False pancreas divisum is when a stricture in the fused portion of the pancreatic appears as pancreas divisum. Pancreas divisum is typically divided into three types.

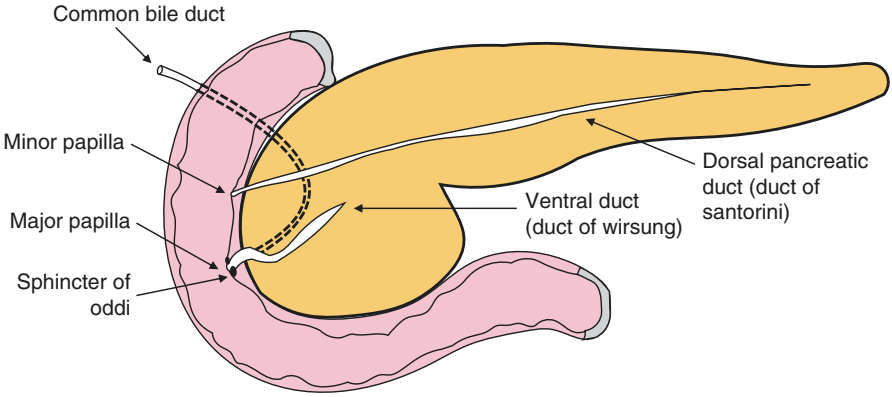

Fig. 3.3 Pancreatic ductal system malformation. The two main pancreatic ductal systems' failure to fuse results in pancreas divisum; therefore, the majority of the pancreas must drain through the narrow minor papilla

Type 1 (classic): no connection at all, which occurs in the majority of pancreas divisum cases (about 70% of all cases).
Type 2 (absent ventral duct): minor papilla drains all of pancreas, while the major papilla (ampulla of Vater) drains bile duct only (20–25%).
Type 3 (functional): filamentous or inadequate connection between dorsal and ventral ducts (5–6%).

Common Channel Syndrome In rare circumstances, an abnormally long common pancreatobiliary channel (>10 mm in children) may be encountered. The junction remains outside the duodenal wall and lacks the normal sphincter. This may result in pancreatobiliary reflux of the duodenal contents including biliary and pancreatic secretions, resulting in injury to the extrahepatic bile duct and pancreas leading to the development of cholangitis and/or recurrent acute pancreatitis [9–11].

Annular Pancreas This rare abnormality (~3/20,000 autopsies) is characterized by a band-like pancreatic tissue that completely encircles the second portion of the duodenum. It may cause duodenal stenosis or obstruction. Annular pancreas is thought to result from fixation of the ventral pancreatic bud and failure to rotate during embryogenesis. This hypothesis is supported by the usual finding that the pancreatic duct encircles the pancreas from anterior to posterior around the right side to join the common bile duct. Other variants may also occur. Annular pancreas can be associated with other congenital defects including intestinal malrotation, Meckel's diverticula, cardiac defects, imperforate anus, and spinal defects. It is more common in Down's syndrome. The classic presentation in an infant who presents with vomiting is the "double bubble" sign on plain radiology, indicative of a duodenal stenosis [12, 13].

Ectopic Pancreatic Tissue Ectopic pancreatic tissue ("pancreatic rest") is relatively common on careful histologic examination (1–14% of autopsy cases) [14], but has no clinical significance. Ectopic tissue is most often seen in the stomach, duodenum, and jejunum, but foci of pancreatic tissue have been reported throughout the GI tract. Pancreatitis or pancreatic cancer rarely develops from ectopic pancreatic tissue.

3.3 Acinar Cells for the Synthesis and Secretion of Digestive Enzymes

The acinar cells make up the vast majority of the pancreatic mass, about 80% of total. They are polarized epithelial cells that have the machinery to synthesize huge amounts of proteins, process them, and to secrete them upon stimulation. The key features are rich in rough endoplasmic reticulum (RER), numerous mitochondria that tend to surround the nucleus and form a seeming "barrier" between the apical and basolateral poles, and zymogen granules, which are the pancreatic digestive enzyme storage units [15–17]. The major pancreatic enzymes secreted by acinar cells are summarized in Table 3.1.

Table 3.1 Pancreatic acinar cell secretory products

Proenzymes	Cationic trypsinogen
	Anionic trypsinogen
	Mesotrypsinogen
	Chymotrypsinogen (A, B)
	Kallireinogen
	Procarboxypeptidase (A, B)
	Prophospholipase
	Proelastase
Enzymes	Amylase
	Carboxylesterase
	Sterol esterase
	Lipase
	DNase
	RNase

Proenzymes listed are stored in the pancreas and secreted into the duodenal lumen as inactive proenzyme forms. If these enzymes were active in the pancreas, they would digest the pancreatic gland. Other enzymes such as amylase and lipase are stored and secreted in their active forms (Adapted from Gorelick F, Pandol SJ, Topazian M: Pancreatic physiology, pathophysiology, acute and chronic pancreatitis. Gastrointestinal Teaching Project, American Gastroenterological Association, 2003)

3.4 Duct Cell for Secretion of a Bicarbonate-Rich Secretion

The ductal cells make up less than 5% of the total pancreatic mass, yet are responsible for the large volume of bicarbonate-rich pancreatic fluid secreted to carry the digestive enzymes to the duodenum. The intralobular ductules emanating from the acinus are composed of cuboidal cells originating with centroacinar cells that are incorporated into the acinar. The cells lining the main pancreatic duct are similar to the interlobular cells.

The duct cells are polarized epithelial cells with a basolateral and an apical surface. The cystic fibrosis transmembrane regulator (CFTR) channel is a key participant in fluid secretion in the ductal system and is present on the apical surface facing the duct lumen. The cells of both the acinus and duct are surrounded by tight junctions to keep the secretions from leaving the acinus and ductal system and causing damage to the interstitium of the pancreas. One of the members of the tight junction system is protein claudin-2 that forms channels that allow water and sodium to cross into the lumen to join bicarbonate which is secreted in response to CFTR channel activation. Pancreatic bicarbonate secretion is derived from the centroacinar as well as the remainder of the ductal system. The electrochemical gradient resulting from bicarbonate secretion provides the force for water and sodium to enter the ductal secretion across the tight junctions completing the formation of the ductal fluid that carries the acinar secretions to the duodenum [18].

Cellular Composition of the Acinar Cell The acinar cell is polarized (Figs. 3.4 and 3.5) with the perinuclear region rich in rough endoplasmic reticulum (RER) and

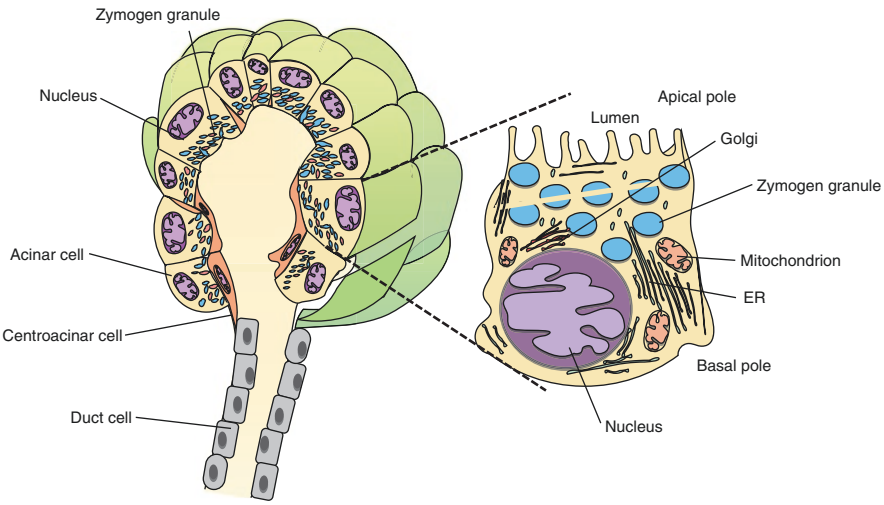

Fig. 3.4 Schematic representative of acinus and acinar cell. The acinus is an organized group of acinar cells that empty into a duct formed by duct cells; at the basal pole, there are plenty of mitochondria and ER which are components for protein synthesis, while at the apical pole, cluster of zymogen granules which are for storage and secretion of pancreatic enzymes (Adapted from Gorelick F, Pandol SJ, Topazian M: Pancreatic physiology, pathophysiology, acute and chronic pancreatitis. Gastrointestinal Teaching Project, American Gastroenterological Association, 2003)

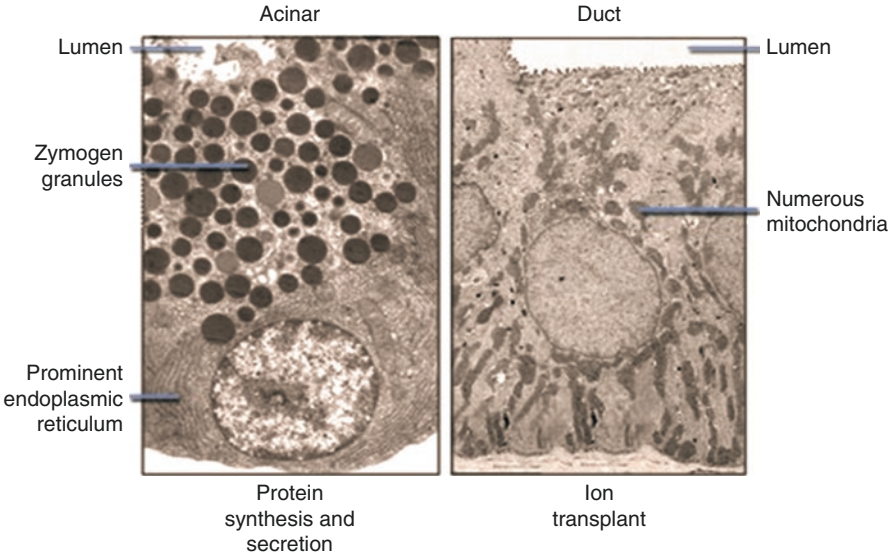

Fig. 3.5 Electronic ultrastructure of the pancreatic exocrine cells. The pancreatic acinar cells (left) and duct cell (right) are both polarized, with clearly defined apical (luminal), lateral, and basal domains. The pancreatic acinar cell has prominent basically located rough endoplasmic reticulum for the synthesis of digestive enzymes and apically located zymogen granules for storage and secretion of digestive enzymes. The pancreatic duct cell contains numerous mitochondria for energy generation needed for its ion transport functions (Adapted from Gorelick F, Pandol SJ, Topazian M: Pancreatic physiology, pathophysiology, acute and chronic pancreatitis. Gastrointestinal Teaching Project, American Gastroenterological Association, 2003)

the apical pole dominated by zymogen granules. The acinar cell is a protein synthesis factory with the digestive enzymes being synthesized in the RER, processed in the Golgi apparatus and condensing vacuoles, and stored as zymogens (inactive digestive enzymes) in the apically located granules. The mitochondria are critical for the synthesis of ATP (adenosine triphosphate). Receptors that are necessary for regulation of acinar cell secretion are located on the basolateral membrane.

Acinar Cell Physiology The receptors on the basolateral membrane of the acinar cells interact with circulating hormones and transmitters released from nerve terminals adjacent to the basolateral plasma membrane. The most important physiologic role for receptor activation by hormones and neurotransmitters is the secretion of digestive enzymes into the lumen of the acinus in response to a meal. The type of receptors involved in secretion is G-protein-coupled receptors. The acinar cell has two major groups of G-protein-coupled receptors on its cell surface that mediate responses through intracellular second messengers. One group generates a calcium signal including muscarinic receptors that mediate the effects of acetylcholine, the cholecystokinin (CCK)1 receptor, and the gastrin-releasing peptide (GRP) receptor. The other group of receptors induces a cAMP signal in the acinar cell including those that bind secretin, pituitary adenylate cyclase-activating peptide (PACAP),

and vasoactive intestinal polypeptide (VIP). Although there is a tendency to focus on the physiologic effects of receptor stimulation, it is important to note that stimulation of the acinar cell receptors with supraphysiologic concentrations of hormones and neurotransmitters can cause pathologic responses in both cell signaling and cellular responses. For example, supraphysiologic stimulation of CCK or muscarinic receptors on the acinar cell results in inhibition of enzyme secretion and the pathologic activation of digestive zymogens in the acinar cell [19–22]. In fact, the pathological responses elicited by supraphysiologic CCK stimulation are commonly used to generate acute pancreatitis in animal models where the findings are relevant to human acute pancreatitis.

The reason for having receptors on the acinar cell that respond with calcium and cAMP is likely related to the synergism between these two signaling pathways. The secretory response to increasing both messengers is greater than the additive effect of the signals [23]. This also provides a mechanism to modulate pancreatic secretion in response to low levels of increase of the individual signals.

3.5 Pancreatic Enzymes

One of the major purposes of the exocrine pancreas is to synthesize digestive enzymes and deliver them to the intestine where they play a critical role in digestion of ingested nutrients. Because the digestive enzymes could have damaging effects by initiating digestion in the acinar cell, they are synthesized as inactive forms, and together they are called zymogens. Most of the enzymes, >75% by weight, are proteases.

3.6 Enzyme Action

Enzymes are synthesized as zymogens and become activated when they reach the intestinal lumen. Within the intestinal lumen, trypsin activates other proenzymes. Amylase and lipase are synthesized in their active form and are important in the diagnosis of acute pancreatitis when the serum levels reach more than three times the upper limit of normal in patients with typical pancreatic pain.

3.6.1 Function of Digestive Enzymes

Pancreatic digestive enzymes generally target large, complex macromolecules in the gut lumen, whereas intestinal brush border enzymes target smaller molecules (e.g., di- and tripeptides and oligosaccharides) so that monomers of these nutrients can be carried across the intestinal epithelium by specific facilitated transport mechanisms.

Amylase is secreted by the salivary glands and the pancreas. Both catalyze the cleavage of interior 1,4 glucose linkages of complex carbohydrates to produce short dextrins. The brush border enzymes cannot digest complex carbohydrates but do digest dextrins by enzymes such as maltase and isomaltase presenting products to the intestinal cell for absorption.

Ninety-five percent of dietary lipids in Western diets are triglycerides, which cannot be digested by brush border enzymes. Pancreatic triglyceride lipase cleaves the majority of fatty acids from dietary triglycerides, usually at the sn-1 and sn-3 positions producing monoglyceride and free fatty acids. Pancreatic triglyceride lipase activity is enhanced by another protein secreted by the acinar cell, colipase. Carboxyl ester lipase has a broad substrate specificity and is important in digesting cholesterol esters and in the absorption of vitamin A.

Pancreatic proteases and gastric pepsin digest all of the complex dietary proteins into short peptides and amino acids for further digestion by brush border enzymes for absorption. The most abundant protease is trypsin, and it is produced in three forms. The most abundant is cationic trypsinogen, coded by the PRSS1 gene. Anionic trypsinogen (PRSS2) and mesotrypsinogen (PRSS3) are similar to PRSS1 in that they all act on exposed arginine or lysine residues within a peptide chain (i.e., an enteropeptidase). Other proteases are categorized by the amino acid side chain they prefer, by the part of the peptide chain they attack, and by the type of catalytic site [24].

3.7 Enzyme Activation Cascade

Trypsin is the key enzyme controlling zymogen activation. Many of the zymogens including trypsinogen are usually inactive when they are secreted from the pancreas into the intestine. When trypsinogen comes in contact with enterokinase (an enzyme of the brush border of the duodenum), a ten-amino acid peptide is cleaved from trypsinogen's N-terminal. This cleaved peptide is called trypsinogen activation peptide, and the active enzyme is called trypsin. Trypsin then activates itself and the other zymogens by cleaving their corresponding activation peptides, and the digestion begins.

Since there can be some activation of trypsin in the acinar cell, there is a potential of prematurely initiating the pancreatic enzyme cascade while the pancreatic enzymes are still in the pancreas. Thus, a number of protective mechanisms are employed to protect the pancreas from autodigestion. (1) Most digesting enzymes (except lipase and amylase) are synthesized in inactive "proenzyme" forms. (2) The activating enzyme (enterokinase) is physically separated from the pancreas and located in the duodenum and jejunum. (3) Digestive enzymes are compartmentalized in the acinar cells within zymogen granules physically separated from the rest of the cell. (4) Intracellular calcium concentrations are low, limiting trypsin activation and survival. (5) The acinar cells synthesize pancreatic secretory trypsin inhibitor which is packaged in the zymogen granule along with the digestive enzymes. If trace levels of trypsin activation occur in the zymogen granules, then pancreatic

secretory trypsin inhibitor inactivates trypsin. (6) Trypsin is destroyed by chymotrypsin C (CTRC), another digestive enzyme [25]. (7) Trypsin activity outside the acinar cell leads to protease activated receptor (PAR) activation which protects acinar and duct cells during acute pancreatitis [26]. (8) The duct cells secrete a large amount of bicarbonate-rich fluid to flush digestive enzymes out of the pancreatic duct. (9) High bicarbonate levels in the pancreatic duct maintain trypsin in a trypsinogen conformation (i.e., inactive). (10) The liver produces two inhibitors, 1-antitrypsin and 2-macroglobulin, which immediately inhibit any trypsin that leaks out of the acinar cells or ducts.

3.8 Acinar Cell: Functional Reserve

The pancreas has enormous protein (digestive enzyme) synthesis capabilities that greatly exceed the amounts required for normal digestion. More than 90% of the pancreas can be lost before there is significant functional exocrine insufficiency and the development of clinical steatorrhea. Thus, signs and symptoms of pancreatic exocrine failure based on malabsorption only occur when a significant proportion of the acinar cell mass is lost [27]. This suggests that there can be significant subclinical pancreatic enzyme insufficiency without clinical evidence of steatorrhea.

3.9 Duct Cell Physiology

Duct secretion is highly responsive to stimulation. At low flow rates, the bicarbonate concentration in pancreatic juice is similar to that of plasma. With stimulation by secretin or vasoactive intestinal peptide (VIP), the fluid volume markedly increases, bicarbonate concentration increases, and chloride decreases. The key elements are shown in Fig. 3.6. Secretion begins with the cystic fibrosis transmembrane regulator (CFTR) via its action to increase cAMP in the duct cell. CFTR is both a chloride- and bicarbonate-conducting anion channel [28]. Mutations in CFTR cause decreased bicarbonate secretion resulting in cystic fibrosis which involves the pancreas as well as other organs [29].

3.9.1 Control of Pancreatic Exocrine Function

In humans, the pancreas is primarily under neural and endocrine control. Stimulatory input comes from multiple directions. Traditionally, pancreatic secretion has been conceptualized into three phases based on the stimuli and mediators of pancreatic stimulation and their relative contribution. The cephalic phase (25%) is initiated by the sight and smell of food. The gastric phase (10%) is initiated by distention of the stomach. The intestinal phase is initiated by meal contents and acid secreted from the stomach into the duodenum which, in turn, stimulates the release of hormones CCK and secretin from intestinal endocrine cells.

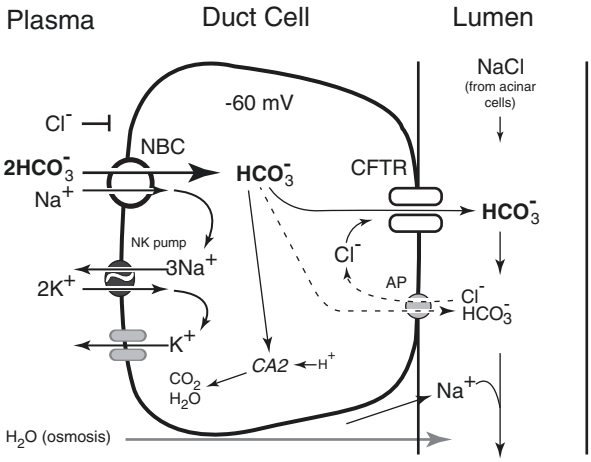

Fig. 3.6 Duct cell model of bicarbonate secretion. Bicarbonate (HCO_3^-) enters through the sodium bicarbonate cotransporter (NBC) and exits through CFTR. The NaK pump keeps the intracellular sodium low so that there is a continual electrochemical driving force of bicarbonate into the cell through NBC (Adapted with modification from Gorelick F, Pandol SJ, Topazian M: Pancreatic physiology, pathophysiology, acute and chronic pancreatitis. Gastrointestinal Teaching Project, American Gastroenterological Association, 2003)

Sensory input from gastric distension and the interaction of CCK with its receptors on sensory neurons are carried via afferent vagal nerves to the dorsal vagal complex. These inputs as well as those from the cephalic phase activate motor (efferent) neurons that project onto ganglia within the pancreas via vagal efferents. The postganglionic fibers innervate the acinar cells and duct cells (and islets) which together stimulate pancreatic secretion. In addition, there may be some direct neural connections between the stomach and duodenum to the pancreas [30].

The nervous system controls pancreatic zymogen secretion. Most stimulatory nerves are cholinergic with extrinsic innervation via the vagal and subsequent intrapancreatic cholinergic nerves. Vagal stimulation matches maximal meal-stimulated pancreatic secretion. CCK is the most important hormone-stimulating pancreatic enzyme secretion, but in man, at physiologic concentrations, CCK stimulates pancreatic enzyme secretion by stimulating sensory vagal and intrapancreatic nerves although there are CCK receptors on acinar cells which can also mediate digestive enzyme secretion. The hormone secretin is released in response to gastric acid emptied into the duodenum. Secretin is responsible for stimulating ductal water and bicarbonate secretion which in addition to carrying acinar cell digestive enzymes to the duodenum provides a neutral pH in the intestine needed for optimal digestive enzyme activity [31, 32]. The integration of the pancreatic secretory control mechanisms allows pancreatic secretion to be continuously adjusted according to the size of the meal, the meal content, the rate of digestion, and the external factors (Fig. 3.7).

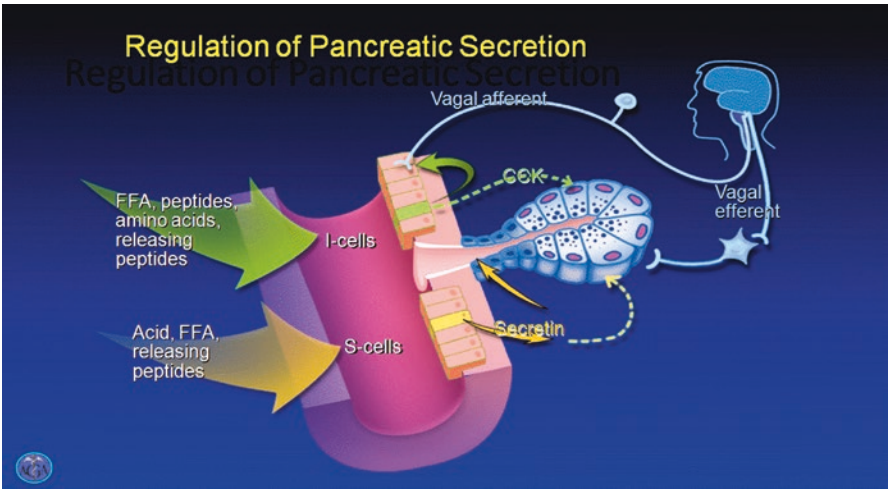

Fig. 3.7 Schematic representative of the regulation of pancreatic secretion. Meal nutrients such as peptides, amino acids, and fatty acids delivered into the duodenum stimulate the local release of CCK from the CCK-containing I cells to the area around the basolateral surface of the I cells, and Secretin from the secretin-containing S cells which act on the acinus duct cells to mediate ion and bicarbonate secretion. The released CCK can activate vagal efferent neurons that transmit the signal to the dorsal vagal complex, where the sensory information is integrated and vagal efferents are activated. Vagal efferents synapse with neurons in the pancreatic ganglia. In turn through neurotransmitter acetylcholine (Ach), gastrin-releasing peptide (GRP), and vasoactive intestinal polypeptide (VIP), effector neurons in the pancreatic ganglia activate secretion by pancreatic parenchymal cells. CCK released by the I cells and secretin secreted by the S cells enter the general circulation and may act as a hormone on the pancreatic acinar and duct cells to cause secretion. However, the importance of direct hormonal stimulation is questionable because CCK receptors are not present on human acinar cells (Adapted from Gorelick F, Pandol SJ, Topazian M: Pancreatic physiology, pathophysiology, acute and chronic pancreatitis. Gastrointestinal Teaching Project, American Gastroenterological Association, 2003)

3.10 Meals and System Integration

Normally, food empties slowly from the stomach over 6 to 8 h (i.e., breakfast may not be gone before lunch is added). Pancreatic exocrine secretion is at maximal capacity while food is emptying. With the first meal, vagal stimulation drives pancreatic exocrine and endocrine secretion (CCK, secretin). Hind gut hormones (PYY, GLP-1) respond to nutrients by slowing gastric emptying and motility ("ileal brake"), while GLP-1 enhances beta cell function and insulin secretion. Asynchrony between gastric emptying, nutrient digestion, and absorption and insulin delivery may lead to suboptimal glucose control.

3.11 Pancreatic Function Tests

A group of tests have been developed to measure pancreatic exocrine (secretory) function. These tests are generally classified as direct and indirect tests [33–35]. Direct tests are the gold standard but are inconvenient and not widely available, while indirect tests are largely noninvasive, more convenient, and available but less sensitive to mild and moderate functional insufficiency than the direct tests. Clinically, which test should be used mainly depends on the clinical question and the availability of the particular test. Maldigestion or malabsorption normally does not occur until the pancreatic functional capacity measured by CCK-stimulated digestive secretion is reduced to about 10% of the normal [36, 37] as the pancreatic exocrine function has a large reserve. Therefore, most of the indirect tests that measure digestive enzyme activity would have a low sensitivity and do not detect mild and moderate exocrine pancreatic insufficiency. On the other hand, the direct tests have greater sensitivity but require duodenal intubation which is not widely available in medical institutions. Improved imaging studies have been replacing the traditional direct and indirect pancreatic secretory tests. For example, noninvasive secretin magnetic resonance cholangiopancreatography (MRCP) has been used in the evaluation of pancreatic exocrine function and functional reserve in patient with chronic pancreatitis [38–40]. Endoscopic ultrasound (EUS) has taken a lead role in determining morphologic changes that correlate with decreased pancreatic function such as occurs in chronic pancreatitis [35]. Study has shown that secretin EUS, which is a combination of EUS and secretin endoscopic pancreatic function test, has improved the sensitivity of diagnosis of early chronic pancreatitis to 100% [41]. Further, recent advances in EUS, particularly the introduction of elastography through measuring tissue fibrosis, have tended to decrease the use of pancreatic function tests [33, 35].

Direct Tests The principle of direct tests is measurement of acinar and ductal cell secretory function by measuring enzyme and bicarbonate secretion after stimulating the pancreas with CCK, secretin, or combination of both. The combination of CCK and secretin enables measurement of both bicarbonate and the digestive enzymes, respectively, and representing both functional units of the exocrine pancreas. The direct tests are based on the principle that maximal volume and bicarbonate and enzyme secretion correlate with the functional mass of the pancreas [42]. For these studies, both the stomach and duodenum need to be intubated in order to remove gastric secretions that would interfere with the ability to measure the volume and bicarbonate secretion from the pancreas, while the duodenal tube is used to infuse nonabsorbable marker and collection of pancreatic secretions. An adaptation of the direct secretory test to upper endoscopy has also been described. At the time of endoscopy, either secretin or CCK or the combination is administered intravenously, and pancreatic secretions are collected via the endoscope and analyzed [43–46].

The use of intravenous secretin alone is the most common direct function test performed, and it is sensitive in detecting moderate and severe pancreatic insufficiency. False-positive results have been reported in certain patients such as those with diabetes mellitus, celiac disease, and cirrhosis and patients after antrectomy with Billroth II anastomosis [47]. However, given the recent advance in endoscopic ultrasonography, particularly the introduction of elastic ultrasonography, it is envisioned that the available traditional direct pancreatic function tests will have more role in future clinical practice [33, 35].

Indirect Tests The indirect tests generally measure pancreatic enzymes in blood or stool; or the effect of pancreatic enzymes on an orally administered substrate with collection of metabolites in blood, breath, or urine.

Lundh Test This is the oldest test and is largely of historic interest. It is used to evaluate the pancreatic exocrine function and was first described by Lundh in 1962 [48]. Comparisons of the Lundh test meal with the secretin CCK test show that the latter is more sensitive in detecting mild forms of pancreatic disease, whereas the tests are comparable for advanced disease [49].

Fecal Fat Measuring 72-h fecal fat after ingestion of a fatty meal (70–100 gm/day) is a traditional test for evaluating patient with severe exocrine pancreatic insufficiency and is abnormal when stimulated lipase output drops to less than 5–10% of normal [36]. Alternatively, a simple microscopic qualitative examination of a single stool for oil droplets is almost as sensitive as quantitative measurements for fat [49]. Normally 7% or less ingested fat appears in the stool, because steatorrhea occurs only with advanced pancreatic disease; therefore, measurement of fecal fat is not useful in the diagnosis of mild or moderate diseases.

3.12 Fecal Chymotrypsin and Elastase 1 Tests

Fecal chymotrypsin and elastase 1 tests have been used for the measurement of pancreatic exocrine function, but both tests are limited by the low sensitivity for mild to moderate pancreatic disease, although the latter test using a monoclonal antibody against human elastase 1 has received significant interest as both are tubeless indirect test and do not require intravenous or oral administration of substrates. It was reported that the fecal chymotrypsin test has an 85% sensitivity in advanced pancreatic disease, which is similar to fecal elastase 1 test [49–51].

3.13 Other Tests

Other indirect tests with good sensitivities for identifying the advanced pancreatic disease include the NBT-PABA and fluorescein dilaurate (pancreolauryl) tests.

The NBT-PABA is a synthetic peptide and is specifically cleaved by chymotrypsin to NTB (*N*-benzoyl-L-tyrosyl) and PABA (para-aminobenzoic acid); the PABA is absorbed in the small intestine, conjugated in the liver, and excreted in the urine; therefore, the PABA metabolites can be measured in serum or urine and small bowel diseases, liver disease, and renal insufficiency, and many drugs such as acetaminophen, sulfonamide, and thiazides may interfere with the measurement.

Fluorescein dilaurate (pancreolauryl) is an ester and is hydrolyzed by pancreatic carboxylesterase into lauric acid and water-soluble fluorescein. The latter is absorbed into the small intestine, conjugated in the liver, and excreted in urine which can be measured. Like NBT-PABA test, interference is possible, which impacts on its clinical utility.

Although significant efforts have been devoted to improving the sensitivity and specificities of noninvasive function tests to identify the milder forms of pancreatic diseases, few are used in clinical practice. These include triglyceride (TG) and cholesterol breath test, H_2 and CO_2 breath test, plasma measurement of pancreatic polypeptide and amino acids, and the dual-label Schilling test. However, all those tests have not been shown superior to other indirect tubeless tests, and several of them in fact require the use of radioactive isotopes, making them less useful [47, 49, 52]. Data show that although some of those tests (e.g., mixed TG breath test) may not change the sensitivity in diagnosing mild to moderate chronic pancreatitis or insufficiency, it is suggested that it may have a potential role in guiding enzyme replacement in patients with known pancreatic insufficiency [53–55].

In summary, the direct tests remain the gold standard for the diagnosis of mild to moderate exocrine pancreatic insufficiency, while for advanced pancreatic insufficiency resulting in steatorrhea, many of the tests described also have appropriate sensitivity.

3.13.1 Common Implications in Surgical Patients

Exocrine pancreatic insufficiency is under-recognized in preoperative patients; recent study indicated that 42–45% of patients undergoing pancreaticoduodenectomy (PD) experience exocrine pancreatic insufficiency preoperatively. The postoperative incidence is higher (56–98%) after PD and after distal and central pancreatectomy (12–80%) [56]. Untreated exocrine pancreatic insufficiency is associated with poor quality of life [57], micronutrient deficiency [58–60], and reduced survival [61], but it is difficult to diagnose following pancreatic resection. Many factors including the extent of the surgery, the health of the residual pancreas, and the type of reconstruction must be considered. Pancreatic function tests lack specificity and need to be interpreted in clinical context following pancreatic resection. Given the high incidence of exocrine pancreatic insufficiency (EPI), and potential significant consequences, pancreatic enzyme replacement therapy (PERT) should be commenced routinely in all patients before and after major pancreatic resections. The impaired pancreatic exocrine function can often lead to malnutrition and maldigestion; therefore, postoperative evaluation of exocrine pancreatic function is important as a guide to proper nutritional management of patients after

pancreatectomy [62–64]. A recent study suggested that the histological loss of acinar cells in the remaining pancreas is strongly associated with postoperative exocrine pancreatic insufficiency [65]. Histological evaluation of pancreatic exocrine cell in the resected pancreatic specimen may predict the likelihood of postoperative pancreatic exocrine function.

Conclusion

The exocrine pancreas is an exquisite organ with great reserve and the capacity to secrete prodigious amounts of digestive enzyme protein coordinated with delivery of meal contents to the gastrointestinal tract. Only rarely does injury of the pancreas leading to pancreatitis occur when there is inappropriate activation of the digestive enzymes in the organ—either in the acinar cells or in the duct because of abnormalities of water and bicarbonate secretion. Recurrent episodes of injury and pancreatitis can lead to chronic pancreatitis and pancreatic insufficiency. Also, surgery, which significantly decreases the capacity for the synthesis of digestive enzymes, or alterations in delivery of digestive enzymes for appropriate mixing with the meal can lead to insufficiency. In these situations, the surgeon needs to be aware of the likelihood of exocrine pancreatic insufficiency and consider the approaches to diagnosis presented in this chapter and thereafter institute enzyme replacement, if indicated.

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Gallbladder Stones and Common Bile Duct Stones

4

Michael R. Cox

4.1 Introduction

Gallstone disease and complications from gallstones are a common clinical problem throughout the world. The clinical presentation ranges between asymptomatic gallstones and patients with recurrent attacks of biliary pain requiring elective laparoscopic cholecystectomy (LC) through to patients with severe illness such as cholangitis or severe acute biliary pancreatitis.

Most cases of symptomatic or complicated gallbladder disease can be managed with LC. Common bile duct (CBD) stones associated with gallbladder stones may be managed either at the time of LC with other laparoscopic techniques or with post-operative endoscopic retrograde cholangio-pancreatography (ERCP). The one exception is patients with severe cholangitis where urgent ERCP is the initial treatment to obtain source control of the sepsis. CBD stones after cholecystectomy are usually managed with ERCP.

This chapter shall discuss the epidemiology, natural history, pathological processes, clinical presentations, management and complications of treatments. Most of the illustrations are factitious case scenarios describing relevant facets to provide clinical explanations and augment the main manuscript.

M. R. Cox, MB, MS, FRACS
Department of Surgery, University of Sydney, Nepean Clinical School, Nepean Hospital, Penrith, NSW, Australia

Department of Surgery, Nepean Blue Mountains Local Health District, Penrith, NSW, Australia
e-mail: m.cox@sydney.edu.au

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4.2 Epidemiology

Gallstones are common, with a prevalence of 10–15% in adult Caucasian populations [1, 2]. In certain ethnic groups, particularly American Indians in both North and South America, the prevalence of gallstones is up to 70% [3, 4]. Asian populations including China, Japan and the Indian subcontinent have a lower prevalence of between 2 and 6% [4, 5]. The prevalence in sub-Saharan Africa is even lower, between 1 and 2%, and even lower than that in Masai and Bantu tribes [6].

Although, the annual incidence of patients who develop gallstone-related symptoms and complications requiring surgical intervention is only 1–2%, the high prevalence results in a high disease burden. Emergency presentations with acute complications of gallstone disease are the second most frequent reason for acute gastrointestinal admissions [7]. The annual number of laparoscopic cholecystectomies performed in the USA and UK exceeds 700,000 and 57,000, respectively [2, 8].

The majority (greater than 80%) of gallstones are cholesterol stones; the remainder are pigment stones or mixed stones. Cholesterol stones arise from the combination of supersaturation of cholesterol, biliary stasis, accelerated nucleation of cholesterol crystals and mucus hypersecretion of the gallbladder [9]. The supersaturation of cholesterol is due to the imbalance of the three components of bile: cholesterol, lecithin and bile salts. This results in the production of cholesterol microcrystals. The accelerated nucleation of these crystals with subsequent aggregation leads to the formation of gallstones. The risk factors for cholesterol stones can be grouped as non-modifiable and modifiable (see Table 4.1).

Table 4.1 Risk factors for the development of cholesterol gallstones

Non-modifiable factors	*Mode of action of non-modifiable factors*
Family history	Genetic and environment (diet)
Female gender	Increased oestrogen with modification of hepatic lipoprotein receptors and promotion of cholesterol production
Pregnancy	Increased oestrogen with modification of hepatic lipoprotein receptors and promotion of cholesterol production in addition to stasis secondary to the effect of progesterone
Increasing age	Increased cholesterol supersaturation due to a reduction in bile salt synthesis
Modifiable factors	*Mode of action of modifiable factors*
Gastric surgery or vagotomy	Biliary (gallbladder and CBD) stasis
Obesity	Increased biliary cholesterol
Rapid weight loss	Increased supersaturation of bile and biliary stasis
Prolonged fasting	Gallbladder stasis
Spinal cord injury	Biliary stasis
Crohn's disease or ileocolic resection	Reduced bile salt reabsorption with subsequent reduction in bile salt concentration in the biliary tree
Genetics	Lith genes

Pigment stones fall into two categories: black and brown. Black pigment stones arise from either an increased level of conjugated bilirubin due to chronic or recurrent haemolysis (e.g. sickle cell disease and autoimmune haemolysis) or increased levels of unconjugated bilirubin associated with hepatic cirrhosis or alcohol abuse. Brown stones or mixed stones (calcium bilirubinate) occur secondary to bacterial (less commonly parasitic) degradation of bile and are usually associated with biliary stasis. This process can occur within the gallbladder, the common bile duct (CBD) or the intrahepatic ducts. When this process occurs in the CBD, these are considered primary CBD stones and usually associated with a dilated bile duct, a duodenal diverticulum and/or ampullary stenosis. Patients with previous endoscopic biliary interventions for benign or malignant disease are also prone to the development of these primary bile duct (brown pigment) stones due to poor drainage related to either sphincterotomy stenosis or a chronically dilated CBD.

4.3 Natural History of Gallstones

Of patients with gallstones, over 80% remain asymptomatic and never suffer from complications of the gallstones [1, 9]. The risk of developing symptoms or complications ranges between 1 and 2.3% per annum [10–15]. The majority of asymptomatic gallstones do not require surgery until symptoms or complications develop [16, 17] or in the presence of coexisting pathologies such as porcelain gallbladder, associated polyps or recurrent salmonella infection. Symptoms are usually due to obstruction of the gallbladder outlet (with gallstone impacted in Hartmann's pouch, neck or cystic duct), the CBD or the ampulla of Vater.

4.4 Gallstone Symptoms

The dominant symptom of gallstone disease is biliary colic or more correctly biliary pain as the pain of the gallbladder is not cramping but constant. Biliary pain occurs when the outlet of the gallbladder (Hartmann's pouch, neck or cystic duct) is obstructed with a stone. The pain is usually of rapid but not sudden onset. It is often the most severe pain ever experienced by the patient. It most often arises in the right upper quadrant but can occur in the epigastrium, the retrosternal area or even the left upper quadrant. Biliary pain typically radiates to the right scapular area. Radiation to the right shoulder occurs in association with significant gallbladder inflammation, as with acute cholecystitis. The patient with biliary pain is restless and often feels nauseated. Vomiting may be associated with severe pain. The pain may occur at any time of the day but typically occurs either 15–30 min after a meal (due to cholecystokinin-induced gallbladder contraction) or during the night. The relatively constant pain rises to a peak for over 30–60 min and typically lasts for several hours before remitting. Biliary pain will usually resolve completely, although some patients will report a low-grade pain for a longer period after the

resolution of severe pain. Some patients also have minor episodes of discomfort, typically after a fatty meal, and this is better termed fatty food intolerance. Biliary pain is common and is often associated with other symptoms including flatulence, dyspepsia and abdominal bloating. Having said that, the *sine qua non* is biliary pain and it is the frequency and severity of that which determines whether a cholecystectomy is required.

When biliary pain persists for 12 h or more, acute cholecystitis is likely to supervene. In this setting the symptoms include a fever and patients may have a tachycardia, as part of the systemic inflammatory response.

Symptoms associated with common bile duct (CBD) stones include biliary pain, which usually cannot be distinguished from pain associated with gallbladder stones. These patients may also have evidence of cholestasis with jaundice, dark urine and pale stools or may only have evidence of cholestasis on liver function tests (LFT). The diagnosis of acute cholangitis is a clinical one, and it is essential to determine whether the biliary pain is associated with jaundice and fever with rigours (Charcot's triad). Common bile duct stones can also cause acute biliary pancreatitis, and the pain associated with this can usually be distinguished from pain due to bile duct stones. In this setting there is a constant epigastric pain that radiates directly through to the back, in the mid-thoracic area.

4.5 Pathological Complications of Gallstones

The complications of gallstones are related to the persistent obstruction of the biliary tree with either acute or chronic inflammation (Table 4.2). Of note, most patients with symptomatic gallstones present with biliary colic as described above. This is an episode of pain where the pain resolves completely.

Table 4.2 Complications of gallstones

Acute cholecystitis • Mucocoele • Empyema • Gangrenous cholecystitis • Emphysematous cholecystitis
Chronic cholecystitis
Obstructive jaundice
Cholangitis
Biliary pancreatitis
Mirizzi syndrome
Cholecysto-duodenal fistula • Gallstone ileus
Cholecysto-choledochal fistula • Gastric outlet obstruction
Cholecysto-colonic fistula

Table 4.3 Sequelae of acute cholecystitis

Resolution
Mucocoele
Empyema
Gangrenous cholecystitis
Perforation
Emphysematous cholecystitis
Chronic cholecystitis

4.5.1 Gallbladder Stones

4.5.1.1 Acute Cholecystitis

Acute cholecystitis occurs when the obstruction of the gallbladder outlet by the stone persists beyond 12 h. This results in acute inflammation due to the increase in intraluminal pressure caused by a combination of outlet obstruction and an influx of fluid into the gallbladder lumen. Secondary bacterial infection in the static bile may occur; however, the majority of cases of acute cholecystitis do not develop secondary infection. The pathological sequelae of acute cholecystitis are (Table 4.3):

- *Resolution*
  When managed nonoperatively, an episode of acute cholecystitis shall resolve in all but 10–20% of cases [18–22]. Although there may be clinical resolution, the acutely inflamed gallbladder does not return to its normal state. There may be ongoing inflammation resulting in the development of a thick walled and indurated gallbladder leading to chronic inflammation and fibrosis. This progression of inflammation despite the lack of symptoms is relevant to the management of patients presenting with acute cholecystitis.
- *Mucocoele*
  Persistent obstruction of the gallbladder outlet without secondary infection may result in a mucocoele. The gallbladder mucosa reabsorbs the bile and excretes mucin into the gallbladder lumen causing distension of the gallbladder. An ultrasound some weeks after an episode of prolonged pain will demonstrate a stone impacted in the neck of the gallbladder with a large distended gallbladder (Fig. 4.1).
- *Empyema*
  Secondary infection of the obstructed gallbladder results in the development of an empyema. This may be associated with a clinical presentation of acute cholecystitis 3–4 days into the acute episode. However, an empyema may also be detected at delayed surgery in the case of a failed trial of conservative treatment after the initial episode of acute cholecystitis (Fig. 4.2). At the delayed operation, the gallbladder is chronically inflamed with pus in the lumen. These patients may not have had any evidence of sepsis.

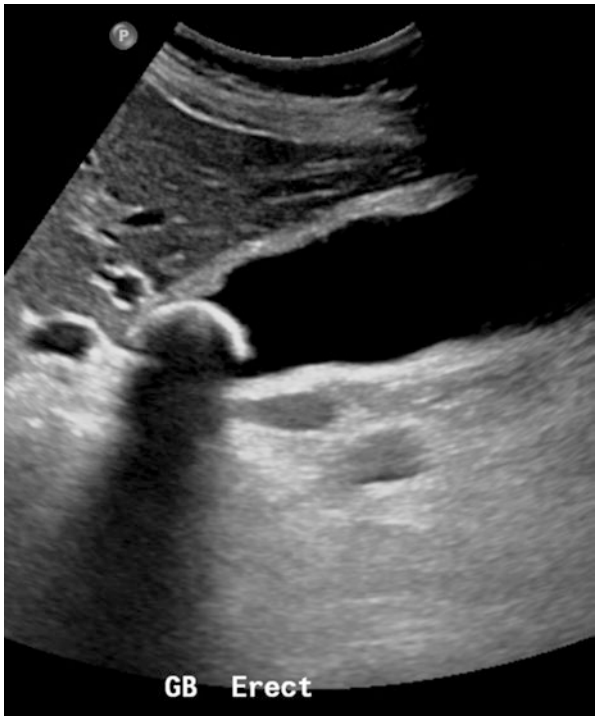

Fig. 4.1 An ultrasound in a 32-year-old woman who presented with an episode of biliary colic lasting >36 h, 6 weeks earlier. She did not seek medical assistance at that time. She presented at the time of the ultrasound with an easily palpable mass in right upper quadrant. The ultrasound confirmed a stone impacted in the neck with a grossly distended gallbladder with a thickened wall. At surgery, the gallbladder was drained and contained mucin

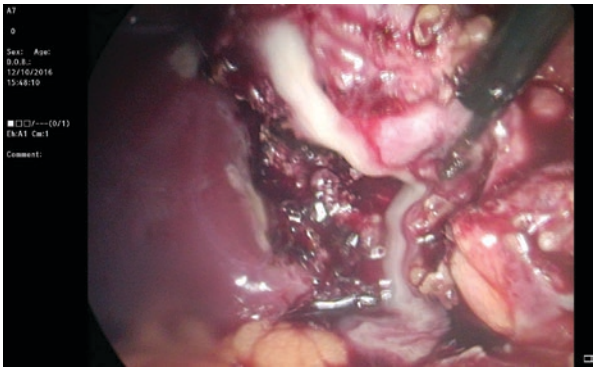

Fig. 4.2 A 42-year-old man that presented with a prolonged episode of pain for 2–3 days to his General Practitioner (GP) 8 weeks prior to the surgery. The GP managed this with oral analgesia and oral antibiotics. He was then assessed surgically and a LC organised. At LC he had a severely chronic inflamed gallbladder with a stone impacted in the Hartmann's pouch. The illustration was taken mid-way through the dissection, note the pus flowing down from the hole higher in the gallbladder. The culture from the pus was negative

- *Gangrenous cholecystitis*
  Gangrenous cholecystitis or gallbladder necrosis (Fig. 4.3) is thought to be due to the reduced blood flow and reduced perfusion of the gallbladder wall due to the increased intramural pressure and the release of various vasoactive peptides associated with the gallbladder sepsis resulting in end arterial thrombosis and ischaemia.
- *Perforation*
  Gangrenous cholecystitis may be complicated by a perforation of the gallbladder wall. In most cases the perforation is walled off and may appear as a pericholecystic abscess on an ultrasound or CT scan (Fig. 4.4). At other times it will be found at cholecystectomy when dissecting the omental adhesions off the inflamed gallbladder will reveal a sealed-off perforation. Occasionally (less than 10%) the perforations are not contained (Fig. 4.5). The patient will present with a sudden onset of severe generalised pain after a period of prolonged biliary pain. These patients will have signs of peritonitis and a differential diagnosis will often include a perforated peptic ulcer. The clue to the diagnosis being gallbladder perforation is the preceding history of prolonged biliary-type pain prior to the sudden onset of generalised pain.
- *Emphysematous cholecystitis*
  Emphysematous cholecystitis is a variation of gangrenous cholecystitis associated with gas either in the gallbladder wall or in the gallbladder lumen (Fig. 4.6). The intraluminal gas needs to be differentiated from gas due to either a previous ERCP and sphincterotomy or the presence of a cholecysto-enteric fistula. The gas is due to secondary infection by gas-forming organisms within the lumen or the gangrenous wall of the gallbladder. Similar to gangrenous cholecystitis, this may be associated with gallbladder perforation (Fig. 4.7).

4.5.1.2 Chronic Cholecystitis

This usually occurs with multiple recurrent episodes of biliary pain associated with some degree of acute inflammation that resolves leading to fibrosis. Chronic cholecystitis is suspected when the ultrasound shows a thick walled, often contracted gallbladder containing stones and little or no fluid (Fig. 4.8). Rarely, chronic inflammation is associated with fistulae formation: cholecysto-choledochal (Mirizzi types II, III and IV), cholecysto-duodenal or cholecysto-colonic fistulae. There is some evidence that chronic inflammation may be associated with the development of gallbladder carcinoma [23].

4.5.1.3 Mirizzi Syndrome

Pablo Mirizzi, an Argentinian surgeon, described this syndrome as obstructive jaundice due to an extrinsic compression of the common hepatic duct (with or without a fistulous communication between the gallbladder and the common hepatic duct) from stones impacted in the cystic duct, gallbladder neck or Hartmann's pouch. Since his initial description, there have been a number of modifications. The most

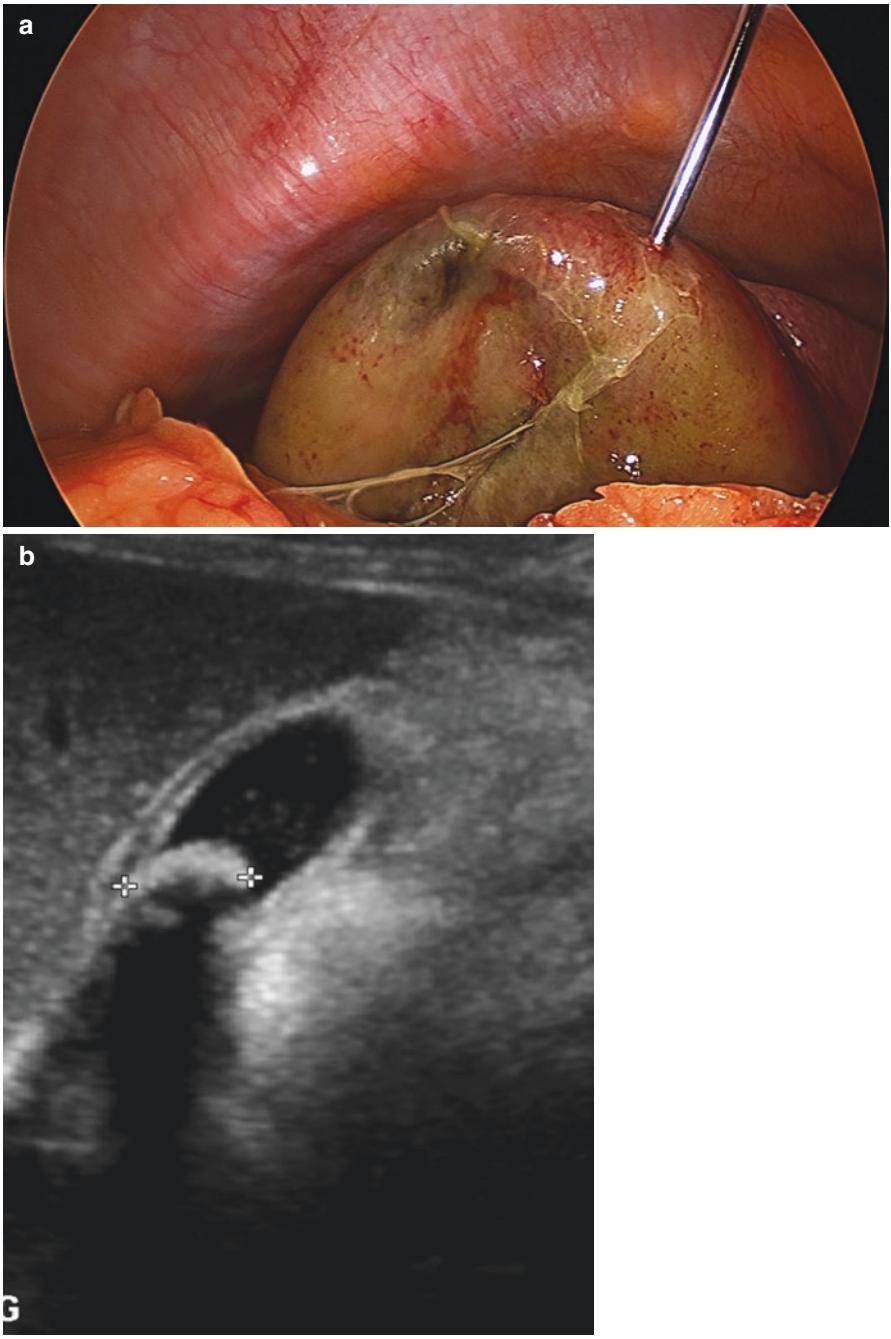

Fig. 4.3 A 52-year-old man who presented with 48 h of prolonged biliary pain with right upper quadrant tenderness and evidence of sepsis with fever, tachycardia and elevated white cell count (22,000). An urgent LC was performed. (**a**) The gallbladder was clearly gangrenous and was very distended and tense, so it was drained with a Concord needle. (**b**) The ultrasound on this confirmed a stone impacted in the neck of the gallbladder with a thickened gallbladder wall associated with pericystic fluid. However, there are no ultrasound features that predicted the gangrenous cholecystitis

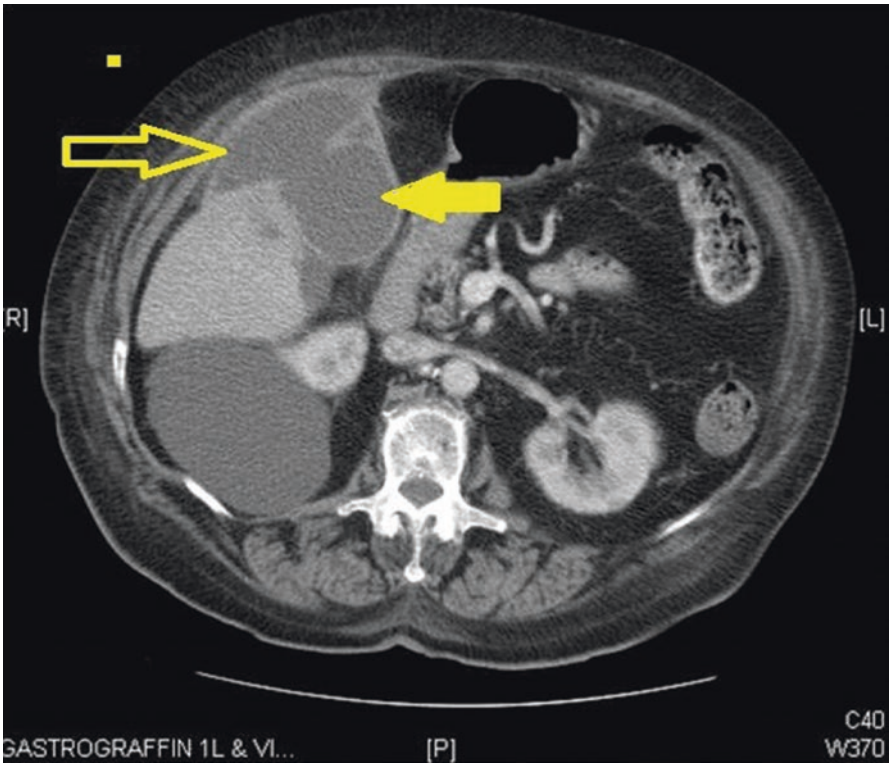

Fig. 4.4 CT scan in a 72-year-old woman who presented with 6 days of upper abdominal pain, fevers and night sweats. The CT revealed an inflamed gallbladder (solid arrow) with an obvious defect in the fundus and a large contained collection (outlined arrow). At operation this was a walled-off perforation. It had been walled off predominantly between the omentum, abdominal wall and liver

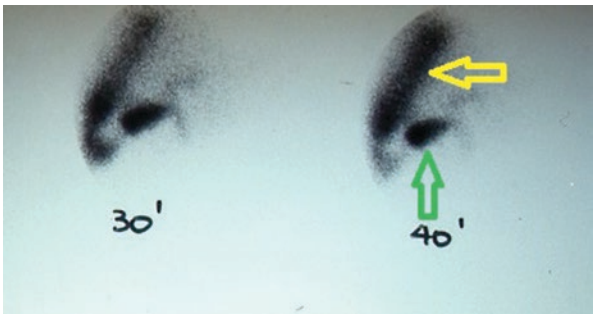

Fig. 4.5 DIDA scan at 30 and 40 min in a patient that presented with a sudden onset of generalised abdominal pain after a 3-day history of prolonged typical biliary pain. An ultrasound confirmed acute cholecystitis with a large amount of free intra-abdominal fluid. The DIDA scan demonstrated the gallbladder (green arrow) with leakage of a large amount of bile into the peritoneal cavity (yellow arrow). Emergency LC revealed a free perforation of a gangrenous gallbladder

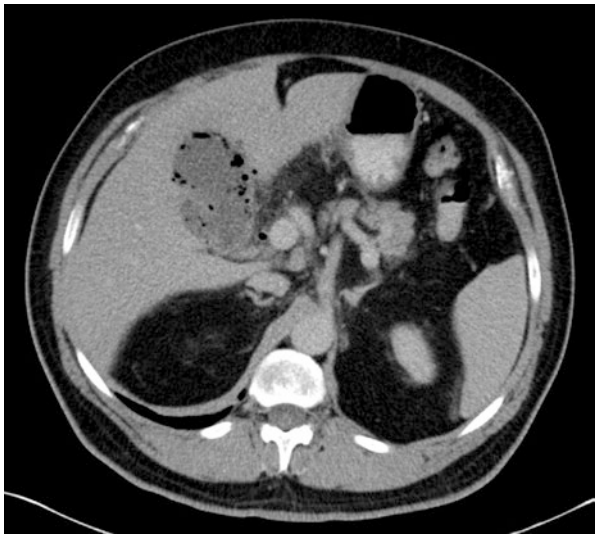

Fig. 4.6 A CT scan demonstrating emphysematous cholecystitis in a 52-year-old man who presented with a 10-day history of biliary pain, fevers and night sweats

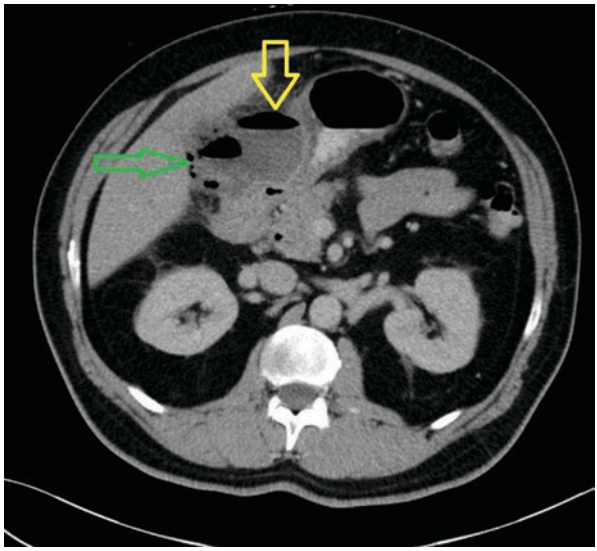

Fig. 4.7 A 56-year-old lady presented with a 2 weeks history of right upper quadrant pain, anorexia, weight loss and night sweats. A provisional clinical diagnosis was made of a hepatic abscess. The CT demonstrated acute emphysematous cholecystitis (green arrow) associated with an abscess (yellow arrow) adjacent to the gallbladder due to a contained perforation

frequently used and pathologically relevant is that by Csendes [24] which considers the presence and extent of any cholecysto-choledochal fistula that is relevant to subsequent management (Fig. 4.9). The development of the cholecysto-choledochal fistula (Fig. 4.10) is related to the severe chronic inflammation produced in the gallbladder and subsequent erosion of a large stone into the common hepatic duct. In types III and IV, this is associated with partial or complete destruction of the mucosa and smooth muscle wall of the common hepatic duct.

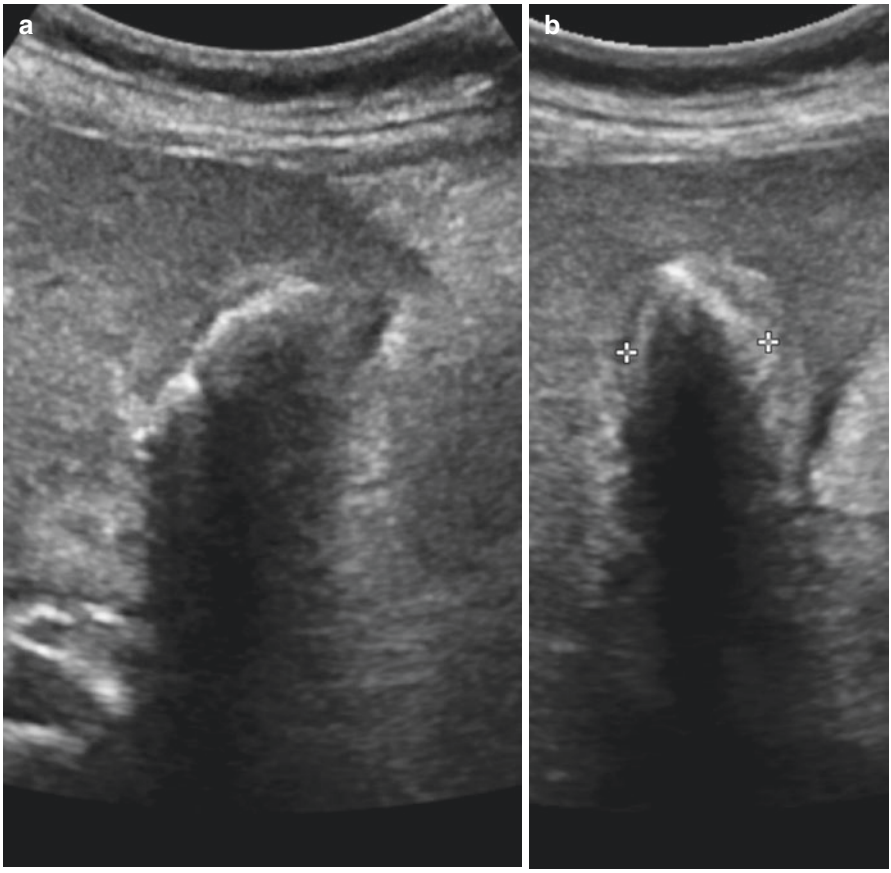

Fig. 4.8 An ultrasound in a 62-year-old lady that had multiple previous episodes of biliary pain, some taking 2–3 days to resolve. The gallbladder is thick walled, contracted, full of stones with virtually no bile in the lumen on both sagittal (**a**) and coronal (**b**) views

4.5.1.4 Cholecysto-enteric Fistula

Chronic inflammation of the gallbladder can cause an adherence and potential erosion into other adjacent organs. The two organs that are most often affected are the first part of the duodenum and the hepatic flexure of the right colon.

Cholecysto-duodenal Fistula

There are several clinical presentations of this problem, and they depend on the size of the gallstones that may migrate through the fistula and the subsequent patency of the fistula.

Gallstone ileus is a well-recognised but rare complication of gallstone disease that is the most common problem associated with a cholecysto-choledochal fistula. It is due to the passage of a large stone through the fistula into

Type	Figure	Description
I		External compression of the common hepatic duct due to a stone impacted at the neck of the gallbladder or at the cystic duct.
II		The fistula involved less than one-third of the circumference of the common bile duct.
III		Involvement of between one-third and two-thirds of the circumference of the common bile duct.
IV		Destruction of the entire wall of the common bile duct.
V		Cholecystoenteric fistula together with any other type of MS.

Fig. 4.9 Csendes classification of Mirizzi syndrome noting the extent of the erosion by the stone through the common hepatic duct [24]

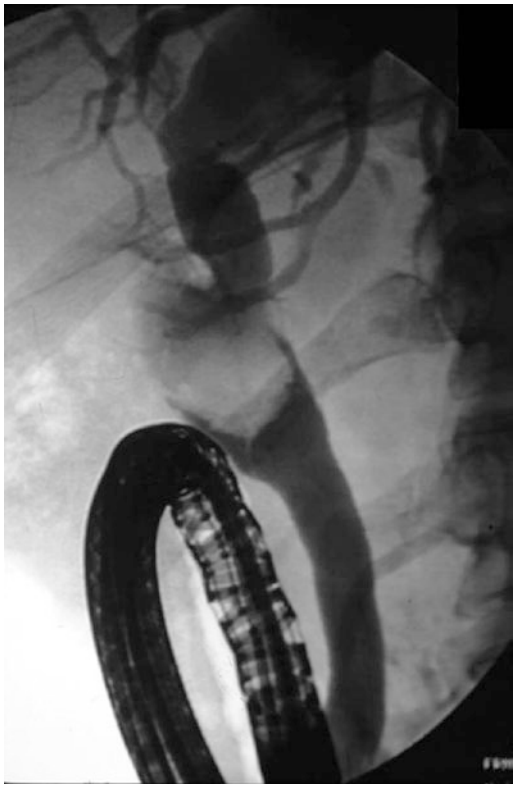

Fig. 4.10 An ERCP of an 82-year-old man that presented with intermittent painless jaundice and low-grade fevers. The large stone lies across the cholecysto-choledochal fistula extending into the common hepatic duct (type II Mirizzi)

the proximal duodenum and subsequent migration of that stone through the small bowel until it causes an obstruction at the midpoint of the small bowel or at the terminal ileum (Fig. 4.11). The clinical presentation is that of a small bowel obstruction. Usually plain abdominal radiography will reveal pneumobilia, with the biliary tree outlined with gas, implicating a patent fistula and cystic duct.

Rarely, the stone passing through the cholecysto-duodenal fistula is so large that it does not migrate through the small bowel but causes gastric outlet obstruction. This is either at the level of the first part of the duodenum or more commonly it moves retrograde into the stomach and obstructs the pylorus.

Occasionally a cholecysto-duodenal fistula would be noted in a patient presenting with cholangitis (Fig. 4.12). Presumably in this instance some of the stones in the gallbladder may have passed through the fistula without causing any intestinal obstruction. Primary or secondary common bile duct stones then causes biliary obstruction. As the biliary tree is already contaminated due to the fistula with the duodenum, sepsis invariably results.

Cholecysto-colonic Fistula

This is a very rare complication of gallbladder stone disease. It may present with episodes of cholangitis and biliary sepsis due to debris within the common bile duct producing a cholangitis-type picture. This will usually require surgical intervention,

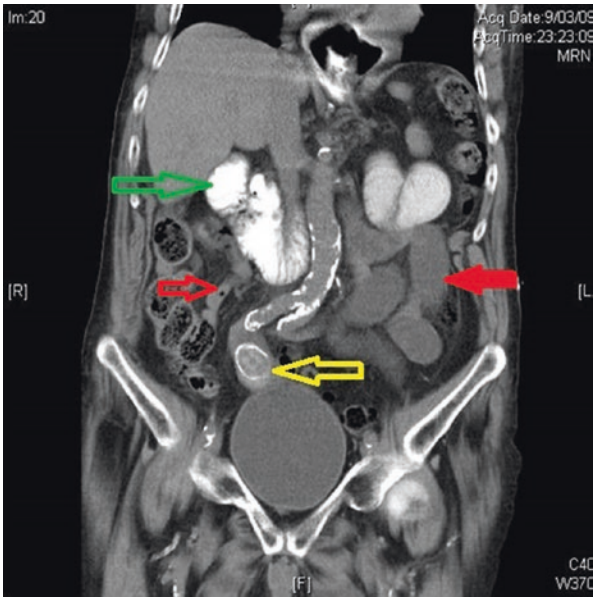

Fig. 4.11 An elderly lady presented with a small bowel obstruction but no prior abdominal surgery. Sagittal views of a CT scan confirmed a distal small bowel obstruction with dilated loops in the left abdomen (solid red arrow) and collapsed loops of small bowel (outlined red arrow) in the right abdomen with a large calcified gallstone in the terminal ileum (yellow arrow). There is contrast in the duodenum flowing back into the contracted gallbladder (green arrow) through the cholecysto-duodenal fistula, but there was no gas seen in the biliary tree

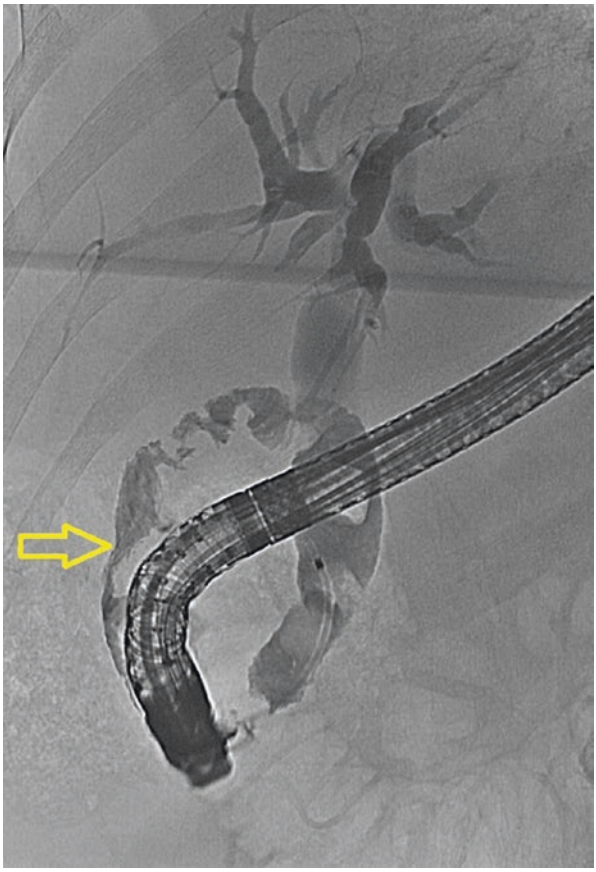

Fig. 4.12 An ERCP in an elderly man who presented with severe cholangitis. There was no prior history of biliary symptoms. The CBD contained three secondary CBD stones. The cholecysto-duodenal fistula is clearly identified (yellow arrow)

by en bloc cholecystectomy with limited colectomy. Like cholecysto-duodenal fistula, a cholecysto-colonic fistula may only become apparent at operation for severe chronic cholecystitis without any other symptoms.

4.5.1.5 Gallbladder Carcinoma in Association with Chronic Cholecystitis

There is some evidence that long-standing chronic inflammation (including the presence of a porcelain gallbladder) may be a factor in the development of gallbladder carcinoma [23]. However, gallstones are unlikely to be the sole factor as gallstones have a very high prevalence (10–15%) in Western societies [1, 2], yet gallbladder carcinoma is relatively rare with an incidence of 1 in 300,000 in the USA [25]. Although the risk of gallbladder carcinoma is 2.3–21 times greater in the presence of gallstones, both share similar risk factors including age, ethnicity (in particular certain South American Indian populations) and female gender [26, 27].

Therefore, at best, gallstones associated with marked chronic inflammation may be a factor in the development of gallbladder carcinoma. (*Gallbladder Cancer will be dealt with in detail in Chapter 15.*)

4.5.2 Common Bile Duct (CBD) Stones

Stones in the CBD may occur due to the migration of stones from the gallbladder into the cystic duct. These are termed secondary CBD stones. Primary CBD stones (brown pigment/mixed stones) arise due to chronic stasis in the CBD (see above). Primary and secondary CBD stones can usually be distinguished by their cause, contents and appearance (Table 4.4). Regardless of whether the stones are primary or secondary, the presentation and complications arising from CBD stones are the same.

- Biliary pain
  At the time of presentation of gallbladder stones with biliary pain, 10–18% of patients will have associated CBD stones, with the vast majority of these being secondary CBD stones [28]. The stones in the CBD may occlude the distal CBD and cause recurrent episodes of biliary pain identical to the pain produced by obstruction of the gallbladder outlet (see above). If the obstruction of the CBD is transient and resolves, the pain resolves with no associated features such as jaundice or sepsis. When the gallbladder is still present, the biliary pain may be due either to obstruction of the gallbladder outlet or the common bile duct stones.
- Obstructive jaundice
  Obstructive jaundice occurs when the obstruction of the common bile duct persists beyond 12–18 h. Unlike malignant causes for obstructive jaundice, the jaundice due to biliary obstruction by a stone will fluctuate over a period of days and may resolve. Obstructive jaundice due to stones is often associated with biliary pain but not invariably so, whereas obstruction due to a malignancy (pancreatic cancer, biliary cancer or external compression by malignant nodes) is usually painless. The other distinguishing feature between obstructive jaundice due to

Table 4.4 Differentiation between primary and secondary CBD stones

Characteristics	Primary CBD stones	Secondary CBD stones
Site of origin	Common bile duct	Gallbladder stones that have migrated into the common bile duct
Composition	Calcium bilirubinate Calcium palmitate Cholesterol	Cholesterol or calcium bilirubinate (pigment stone)
Appearance	Dark yellow to brown	Yellow (cholesterol) and black (pigment)
Shape	Often conforms to the lumen of the common bile duct	Round, mulberry-like or faceted (cholesterol stones), spiculated (pigment stones)

gallstones is that the level of obstruction fluctuates and is usually mild with bilirubin levels rarely over 150 umol/L.

- Cholangitis
  CBD obstruction may be associated with secondary bacterial infection and result in cholangitis leading to septicaemia. The result of an ascending infection of the obstructive biliary tree is due to bacteria, under pressure, entering the systemic circulation via peribiliary lymphatics and/or hepatic veins.
- Acute biliary pancreatitis
  (See chapter on Acute Pancreatitis.)

4.5.3 Gallbladder Polyps

The majority (95%) of gallbladder polyps diagnosed on ultrasound are non-neoplastic, which may be defined as cholesterol polyps (60%), adenomyomatosis (25%) or inflammatory polyps related to cholesterolosis (10%) [29]. The majority of gallbladder polyps are asymptomatic, although cholesterol polyps may occlude the gallbladder outlet causing biliary pain. Some may even pass into the CBD and obstruct the ampulla of Vater causing biliary pain, jaundice or acute biliary pancreatitis. Neoplastic polyps account for less than 5% of gallbladder polyps [29].

4.5.4 Recurrent Pyogenic Cholangitis

Recurrent pyogenic cholangitis (RPC) is characterised by brown pigment stone formation in the intrahepatic bile ducts with associated biliary strictures of the intrahepatic biliary tree. It was originally described by Digby from Hong Kong in 1930 [30] and occurs almost exclusively in people that have lived in Southeast Asian countries [31, 32]. It usually presents in the fourth or fifth decade of life with an equal incidence in males and females [33, 34]. The precise pathogenesis of RPC is not known.

4.6 Clinical Presentation and Investigation

The distinction between different gallstone-related pathologies is achieved by a combination of clinical, laboratory and imaging studies. Although there is a spectrum of pathologies and an overlap between clinical presentations, a series of discrete clinical presentations will be discussed.

4.6.1 Asymptomatic Gallstones

Incidental gallstones usually present when an ultrasound or CT scan has been performed for another reason. The additional assessment required is a careful clinical history to ensure that these are truly asymptomatic and the patient has not had any episodes of biliary pain or fatty food intolerance (see above). A patient with apparent asymptomatic gallstones may initially deny any of these symptoms, but when a

Table 4.5 Symptoms that may be attributed to gallstone disease but are not due to gallstone disease

Fatty food intolerance
Nausea (not associated with episodes of pain)
Episodic vomiting (not associated with episodes of pain)
Abdominal bloating
Dyspepsia
Heartburn/belching
Altered bowel habits/diarrhoea
Flatus
Non-specific food intolerance

detailed clinical description of typical biliary pain is given, they will then remember and state this has occurred in the past. Almost invariably an alternative diagnosis has been made, such as gastritis, peptic ulcer disease, gastro-oesophageal reflux disease and ischaemic heart disease. The gallstones are then considered symptomatic and managed accordingly. If there are no episodes of biliary pain, there may be other gastrointestinal symptoms, as detailed in Table 4.5. In the absence of any episodes of biliary pain, the gallstones should be considered asymptomatic and surgery is not indicated.

The possibility of CBD stones should always be considered when there is a diagnosis of gallbladder stones, even if asymptomatic. CBD stones can remain asymptomatic for many years. This is supported by the data that shows that the median time following LC to the presentation of symptomatic retained common bile duct stones is 4 years [35]. When CBD stones become symptomatic, almost half of the patients develop a significant problem with cholangitis or acute pancreatitis [35]. The assessment for the presence of CBD relates to identifying elements of Charcot's triad (see above). Liver function tests are examined for evidence of cholestasis. An ultrasound is reviewed to determine if the bile duct is dilated (greater than 6 mm) and if stones are seen in the CBD. This is not an ideal method of diagnosing CBD stones, because of the presence of duodenal gas. If the patient has risk factors for CBD stones (e.g. cholestasis and/or dilated CBD), the bile duct should be imaged by MR or CT cholangiography.

4.6.2 Biliary Pain

Biliary pain is the dominant symptom upon which decisions based around the management of gallstones are made. Many call it biliary colic, but this is a misnomer as the pain is constant and not crampy in nature. Biliary pain occurs when a gallstone obstructs the outlet of the gallbladder (Hartmann's pouch, neck or cystic duct) or obstructs the CBD (usually at the ampulla). The pain is sudden in onset, constant and usually severe that arises in the lower chest, epigastric or right upper quadrant of the abdomen. It may then become more widespread and may radiate to the back in the mid-thoracic or right subscapular area or radiate to the right shoulder. The duration is longer than 15 min and may last up to 8 h, after which it usually resolves completely, although some patients report a period of discomfort after the severe pain resolves. During the pain the patient will describe being restless and unable to get comfortable. Between episodes of pain their patient is well and pain free.

In association with biliary pain, the patient may complain of nausea and occasionally vomiting. Others may complain of sweating and an uneasy feeling. The pain may occur after a meal which may be fatty, although this is often not consistent. Patients with recurrent episodes often report that some of the episodes will wake them from sleep in the middle of the night. Other symptoms that patients and non-surgical clinicians may attribute to the gallstones are summarised in Table 4.5. Note that these occur independent of the episodes of pain. As a general rule these symptoms which can be defined as functional gut symptoms are not caused by the gallstones. In a large population-based study, 88% of the patients presenting for LC for pain had these functional gut symptoms. While the biliary pain resolved in over 90% of patients, the functional gut symptoms were unchanged in over two-thirds of the patients following their cholecystectomy [36].

4.6.3 Recurrent Biliary Pain

Recurrent biliary pain is where there are repeated episodes of biliary pain that resolve completely and often last for less than 8 h. The clinical examination may reveal a palpable gallbladder mass that would suggest a mucocoele (Fig. 4.1). Although unlikely in recurrent biliary pain, evidence of jaundice needs to be looked for.

Investigations are used to confirm the diagnosis of gallstones and determining whether there is any complication or specific pathology associated with the gallstones.

Liver Function Tests (LFT) These are used to assess the possibility of CBD stones or some degree of biliary obstruction such as Mirizzi syndrome. Normal LFT have a reasonable negative predictive value with only 3% of patients coming to cholecystectomy with normal LFT having CBD stones identified on routine operative cholangiography (OC) [37]. Elevated LFT may indicate a CBD stone, but it has been known for a long time that the sensitivity, specificity and positive predictive values of these tests are low [38, 39]. Nonetheless, it is important to assess and to discuss the possibility of CBD stones and how this would be managed when discussing LC with a patient with recurrent biliary colic.

Ultrasound Ultrasound is the best initial imaging for the investigation of gallstone disease. Most patients presenting with recurrent biliary colic due to gallstones will have either a single or multiple stones that are mobile in the gallbladder with no associated gallbladder wall thickening, pericystic fluid or duct dilatation (Fig. 4.13). The ultrasound may reveal a stone that is impacted in the gallbladder neck with or without associated sludge but with no evidence of inflammation (thickened wall, pericystic fluid or local tenderness) (Fig. 4.14). These patients with this ultrasound finding are more likely to have frequent episodes of biliary pain or developed acute cholecystitis. Alternatively, the ultrasound may reveal a mucocoele (Fig. 4.1). Other

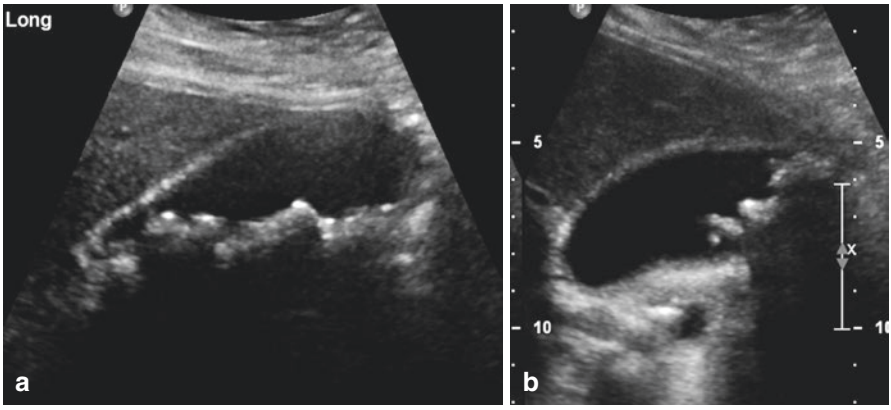

Fig. 4.13 An ultrasound in a 62-year-old woman presenting with recurrent biliary colic with five episodes in the last month. (**a**) Supine study shows multiple stones in the gallbladder. The gallbladder wall is not thickened or contracted. (**b**) Erect study reveals all the stones are mobile with no stones in the region of the gallbladder neck

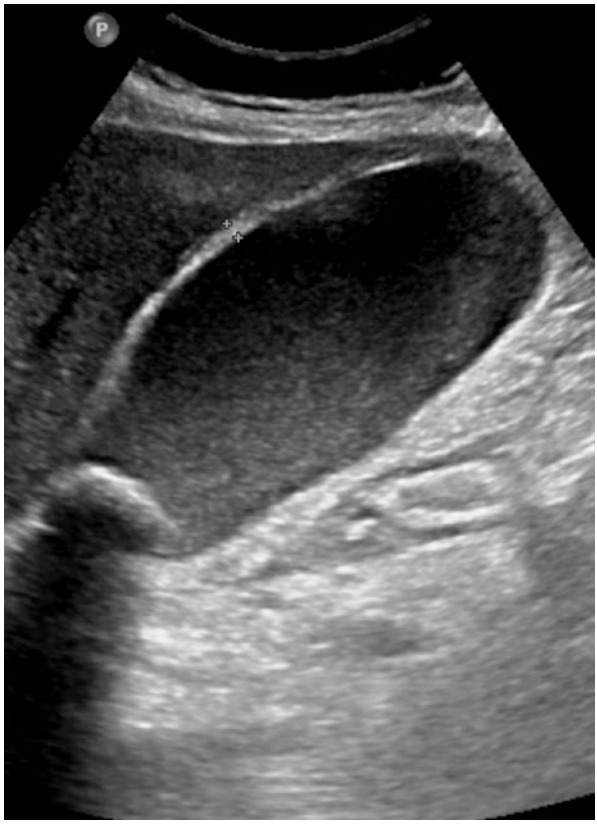

Fig. 4.14 A 28-year-old male presented with one episode of biliary colic that resolved. An ultrasound performed 10 days later revealed a stone impacted in the neck of the gallbladder, a moderate amount of sludge but a normal gallbladder wall and no focal tenderness. A similar ultrasound finding may be seen in a patient presenting with clinical acute cholecystitis

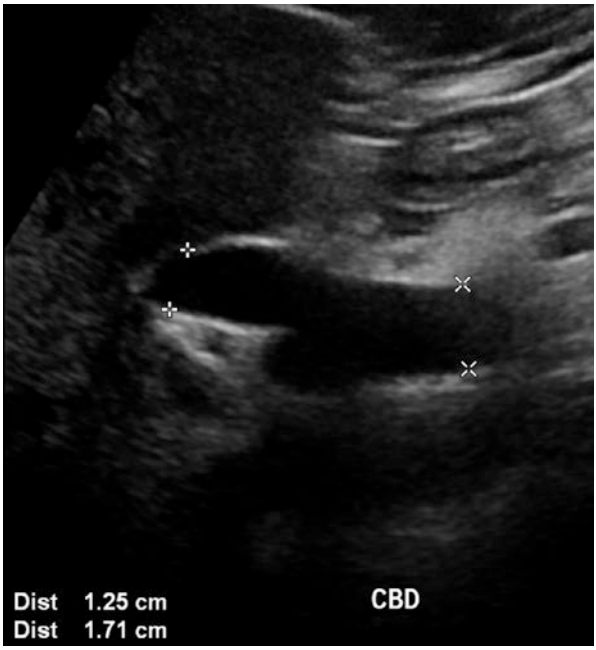

Fig. 4.15 An ultrasound in a 68-year-old woman that presented with recurrent biliary colic. Her LFT were elevated and the ultrasound revealed a dilated common bile duct of 12.5 mm. At laparoscopic cholecystectomy, the cholangiogram revealed a single 8 mm CBD stone

patients with recurrent biliary colic may have a gallbladder with a thickened wall which is contracted around the stone(s) indicating marked chronic inflammation (Fig. 4.8).

The diameter of the CBD is also relevant. A patient with a duct diameter of less than 6 mm with normal LFT is unlikely to have CBD stones. A dilated CBD (Fig. 4.15) may be associated with CBD stones. As with LFT, dilation of the CBD has a low sensitivity and specificity but is certainly associated with a higher incidence of CBD stones. Like elevated LFT, this information is used to discuss with the patient (and family) the possibility of CBD stones at LC and their management. The demonstration of a stone within the CBD on ultrasound is highly predictive of CBD stones at surgery (Fig. 4.16).

Further biliary imaging with CT cholangiography, magnetic resonance cholangio-pancreatography (MRCP) or endoscopic ultrasound are seldom required in patients presenting with recurrent biliary colic unless there is suspicion of another associated pathology (e.g. malignancy).

4.6.4 Acute Cholecystitis

Acute cholecystitis is defined as a patient presenting with typical biliary pain that persists beyond 24 h. If there is secondary bacterial infection, there may be symptoms such as fever or night sweats. Rigours would be an uncommon occurrence in acute cholecystitis and is a clinical indication that the cause of the sepsis is more likely to be cholangitis, rather than acute cholecystitis. When the pain has been

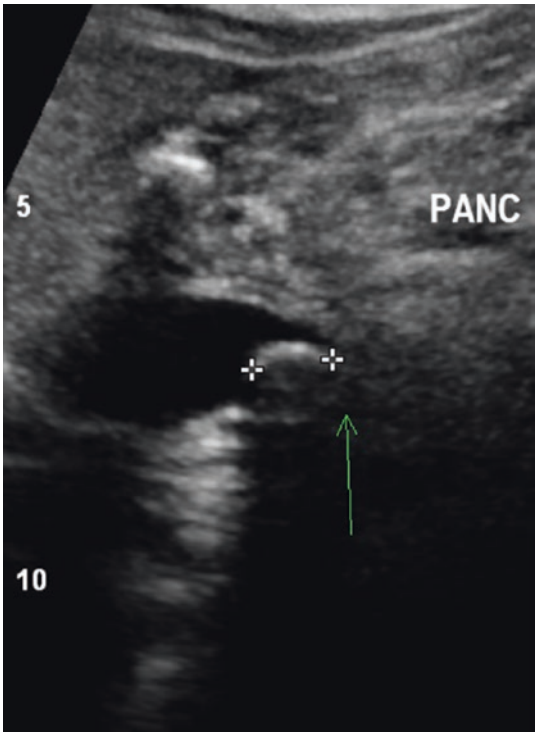

Fig. 4.16 An 88-year-old lady who presented with recurrent biliary pain and intermittent episodes of obstructive jaundice. An ultrasound revealed a stone in the distal common bile duct adjacent to the pancreas in a dilated common bile duct. The cholangiogram at LC revealed multiple CBD stones

present for over 36 h, fevers and night sweats may indicate the development of either acute gangrenous cholecystitis (Fig. 4.3a), an empyema of the gallbladder (Fig. 4.2), emphysematous cholecystitis (Fig. 4.6) or a walled-off perforation (Fig. 4.7).

Clinical examination may reveal the presence of a fever and tachycardia in the patient with associated sepsis. However, many patients with acute cholecystitis do not have secondary bacterial infection and shall be afebrile and usually not have a tachycardia.

Abdominal examination almost always reveals upper abdominal tenderness which is either localised to the right upper quadrant or more generalised. The tenderness is usually made worse with deep inspiration, when it is often incorrectly called Murphy's sign. The clinical examination may detect right upper quadrant tenderness or a positive Murphy's sign. Murphy's sign is where there is initially no pain on palpation of the right upper quadrant and then with deep inspiration the patient complains of localised pain. This is due to the inflamed gallbladder which is initially not palpable moving down with deep inspiration and coming against the palpating fingers. This would indicate an ongoing transmural inflammation and that there may be some degree of acute cholecystitis which may be either ongoing or resolving. Like recurrent biliary colic, the investigations focus on establishing the diagnosis of gallstones and the assessment of the severity of the disease.

Liver Function Tests LFT are done to assess the likelihood of CBD stones as previously discussed. A derangement of LFT may occasionally be present in patients

Fig. 4.17 The operative cholangiogram of a 42-year-old male presenting with acute cholecystitis with pain of 3-day duration. His LFT were raised with a bilirubin of 29. The ultrasound revealed multiple stones in a thick-walled gallbladder with pericholecystic fluid. There was no duct dilation. The operative cholangiogram revealed a type I Mirizzi syndrome with the stone impacted in the cystic duct compressing the common hepatic duct, and a non-dilated CBD

with severe acute cholecystitis, with severe gallbladder inflammation involving the adjacent liver. In patients with acute cholecystitis, clinically elevated liver function tests may also be associated with type I (Fig. 4.17) or type II Mirizzi syndrome.

Inflammatory Markers The main inflammatory marker used clinically in acute cholecystitis is the white cell count. Leucocytosis (greater than 15,000) indicates the likelihood of secondary bacterial infection, which despite being commonly used is seldom referred to in studies on acute cholecystitis [20, 21]. Similarly, C-reative protien (CRP) may be used but this is not a common clinical practice as it does not impact on the management of the patient.

Ultrasound This will detect the presence of gallbladder stones, and in acute cholecystitis, it will usually demonstrate a stone impacted in the neck of the gallbladder (Fig. 4.3b). Other features include thickening of the gallbladder wall, pericystic fluid (Fig. 4.18) and localised tenderness solicited by pressing the ultrasound probe over the gallbladder (‘ultrasonographic Murphy’s sign’). The presence of sludge (Fig. 4.19) may also occur in patients with acute cholecystitis but is not diagnostic of acute cholecystitis. Some patients may not have demonstrable stones but have a thickened gallbladder wall, pericystic fluid and sludge (Fig. 4.19). These patients usually have small stones obstructing the cystic duct which escape detection by ultrasound even while there are other features of acute cholecystitis.

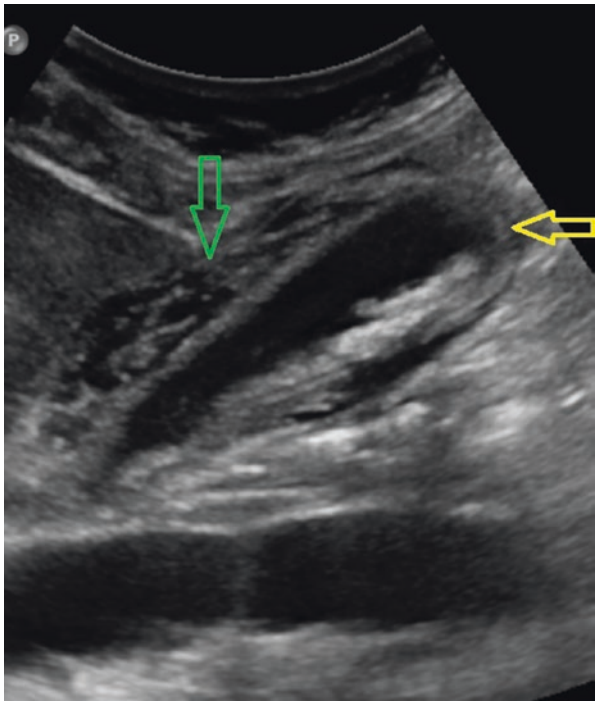

Fig. 4.18 A 22-year-old woman who was 3 months post-partum presented with 24 h of biliary pain. The ultrasound revealed multiple gallstones, marked pericystic oedema (green arrow) and a thickened fundal area (yellow arrow)

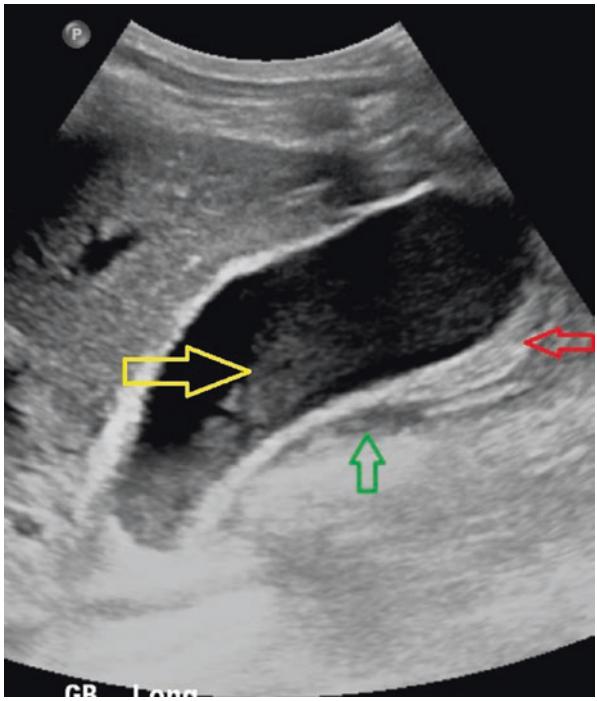

Fig. 4.19 A 50-year-old lady presenting with 4-day history of constant biliary pain. An ultrasound demonstrated a thickened oedematous gallbladder wall (red arrow) with pericystic fluid (green arrow) and a large amount of sludge (yellow arrow) within the gallbladder lumen. No stones could be demonstrated in the gallbladder. At urgent LC she had gangrenous cholecystitis with a 4 mm stone impacted in the cystic duct

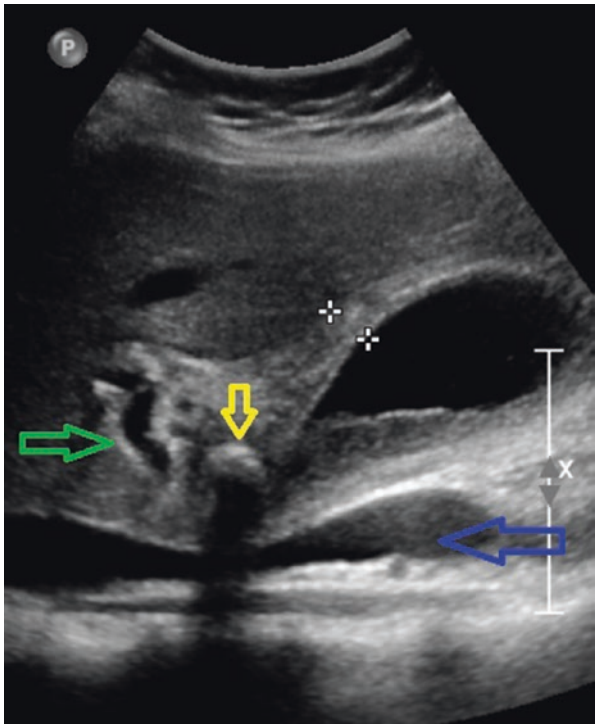

Fig. 4.20 A 28-year-old woman was 6 weeks post-partum with acute cholecystitis clinically and a mild elevation of LFT. The ultrasound demonstrated a stone impacted in the gallbladder neck/cystic duct (yellow arrow) with associated gallbladder wall oedema and sludge. The stone is close to the common hepatic duct with mild dilation (green arrow). The posterior structure (blue arrow) is the portal vein. At LC a type I Mirizzi syndrome was confirmed

In patients presenting with acute cholecystitis, the ultrasound may indicate the possibility of Mirizzi syndrome. This would be a stone impacted in the neck of the gallbladder in close proximity to the common hepatic duct with or without dilatation of the common hepatic duct and intrahepatic ducts (Fig. 4.20). While the stone may be large, this is not always the case. Such patients with this finding will invariably have elevated LFT.

4.6.5 Obstructive Jaundice

Obstructive jaundice is most often due to a stone within the CBD. The various types of Mirizzi syndrome (Fig. 4.9) may also present with obstructive jaundice. Presentation with obstructive jaundice may have an episode of prolonged pain where the pain settles but the jaundice persists for a period of time. Alternatively, obstructive jaundice may be associated with persistent pain. It is important that patients that present with pain and obstructive jaundice but do not have sepsis be considered differently from patients with cholangitis.

The clinical assessment is the same as that for biliary colic and acute cholecystitis. As gallstones and cancer can coexist, it is important to consider a malignant cause in patients presenting with obstructive jaundice. Therefore, clinical features suggestive of a malignant cause need to be considered (Table 4.6).

Table 4.6 Clinical features that may indicate a malignant cause for obstructive jaundice rather than CBD stones

Absence of biliary pain
Previous malignancy (gastrointestinal, breast, melanoma or lymphoma)
Loss of weight
Anorexia
Persistent worsening jaundice (greater than 5 days)
Recent onset diabetes
Steatorrhoea
Pruritus
Palpable gallbladder
Ascites
Sister Mary Joseph's nodule
Cervical lymphadenopathy

Laboratory Investigations LFT are key to the assessment of a patient with jaundice. An elevated alkaline phosphatase (ALP) or gamm-glutamyl transpeptidase (GGT) may indicate a more chronic obstruction. However, when the biliary obstruction is acute, the aspartate aminotransferase (AST) and alanine transaminase (ALT) may be markedly elevated (above 500) with a normal or mildly elevated ALP. This is not due to a hepatic insult, but due to the sudden acute biliary obstruction with a stone. A bilirubin over 200 ug/L is unusual in obstructive jaundice due to CBD stones and should arouse suspicion at the possibility of a malignant obstruction. Tumour markers such as Ca19-9, CEA and LDH may be assessed when considering a malignant cause. Note, however, that Ca19-9 is usually elevated in obstructive jaundice for benign causes as well as malignant causes and should be considered unreliable for the prediction of a malignant cause.

Imaging Ultrasound should confirm a diagnosis of gallstones and may also demonstrate a dilated CBD (Fig. 4.15) or stones in the CBD (Fig. 4.16). An ultrasound may also indicate the possibility of Mirizzi syndrome (Fig. 4.20). There are a series of features on ultrasound that may raise concern that the cause of the obstructive jaundice may not be a CBD stone but may be a malignancy (Table 4.7). In these circumstances the imaging with CT scan, MRCP or endoscopic ultrasound should be performed. Similarly, where there are clinical indicators (Table 4.6) that there could be a risk of malignancy, further imaging is required.

4.6.6 Cholangitis

Cholangitis is suspected clinically by the presence of either Charcot's tirad (pain, fever and jaundice) or Reynolds' pentad [40] (pain, fever, jaundice, confusion and hypotension). The clinical assessment is for acute cholecystitis and obstructive jaundice. The additional features are the evidence of sepsis and presence of systemic inflammatory response syndrome as seen in patients with acute cholecystitis.

Table 4.7 Ultrasound findings suggesting a cause other than common bile duct stones for obstructive jaundice

No stones in the gallbladder
Dilated intrahepatic ducts but no stone impacted in the neck of the gallbladder or in close proximity to the common bile duct
Mass in the gallbladder wall
Mass in the porta hepatis
Hypoechoic liver lesions
Mass in the head of the pancreas
Dilated pancreatic duct
Ascites

Laboratory investigation These include LFT as well as white blood cell count. A mandatory laboratory investigation when cholangitis is considered are blood cultures to confirm bacteraemia and aid selection of subsequent antibiotics.

Imaging Similar to acute cholecystitis or obstructive jaundice, imaging is initially with an ultrasound; although in a septic patient, CT scan may be useful to exclude other causes such as an hepatic abscess or an infected collection elsewhere in the abdominal cavity. Patients that live in or have immigrated from Southeast Asian countries presenting with cholangitis need to have the possibility of RPC considered and an MRCP [41, 42] performed in addition to an ultrasound.

The key feature in the assessment of cholangitis is to accurately diagnose and then assess the severity of the cholangitis. The Tokyo guidelines for the management of acute cholangitis and cholecystitis were first published in 2007 [43] and reviewed and updated in 2013 [44]. The diagnosis is based on the assessment of three criteria: systemic inflammation, cholestasis and imaging (Table 4.8). This allows the diagnosis to be categorised as either suspected or definite (Table 4.8). The severity of cholangitis is classified as grade I (mild), grade II (moderate) or grade III (severe) (Table 4.9). The diagnosis and severity are then used to determine the treatment which will be discussed later in this chapter.

4.6.7 Acute Biliary Pancreatitis

Acute biliary pancreatitis is discussed in detail in the chapter on acute pancreatitis. Briefly the clinical diagnosis is established by the presence of two or three criteria [45]:

1. Typical clinical picture with severe abdominal pain
2. Elevated serum lipase and/or amylase
3. Imaging (ultrasound, CT or MRI) confirming the presence of acute pancreatitis

Further assessment and investigation aim to confirm the diagnosis of biliary cause and assess the severity of pancreatitis.

Table 4.8 Criteria for the diagnosis of cholangitis [44]

A	*Systemic inflammation*
A-1	Fever and/or rigours
A-2	Laboratory data; evidence of inflammatory response (leucocytosis, elevated CRP)
B	*Cholestasis*
B-1	Clinical obstructive jaundice
B-2	Laboratory data; abnormal LFT
C	*Imaging*
C-1	CBD dilatation
C-2	Evidence of the aetiology on imaging (stricture, stone, stent, etc.)

Suspected diagnosis	One item in A + one item in either B or C
Definite diagnosis	One item in A, one item in B and one item in C

Table 4.9 Grading of severity of cholangitis [44]

Grade I (mild) acute cholangitis	
Grade I acute cholangitis does not meet the criteria of either grade II or grade III cholangitis at initial diagnosis	
Grade II (moderate) acute cholangitis	
Grade II acute cholangitis is associated with any two of the following conditions:	
• Abnormal white cell count (greater than 12,000/mm^3, less than 4000/mm^3)	
• High fever (greater than 39 °C)	
• Age (greater than 75 years)	
• Hyperbilirubinaemia (bilirubin greater than 100)	
• Hypoalbuminaemia (less than 30)	
Grade III (severe) acute cholangitis	
Grade III acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction in at least one of any of the following organs/systems:	
• Cardiovascular dysfunction	Hypotension requiring dopamine greater than 5 ug/kg/min or any dose of noradrenaline
• Neurological dysfunction	Disturbance of consciousness/reduced consciousness
• Respiratory dysfunction	Pa02/Fi02 ratio greater than 300
• Renal dysfunction	Oliguria, serum creatinine greater than 200
• Hepatic dysfunction	INR greater than 1.5
• Haematological dysfunction	Platelet count less than 100,000/mm^3

4.7 Treatment

The current mainstream treatment for symptomatic gallbladder stones is laparoscopic cholecystectomy (LC). Detailed technical aspects of the operation have been described in the literature [46–48]. The avoidance of bile leak and CBD injury are essential, and the key points for the operation address the following:

1. Division of the peritoneum over the gallbladder infundibulum on both the right and left sides of the gallbladder (Fig. 4.21a,b) [46, 48].
2. Dissection of the gallbladder off the cystic plate of the liver and dissecting the superior portion of Calot's triangle prior to any attempt to dissect out the inferior portion of Calot's triangle (Fig. 4.21c,d) [46, 48].
3. Careful dissection of the fibro-fatty tissue in Calot's triangle to identify the cystic duct and cystic artery (Fig. 4.21e). If in doubt, the junction between the cystic duct and common duct should be displayed [47, 48].
4. Demonstration of the 'critical view of safety' as defined by Strasberg [47] (Fig. 4.21f).

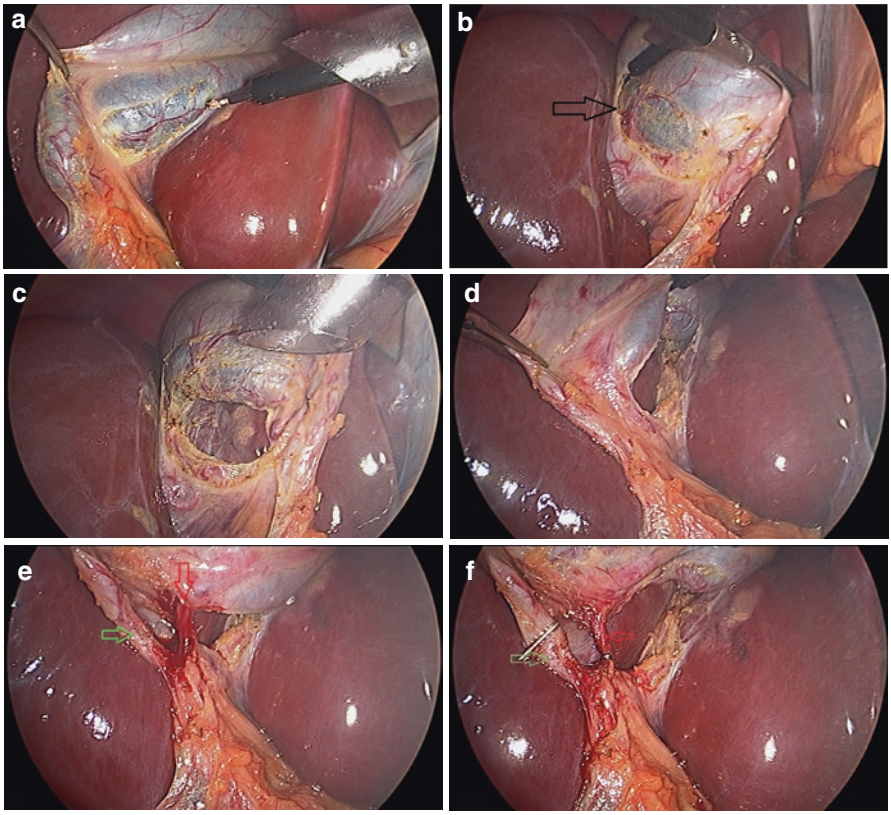

Fig. 4.21 (**a**) Dissection of the peritoneum on the left and (**b**) subsequently on the right side of the gallbladder. This exposes the lower aspect of the cystic plate (arrow). (**c**) Dissection of the gallbladder off the lower portion of the cystic plate from the lateral side of the gallbladder opening the superior part of the Calot's triangle. (**d**) Medial side of the gallbladder demonstrating the dissection of the gallbladder off the cystic plate and dissection of the superior part of Calot's triangle. Note that the cystic duct and cystic artery have not yet been dissected. (**e**) After the dissection of the fatty tissue away from the distal gallbladder, the cystic duct (green arrow) and artery (red arrow) are clearly demonstrated. (**f**) The critical view [47] is achieved with the gallbladder off the cystic plate, and the only two structures going to the gallbladder are the cystic artery (red arrow) and cystic duct (green arrow)

Where the inflammation is severe and prevents the safe dissection of the lower portion of the Calot's triangle, the distal gallbladder that has been mobilised off the lower portion of the cystic plate of the liver can be safely transected (Fig. 4.28a), the stones removed and, if the dissection cannot be continued, the distal stump of the gallbladder be left in situ [49–51]. Any subsequent bile leak can be managed expectantly [50] (Sect. 4.8.2 Bile Leak).

Early in the laparoscopic era, some surgeons were advocating a fundus-down approach as a safe dissection technique for the difficult inflamed gallbladder based on the open surgery fundus-down technique [52]. However, the laparoscopic 'fundus-down' technique is dangerous with a strong association of extreme vasculobiliary injuries reported by Strasberg and Gouma [53]. This occurs due to the lack of retraction of the fundus over the liver that significantly changes the orientation of the tissues compared to that normally obtained. Further to this, the associated inflammation and poor orientation obscure the distal edge of the cystic plate as the dissection descends on the gallbladder and results in the dissection continuing along the liver down to the right portal structures, rather than staying on the gallbladder wall at the commencement of Calot's triangle [53].

The role for routine intraoperative cholangiography (OC) is debated. Good dissection technique and accurate recognition of key structures is most important in avoiding CBD injury [47, 48]. The literature is not particularly helpful in determining the value of OC in reducing the risk of CBD injury because the studies are of poor quality. However, there is good evidence to suggest that the performance and correct interpretation of routine OC may result in early detection of the CBD injury, reducing the extent of the injury and preventing resection of the duct complex. Studies using large databases have demonstrated that the performance of OC is associated with a significant reduction in the incidence and severity of CBD injury [54–58]. Another advantage of routine OC is that it will detect 3% of CBD stones that are unsuspected at the time of LC. Clearly, OC will also detect stones that are anticipated or suspected on the basis of preoperative assessments. Having detected these stones, the OC will then allow for specific treatment and removal of these stones (see later). Finally, the routine use of OC to assess the biliary tree is useful when managing post-operative complications such as bile leaks or jaundice and in patients who present sometime later with recurrent symptoms.

The correct interpretation of the OC is important. All intrahepatic ducts should be displayed, the relationship of the cystic duct to the common hepatic duct identified, CBD diameter measured, a normal tapering of the distal CBD with the absence of any filling defects with free flow of contrast into the duodenum (Fig. 4.22).

4.7.1 Asymptomatic Gallstones

The incidence with patients presenting with asymptomatic gallstones seems to be increasing with increased used of various forms of cross-sectional imaging to assess various abdominal symptoms. Therefore, patients presenting with asymptomatic gallstones is a distinct clinical entity. The natural history of truly asymptomatic

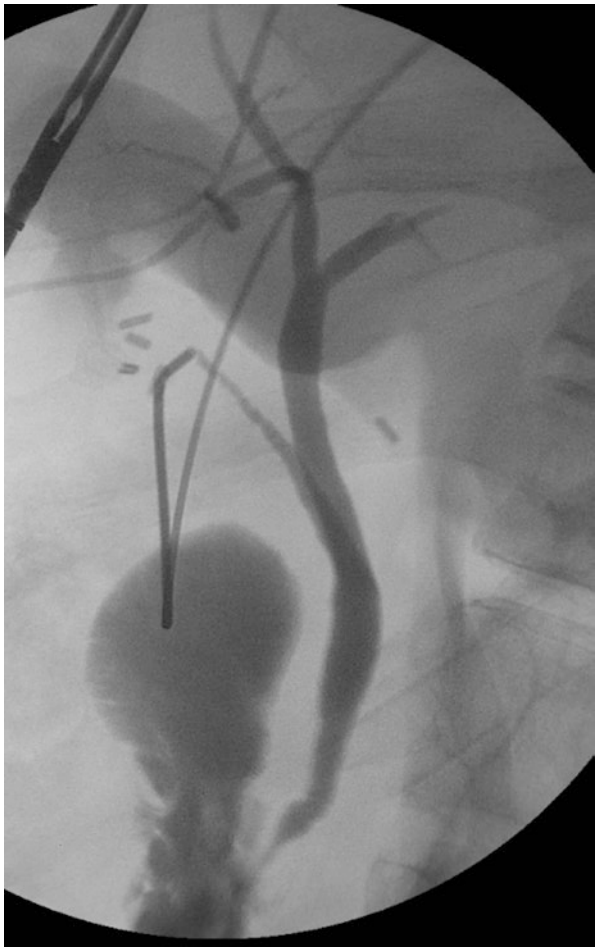

Fig. 4.22 A normal operative cholangiogram. All the intrahepatic ducts are seen, the cystic duct/CHD junction is clearly identified and the CBD is well displayed with no filling defects, a tapered distal end and free flow of contrast into the duodenum. Note there are no instruments across the field to obstruct the view of the bile duct of the biliary tree

gallstones (no biliary pain) is that only 1–2% of patients shall develop symptoms (attacks of biliary pain or complications) each year [13, 14] and that the majority of adults with asymptomatic gallstones shall remain asymptomatic throughout their lives [12]. Using decision analysis techniques to assess the effect prophylactic cholecystectomy compared to nonoperative management, there was a prediction of higher costs (four times) and greater morbidity and mortality if prophylactic cholecystectomy was performed [59]. Two sets of evidence-based guidelines from the Association of Upper Gastrointestinal Surgeons (AUGIS) and the UK National Institution for Health and Care Excellence (NICE) both recommend that patients with asymptomatic gallstones be reassured of the low risk of the development of symptoms and complications and that they should not undergo LC [60, 61]. Therefore, patients with asymptomatic gallstones, that is, gallstones and no episodes of biliary pain, should not proceed to LC.

Patients with other gastrointestinal symptoms (Table 4.5) but no biliary pain need careful consideration but on balance should not proceed to LC. This is due to

the low success rate of resolution of these symptoms after cholecystectomy [27, 36, 62, 63].

An exception for operating on asymptomatic gallstones (no biliary pain) would be in patients who have episodic nausea as their dominant symptom. Patients with episodic nausea and little or no other gastrointestinal symptoms are twice as likely to benefit from LC compared to patients with a spectrum of other gastrointestinal symptoms [64]. In a Dutch meta-analysis, intermittent nausea was seen to resolve in 70% of patients coming to LC where they did not have pain [65]. It is, therefore, reasonable in patients who present with no biliary pain, gallstones and a dominant symptom of intermittent nausea to consider a LC after exclusion of other possible causes for the nausea, including upper gastrointestinal functional disorders such as gastroparesis.

A rare indication in Western counties for LC with asymptomatic gallstones is in a patient identified as being a carrier of *Salmonella typhi*. This is due to the carriage of the *S. typhi* in the gallbladder bile in association with the gallstones and is best managed with LC.

4.7.2 Asymptomatic Gallbladder Polyps

As the majority of gallbladder polyps are non-neoplastic [29], most asymptomatic gallbladder polyps do not require LC. Although less than 5% are neoplastic, the ultrasound has a low accuracy (<20%) for distinguishing between neoplastic and non-neoplastic polyps [66]. Size of less than 10 mm is a very reliable predictor of a benign polyp [67, 68]. As CT scan, MRI and PET all have low predictive values for malignant polyps [69, 70], the common recommendation is to perform LC on asymptomatic polys 10 mm or greater in size on ultrasound [67, 68, 70, 71].

4.7.3 Recurrent Biliary Pain (Colic)

Once gallstones become symptomatic with episodes of biliary pain, LC is recommended. There is only one randomised controlled trial (RCT) in patients with recurrent biliary pain comparing surgery to an observation group, with a 14-year follow-up period [72]. This study reported that in the observational group, 14% of patients developed a significant biliary complication (cholecystitis 9%, complications related to common bile duct stones 4% and biliary pancreatitis 1%). A further 14% developed frequent episodes of biliary colic that resulted in surgical intervention [72]. Although 72% did not require surgery during this 14-year period, there were no reliable predictive factors to determine which patients would develop complications or frequent recurrent pain or which patients would not require surgical intervention. Another longitudinal study of nonoperative observation demonstrated that a 52% of patients with a single episode of biliary colic had no further problems over a 10-year follow-up [10]. Once again there was no single or combination of factors that predicted which patients would go on to develop complications or recurrent biliary pain.

Although there is some evidence to support a nonoperative, observational approach, the UK NICE guidelines recommend that 'laparoscopic cholecystectomy should be offered to patients with symptomatic gallstones' [73]. This is a recommendation based on the balance between a low but definite risk of patients having either recurrent biliary pain or developing a significant complication against the low risk of LC in an elective setting with good outcomes for the cessation of biliary pain (ranging from 92 to 96%) [62, 74, 75]. Although there is no published data, the clinical impression is that most patients with biliary colic would not agree to proceed with nonoperative treatment given the good outcomes associated with LC. Therefore, patients presenting with a single episode of biliary colic can be offered the option of an observational strategy with the provision of the risks and benefits as outlined above. Patients with recurrent episodes of biliary colic should be offered LC.

4.7.4 Acute Cholecystitis

During the open cholecystectomy era, three randomised controlled trials (RCTs) that demonstrated early or urgent open cholecystectomy at the time of clinical presentation had improved outcomes compared with nonoperative management and subsequent delayed surgery at 3 months [76–78]. In these studies, there was a reduced hospital stay, but no associated increase in morbidity or mortality when performing urgent open cholecystectomy. Furthermore, 35% of patients managed nonoperatively were readmitted with further complications of their gallstones prior to their planned elective surgery.

At the commencement of the laparoscopic era in the early 1990s, acute cholecystitis was considered a relative contraindication to LC [79–81]. This was largely based on concerns of an increased risk of bile leak or bile duct injury due to the more difficult dissection in the acutely inflamed state. There were also concerns about increased morbidity and mortality associated with an increased conversion rate in acute cholecystitis [82–84]. This has not proved to be the case with those units that did perform urgent LC for acute cholecystitis with no incidence of CBD injury and a similar incidence of bile leak (0.5–3%) compared to open cholecystectomy for acute cholecystitis [46, 85–87]. In the early experience with LC for acute cholecystitis, the conversion rate was dependent on the severity of the disease: mucocoele (10%), acute cholecystitis (22%), gangrenous cholecystitis (50%) and empyema (87%) [46]. In the last two decades with an increased experience in the technical challenges associated with LC for acute cholecystitis, the conversion rate for all comers with acute cholecystitis ranges between 4.5 and 13.4% [20, 21, 88].

There have been many RCTs comparing early to delayed LC for patients presenting with acute cholecystitis. The majority of these studies have revealed that there is a reduced total hospital stay associated with early LC and that there is no increase in morbidity or mortality. A recent meta-analysis of RCT examined 1548 patients and confirmed that there is a reduced length of stay and demonstrated a tendency towards reduced morbidity in the early LC group [21]. Another recent meta-analysis

Table 4.10 Outcomes of meta-analysis of case controlled studies comparing urgent/early cholecystectomy versus delayed cholecystectomy in patients presenting with acute cholecystitis [22]

	OR (95% CL)	*p* value
Mortality	0.46 (0.33–0.62)	Less than 0.001
Total complications	0.59 (0.50–0.69)	Less than 0.001
CBD injury	0.49 (0.33–0.73)	Less than 0.001
Bile leak	0.51 (0.32–0.8)	Equals 0.001
Wound infection	0.52 (0.35–0.78)	Less than 0.001
Conversion to open	0.66 (0.53–0.81)	Less than 0.001

looking at case-controlled studies examined 40,910 patients revealing a clear benefit with respect to biliary morbidity, general morbidity and mortality when laparoscopic cholecystectomy was performed as an urgent procedure compared to initial nonoperative management and subsequent delayed LC [22]. Furthermore, the conversion rate in the early laparoscopic group was significantly less, and the average length of stay was less than half for the delayed groups (Table 4.10). These results provide clear evidence that where a patient is fit for surgery the best management is an urgent LC.

Percutaneous cholecystostomy using ultrasound or CT guidance has a role in patients with acute cholecystitis that are not fit for a general anaesthetic or surgery. Percutaneous cholecystostomy is successful in resolving the episode of acute cholecystitis in up to 97.5% of cases [89] with a low risk of bile leak (3–6%) when performed transhepatically [90] and a low risk of bleeding (3.3%) [91]. Although drain dislodgement has been reported to be as high as 27% [92], most series have a much lower incidence.

There are three broad categories of patients that may require a percutaneous cholecystostomy rather than proceed to an urgent LC:

1. Acute calculous cholecystitis in a patient who is not currently fit for surgery but may be fit in the future, for example, a patient who has had a myocardial infarction or cerebrovascular accident within the last 6 weeks. In these patients, there is a significant anaesthetic risk that is reduced in 2–4 months' time. These patients may be managed initially with a percutaneous cholecystostomy and consideration given to a delayed LC once their anaesthetic risk is reduced.
2. Acute calculous cholecystitis in someone with multiple comorbidities that shall never be fit for surgery.
3. Acute acalculous cholecystitis in a critically ill patient from another cause (e.g. severe multi-trauma) currently not fit for surgery.

In these scenarios the success rate of percutaneous drainage is high. The drains can be left in for up to 6 weeks for a tract to mature. A percutaneous cholecystogram may help to determine the subsequent management plan with a patent cystic duct having a 21% risk of recurrent acute cholecystitis compared to 36.7% when the cystic duct is occluded [93]. Although delayed LC can be performed, as expected, these are more difficult operations as the gallbladder is often contracted and fibrotic with conversion rates between 23 and 45% [94, 95]. Balancing against this is the risk of recurrent acute cholecystitis or another biliary complication after catheter

removal which ranges from 23% at the 3-month mark up to 49% at 1 year [96]. Apart from a patent cystic duct, there are no other predictive factors for recurrent disease. Therefore, the decision to proceed with an interval LC following an episode of acute calculous cholecystitis treated with a percutaneous cholecystostomy is a balance of risks with no clear decision algorithm available to help in the decision-making process.

Acalculous cholecystitis on the other hand has a much lower incidence of recurrence after removal of the drain (3–14%) [97, 98]. Therefore, in patients with acute acalculous cholecystitis that have a very high operative risk, an initial percutaneous cholecystostomy to resolve the acute cholecystitis and subsequent cholangiogram and removal of the drain with no interval LC is appropriate in the majority of these patients.

4.7.5 Patients at High Risk of Common Bile Duct (CBD) Stone

During the laparoscopic era, there has been debate about the management of patients with a high risk of having common bile duct stones. These patients will have some of the criteria described previously and outlined in Table 4.11. These patients may have presented with recurrent biliary colic, acute cholecystitis, jaundice, mild cholangitis or a recent episode of biliary pancreatitis. The debate largely centres around three options: [1] whether endoscopic clearance of a suspected CBD stone prior to LC should be performed or [2] whether the patient should proceed directly to a LC and subsequent management of stones found at OC at that time or [3] whether the duct is cleared by post-operative ERCP.

Preoperative endoscopic clearance sounds appealing by making the subsequent LC less complicated. However, a meta-analysis comparing preoperative ERCP to initial LC and duct clearance clearly demonstrates that preoperative ERCP and subsequent LC is associated with a higher overall morbidity and an increased mortality. This is in part related to having two separate procedures, with complications being additive. An LC after an ERCP is also associated with an increased conversion rate to open surgery compared to performing the LC as the initial procedure [99]. Therefore, the data indicates that patients with possible CBD stones should proceed directly to a LC and OC and bile duct exploration if indicated. One important provision is that the expertise is available for laparoscopic bile duct exploration, and this is often not as readily available as those with endoscopic (ERCP) expertise. Patients with concomitant cholangitis will require urgent endoscopic bile drainage, if not stone clearance (see Sect. 4.7.6).

Table 4.11 Preoperative risk factors for CBD stones

Recent history of jaundice
Recent history of biliary pancreatitis
Elevated bilirubin
Elevated ALP and/or GGT
Elevated AST and ALT
Dilated (>6 mm) CBD on ultrasound
Stone in the CBD on ultrasound

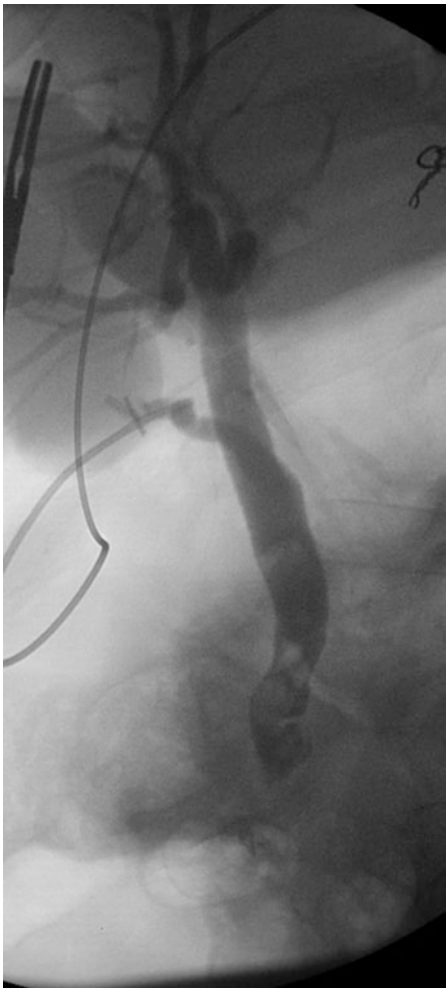

Fig. 4.23 An OC in a 51-year-old man with recurrent biliary colic. The preoperative LFT had a raised AST and ALT during an episode of pain, and the CBD was slightly dilated at 7 mm. At OC there were multiple irregular filling defects in the distal CBD with no flow of contrast into the duodenum and a loss of the tapered distal end of the CBD (compare with Fig. 4.22)

4.7.6 Managment of CBD stones

The next debate concerns the management of the common bile duct stone detected on OC at LC (Fig. 4.23). The options are summarised in Table 4.12.

4.7.6.1 *Sphincter of Oddi (SO) Relaxation and Flushing*

Relaxation of the sphincter of Oddi (SO) with either Buscopan (20 mg IV) or glucagon (1 unit IV) and flushing the CBD via the cholangiogram catheter with saline and then repeating the cholangiogram to check clearance is a technique associated with a success rate of 5–15% [100, 101]. Those cases where it is successful are invariably small stones impacted in the tapered part of the bile duct, or where there is a tapering but no flow. Where there are multiple stones, large stones or stones not impacted in the distal CBD (Figs. 4.23 and 4.24), it is unlikely to be successful. Another technique with a distal stone impacted in the taper of the ampulla is to pass the cholangiogram catheter down the CBD and push the stone into the duodenum. The difficulty

Table 4.12 Options for the management of stones found at operative cholangiography during laparoscopic cholecystectomy

Sphincter of Oddi relaxation and flushing
Transcystic duct exploration
Laparoscopic choledochotomy and common bile duct exploration
Conversion to open surgery for open choledochotomy and CBD exploration
Transcystic biliary stent to facilitate post-operative ERCP
Closure to the cystic duct without inserting a stent and proceeding to post-operative ERCP

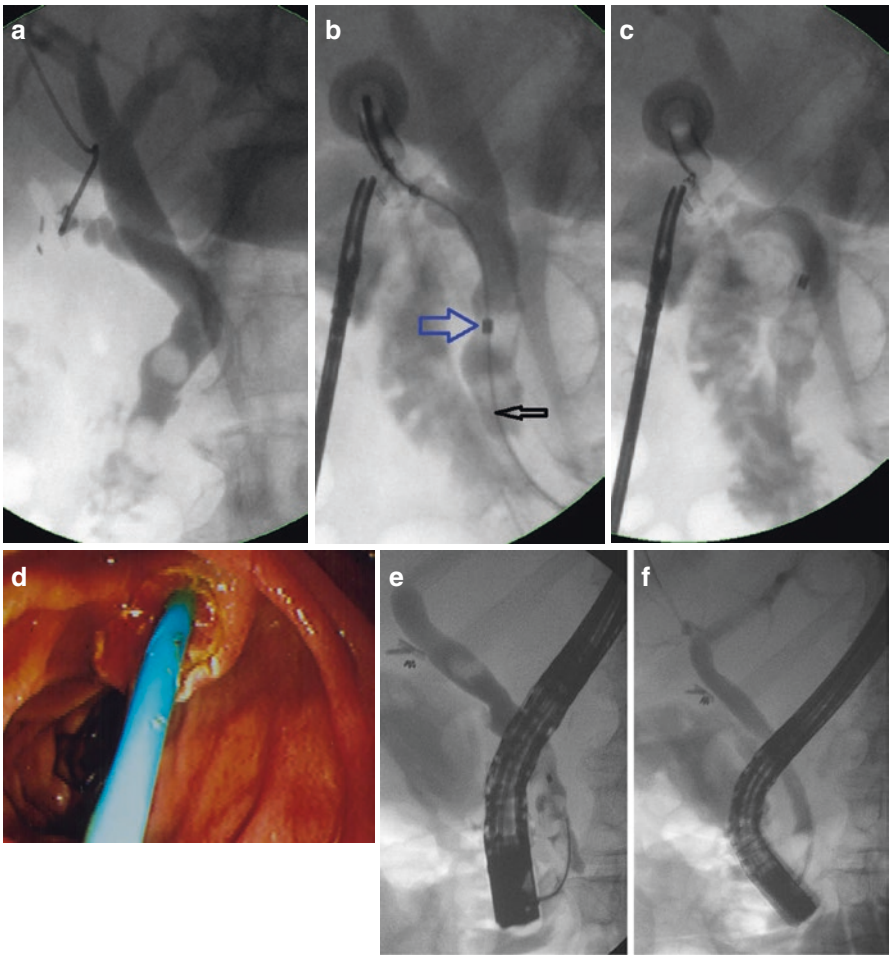

Fig. 4.24 A 64-year-old woman presented with mild (grade I) cholangitis that settled quickly with IV antibiotics. She proceeded to LC 2 days after admission. (**a**) OC demonstrated multiple CBD stones in a dilated (9–10 mm) CBD. (**b**) A wire is passed through the catheter into the duodenum (black arrow) and a 7 Fr. stent deployed (blue arrow) over the wire to lie across the sphincter of Oddi. (**c**) Final position of the transcystic stent with the distal end in the duodenal lumen. (**d**) Endoscopic view of the complete ES over the transcystic stent prior to the removal of a stent with a snare. (**e**) Initial cholangiogram demonstrating the multiple stones. (**f**) The CBD cleared after repeated balloon trawls

with either technique is the possible overlooking of a small stone in the distal CBD on the repeat cholangiogram, the incidence of which has not been assessed in the literature. Any such follow-up studies would need to have at least a 5-year follow-up as the median time for a retained CBD stone to present post LC in 4 years [35].

Laparoscopic transcystic exploration has the advantage of avoiding a choledochotomy or endoscopic sphincterotomy. It has a clearance rate of between 57 and 75% [102, 103]. Failure is usually due to technical issues and/or difficulties in visualising the stone and/or in securing the stone (especially in the CHD and in the liver). When laparoscopic transcystic exploration is unsuccessful, a step-up approach can be considered [103]. *A laparoscopic choledochotomy* when there is a dilated common bile duct (8 mm or greater) will allow a more traditional approach to common bile duct exploration. Once the duct is cleared via the choledochotomy, it is closed either directly or over a T-tube. The former is favoured, especially in the presence of an endoscopic sphincterotomy. Alternatively, the placement of a stent across the ampulla can be readily achieved when transcystic duct extraction fails, and this will facilitate post-operative ERCP, increasing the success rate and reducing the risk of ERCP-associated pancreatitis [100].

Laparoscopic choledochotomy is associated with a higher morbidity including bile leaks and strictures than cases not requiring choledochotomy [103]. A post-operative ERCP in these more difficult cases may involve a separate procedure, but it is associated with a much lower morbidity [100]. A meta-analysis comparing laparoscopic duct exploration to post-operative ERCP could not demonstrate at any statistical difference in outcomes between either approach [99]. However, there is no data to answer the question about whether choledochotomy or transcystic stent is superior after failed transcystic exploration. Therefore, without a direct comparison between laparoscopic choledochotomy and post-operative ERCP, it is difficult to provide an evidence-based approach. However, the increased complexity of performing a laparoscopic choledochotomy with the associated higher morbidity may favour a transcystic stenting and post-operative ERCP.

An alternative strategy to laparoscopic duct exploration via the transcystic approach is to insert a transcystic stent in all patients with common bile duct stones and performing a post-operative ERCP and sphincterotomy in all of these patients with OC-confirmed CBD stones [100] (Fig. 4.24).

In the past, laparoscopic choledochotomy was favoured for very large stones in large dilated ducts, as these large stones were felt to be inappropriate for endoscopic technique. This is no longer as relevant with the availability of techniques such as endoscopic mechanical or laser lithotripsy. During the open era it was felt that such patients required a ‘drainage procedure’ with a choledoch-duodenostomy or hepatico-jejunostomy. This is now considered unnecessary especially in the context of a sphincterotomy which also provides adequate biliary drainage avoiding the need for the biliary bypass.

4.7.7 Cholangitis

The diagnostic criteria and severity of grading have been previously outlined (Sect. 4.6.6, Tables 4.8 and 4.9). Patients with grade III cholangitis should proceed to an urgent biliary drainage. This is usually by an ERCP with sphincterotomy,

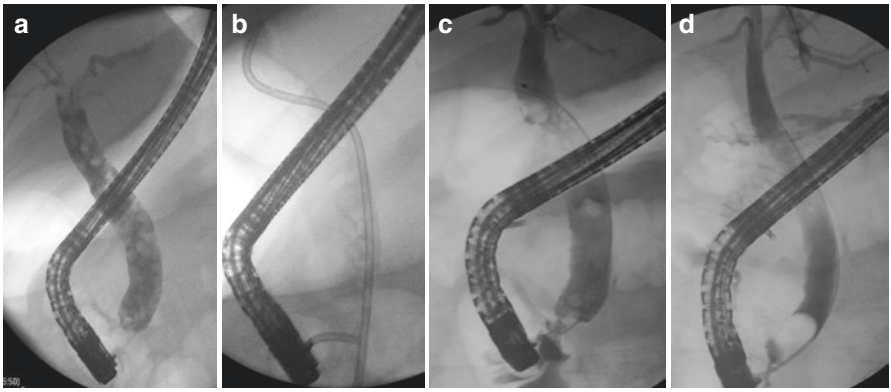

Fig. 4.25 An elderly man presented with grade III cholangitis 25 years after an open cholecystectomy. This was managed with an urgent ERCP. (**a**) The initial ERCP revealed multiple stones in a dilated CBD. (**b**) An ES was performed and some of the stones removed. However, due to being severely septic with hypotension, a stent was deployed to drain the CBD. He was returned to the ICU for ongoing care. (**c**) A repeat ERCP was performed 8 weeks later when fully recovered. The stent was removed and the cholangiogram revealed some residual stones as expected. (**d**) These stones were cleared with repeated balloon trawls

removal of the stones (if possible) and biliary stenting (Fig. 4.25). In patients with a gallbladder still *in situ*, once the cholangitis and sepsis have resolved and the patient is fit for surgery, they should proceed to an early LC, as many of these patients will have associated acute cholecystitis as the ascending infection also involves the gallbladder. Similar to the management of acute cholecystitis, a delayed LC is associated with a much more difficult dissection and, like acute cholecystitis, a higher risk of conversion, biliary morbidity, overall morbidity and presumably mortality [104].

In patients with the gallbladder *in situ* grade I or grade II cholangitis which resolves quickly with nonoperative management, rather than doing an ERCP, these patients should proceed to early LC (within 24–48 h) and any stones in the bile duct managed as described above. Patients having had a previous cholecystectomy that present with grade I or grade II cholangitis should proceed to an early ERCP.

For patients that present with grade I or grade II cholangitis with no prior cholecystectomy that have multiple comorbidities, are frail or are extremely old, it may be reasonable to consider not proceeding to LC and managing the CBD stones with an ERCP and sphincterotomy alone. This is a viable option as there is some evidence that future complications in this group of patients where the CBD stones are managed endoscopically are unlikely to occur during their life [105]. However, the risk is that if they do develop acute cholecystitis, it shall be severe due to the pre-existing contamination of the biliary tree. This decision whether or not to proceed with cholecystectomy in this group of patients requires a careful, considered discussion with the patient and their family.

4.7.8 Mirizzi Syndrome

The treatment of Mirizzi syndrome is dependent on the type (Fig. 4.9) which is determined by the preoperative imaging [24].

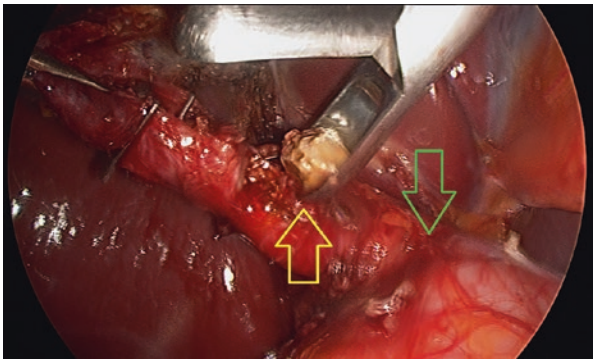

Fig. 4.26 A 69-year-old woman with acute cholecystitis and mild jaundice (bilirubin = 50) was managed with an urgent LC. The cystic duct was dissected and the cystic duct/common hepatic junction noted (green arrow). A 9 mm stone was milked out of the cystic duct and removed with forceps (yellow arrow). The operative cholangiogram was then performed through the hole and this was normal

Type I: This is when the gallstone is impacted in the cystic duct or the neck of the gallbladder (Figs. 4.9 and 4.17). In these patients, it is safe to proceed with LC with careful dissection, being sure to dissect the gallbladder off the cystic plate and dissecting down the cystic duct to obtain the critical view of safety (Fig. 4.21e, f). This may be a difficult dissection due to acute and/or chronic inflammation. Occasionally the stone can be milked out of the cystic duct (Fig. 4.26). More often the stone is impacted at the junction of the cystic duct and the common hepatic duct (Figs. 4.17 and 4.27a) and cannot be milked back into the gallbladder. Dissection down along the cystic duct onto the stone may be performed provided there is a clear margin between the stone and the junction of the cystic duct and common hepatic duct. Where this is no possible conversion, an open surgery may be considered. Another option to manage these difficult cases is transcystic stenting to facilitate post-operative ERCP being performed (Fig. 4.27b). This is certainly appropriate as many of these stones will move into the common hepatic duct allowing withdrawal at the time of ERCP. Stones that do not migrate distally or remain impacted can be managed with endoscopic laser lithotripsy. This combined laparoscopic and endoscopic approach avoids open surgery.

Type II: Here the stone has dilated the cystic duct and is wedged into the common hepatic duct but with no destruction of the duct wall or mucosa (Fig. 4.9). These can be associated with a fibrotic contracted gallbladder. In these situations, the patient can be managed by dissecting down onto the fundus, opening the fundus of the contracted gallbladder, extracting the stone, performing a cholangiogram to demonstrate there are no further stones and then simply closing the fundus, after removing any redundancy. Patients with type II Mirizzi may also present with acute cholecystitis and a distended gallbladder. In these cases, the LC may be attempted by an experienced surgeon. The gallbladder can then be transected distally after the gallbladder has been dissected off the liver. This then allows further dissection down the neck of the gallbladder to then remove the stone. If

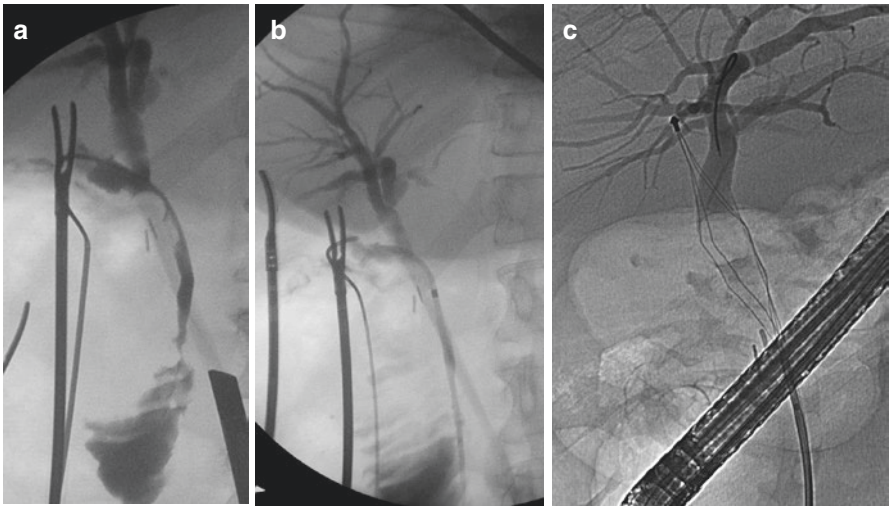

Fig. 4.27 A 58-year-old man with Childs-Pugh A cirrhosis due to hepatitis C presented with acute cholecystitis and raised bilirubin. An ultrasound confirmed multiple gallbladder stones. (**a**) Operative cholangiogram revealed a stone still in the cystic duct or at the junction of the cystic duct and common hepatic duct. The common bile duct had not yet dilated. This stone was not able to be milked out of the cystic duct. Consideration to opening down the cystic duct was given, but decided against due to the concerns about possible bleeding, common bile duct injury and possible vascular injury. (**b**) A transcystic stent was inserted and the cholecystectomy completed. (**c**) An ERCP 4 weeks later found the stone in the common hepatic duct with a still non-dilated common bile duct. The stone was pushed proximally, captured in a lithotripsy basket, crushed and the fragments removed. Had this been unsuccessful an alternative technique would have been endoscopic laser lithotripsy

there is sufficient length on the cystic duct, it can be closed with an endoloop or intra-corporeal suturing. If there is a side hole in the cystic duct and insufficient length, this can be confirmed by inspection and OC; a retrograde biliary stent may be inserted to ensure distal drainage (to reduce biliary pressures and the risk of a leak) and the side hole be closed with sutures (Fig. 4.28).

Types III and IV: Patients with type III or IV Mirizzi syndrome usually present with obstructive jaundice and/or cholangitis. Early imaging with ultrasound will often confirm a contracted gallbladder with a large stone and dilated intrahepatic ducts raising the strong possibility of Mirizzi syndrome. In this clinical setting it is mandatory to obtain more accurate biliary imaging to confirm Mirizzi type III or IV and to plan subsequent treatment. This imaging may be an ERCP where there is associated cholangitis that requires biliary drainage (Fig. 4.9). This would allow confirmation of the diagnosis and treatment of the cholangitis with an endoscopic biliary stent. On the rare occasion that ERCP is not successful, this could be achieved with percutaneous transhepatic cholangiography. In the absence of cholangitis, MRCP usually provides the information required to manage these patients. Type III and type IV Mirizzi syndrome are associated with significant destruction of the common bile duct wall and as such usually require open resection of the distal bile duct and gallbladder and a reconstruction with a hepatico-jejunostomy.

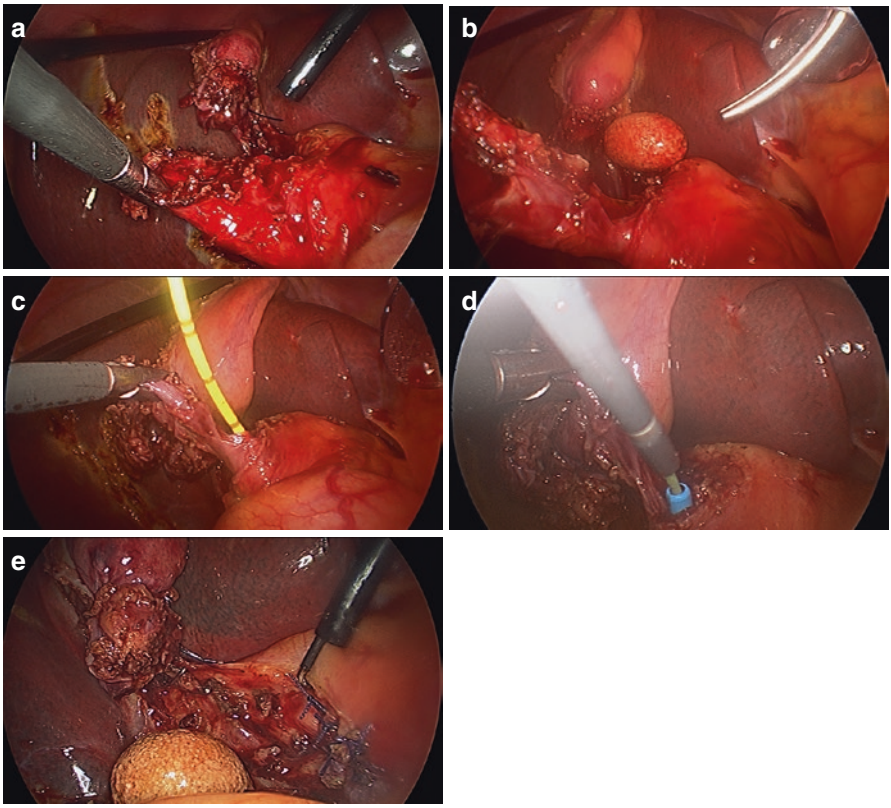

Fig. 4.28 A 36-year-old woman with acute cholecystitis, jaundice and an ultrasound revealing a possible Mirizzi with a stone impacting in the neck of a distended, thick-walled gallbladder close to the common hepatic duct. (**a**) After the gallbladder was dissected off the cystic plate of the liver, it was transected to facilitate more distal dissection. (**b**) The neck of the gallbladder was carefully dissected and opened over the stone away from the common hepatic duct, and the stone removed. (**c**) Operative cholangiogram confirmed the anatomy and that the opening was at the cystic duct/common hepatic duct junction. (**d**) Retrograde stent was inserted across the sphincter of Oddi. (**e**) The side hole was then sutured, post-operatively well with no bile duct, the stent was removed 4 weeks later revealing a normal cholangiogram. Note the diathermy hook is being used only to retract the tissue for better exposure.

4.7.9 Gallstone Ileus

Patients presenting with gallstone ileus (Fig. 4.11) are usually elderly and present with a distal small bowel obstruction (Sect. 4.5.2.3).

The management of gallstone ileus is a laparotomy and enterotomy removal of the obstructing stone and closure of the enterotomy. Occasionally a small bowel resection is required if there is ischaemia and/or perforation associated with the mechanical pressure from the obstructing stone. If the stone is faceted and cylindrical, there may be other stones more proximally. The small bowel proximal to the obstructing stone should be palpated and an endoscopy performed to assess the

stomach and duodenum to look for other stones and prevent the risk of a recurrent episode of gallstone ileus [106–108].

The surgical treatment of the associated cholecysto-duodenal fistula in gallstone ileus is debated. Some advocate a single-stage or two-stage procedure [107]. However, either the primary or the delayed repair of the fistula is associated with the much higher morbidity and mortality compared to the enterotomy alone. Given that many of these patients are elderly with associated comorbidities and that the fistula may spontaneously close and the incidence of recurrent biliary disease following an enterotomy alone is only 15% [106, 108], many surgeons advocate not proceeding with cholecystectomy and closure of the fistula unless there are recurrent biliary symptoms.

4.7.10 Cholecysto-duodenal and Cholecysto-colonic Fistula

Cholecysto-duodenal (Fig. 4.12) and cholecysto-colonic fistula may be suspected or unsuspected and found during LC for a chronically inflamed gallbladder. The clue that there is a fistula is that while dissecting the gallbladder wall away from the adherent surrounding structures, a point is reached where the gallbladder wall and duodenum or colon appear fused. A cholecysto-duodenal fistula can be managed with a cholecystectomy, excision of the fistula tract from the duodenal wall and primary closure of the duodenal wall. This may be done after conversion to open surgery, or an experienced surgeon may not convert and complete the procedure safely with laparoscopic techniques. A cholecysto-colonic fistula also requires a cholecystectomy and excision of the fistula tract from the colon. This normally requires a small formal resection and occasionally a right hemi-colectomy. This is more likely to require conversion to open surgery.

4.7.11 Recurrent Pyogenic Cholangitis (RPC)

The initial treatment to control sepsis when RPC is suspected or known is biliary drainage by either ERCP and stenting or percutaneous transhepatic biliary drainage [109–111]. Most patients will progress to require a formal surgical treatment. The surgical strategy varies depending on the pattern of disease but most commonly involves either a hepatico-jejunostomy with an access limb or stoma for repeated cholangioscopic procedures and/or hepatic resection (frequently segment 2/3) of the dominant component of disease or a combination of both [111, 112].

4.8 Complications of Treatment

The two most frequently performed procedures for the treatment of symptomatic gallstones are LC to treat gallbladder stones and ERCP and ES to treat CBD stones. The discussion regarding complications will concentrate on these two procedures

and discuss the early complications particularly those complications which require early detection and early surgical management to avoid the situation of 'failure to rescue'.

4.8.1 Laparoscopic Cholecystectomy

Early and late complications of laparoscopic cholecystectomy are outlined in Table 4.13.

4.8.2 Bile Leak

Bile leaks occur in between 0.25 and 2% of patients having laparoscopic cholecystectomy. These most frequently occur from either the gallbladder bed (15%) or the cystic duct stump (80%) [113, 114]. These are the type A injuries as classified by Strasberg (Fig. 4.29). Less frequently bile leaks may be associated with type C, D or E injuries to the biliary tree. Bile leaks may be anticipated at the time of surgery.

Table 4.13 Complications of laparoscopic cholecystectomy

Early
Bile leak
Common bile duct injury
Post-operative haemorrhage
Injury to small bowel or colon
Late
Retained common bile duct stones
Common bile duct stricture
Port-site hernias

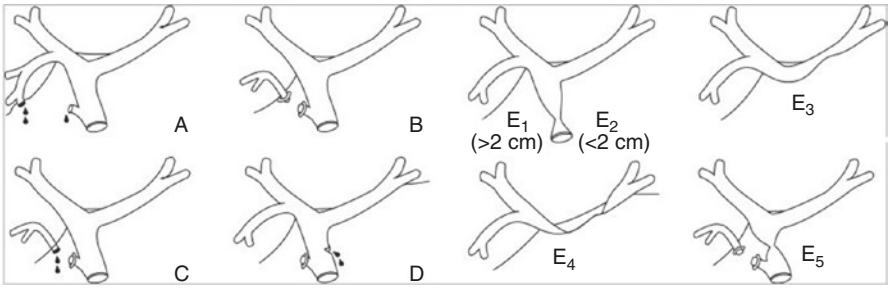

Fig. 4.29 Strasberg classification of CBD injury. (**A**) Bile leak from cystic duct stump or minor biliary radical in gallbladder fossa. (**B**) Occluded right posterior sectoral duct. (**C**) Bile leak from divided right posterior sectoral duct. (**D**) Bile leak from main bile duct without major tissue loss. ($\mathbf{E}_1$) Transected main bile duct with a stricture more than 2 cm from the hilus. ($\mathbf{E}_2$) Transected main bile duct with a stricture less than 2 cm from the hilus. ($\mathbf{E}_3$) Stricture of the hilus with right and left ducts in communication. ($\mathbf{E}_4$) Stricture of the hilus with separation of right and left ducts. ($\mathbf{E}_5$) Stricture of the main bile duct and transection of the right posterior sectoral duct

Table 4.14 Factors that may increase bile leak from gallbladder fossa or cystic duct

Subtotal cholecystectomy for severe acute or chronic inflammation
Cholecystectomy for gangrenous cholecystitis where the cystic duct is necrotic
Difficult dissection of the gallbladder off the liver increasing the likelihood of opening into a subvesical duct
Difficult closure due to cystic duct size, anatomy or severe inflammation

Factors increasing a likelihood of bile leak are listed in Table 4.14. When anticipated, these are best managed and subsequently diagnosed with the insertion of an intraoperative drain into the gallbladder fossa.

Where a drain is not inserted, a post-operative bile leak will present with significant abdominal pain that may be associated with nausea, vomiting and failure to improve following LC. It is absolutely essential that any patient following LC with significant pain must be considered to have a bile leak until proven otherwise. Putting it another way, if the patient is unwell and not able to be discharged within 24 h of LC, consideration should be given to the possibility of a bile leak. Failure to diagnose early leads to delay in treatment with an increased morbidity, length of stay and mortality [115, 116]. It is of utmost importance to diagnose and manage post-operative bile leaks early as 'failure to rescue' has serious consequences.

A less common presentation of a post-operative bile leak is that the patient is well on the first post-operative day, is discharged home but represents 48–96 h after surgery with a sudden (instantaneous) onset of severe generalised abdominal pain associated with signs of peritonitis. These are patients where there has been a diathermy injury either to the sub-vesical ducts in the gallbladder bed, the cystic duct or a hepatic duct. Initially the duct wall was intact, but due to the diathermy injury and subsequent necrosis, there has been a delayed leak some 48–96 h following the surgery. Patients presenting like this need to be treated as bile leaks until proven otherwise for the same reason as early post-operative bile leaks, as delay in diagnosis and treatment is associated with poor outcomes.

The suspected bile leak can be confirmed on imaging. While nuclear medicine scanning (DIDA) has a sensitivity and specificity that approached 100% for bile leaks, it fails to provide any information regarding the site of the leak and any biliary anatomy or other pathology such as bile duct stones contributing to the leak. CT cholangiography (Fig. 4.30) provides a dynamic assessment of the presence of a leak as well as defining the biliary anatomy, the presence of any common bile duct stones and the site and extent of any bile collection. The information obtained with CT cholangiogram is usually all that is required to diagnose and plan management of a bile leak. MRI may be used although this does not provide a dynamic component to prove that the fluid outside the GI tract is from a bile leak.

Once diagnosed, the management of bile leak has three aspects:

1. Treatment of the bile peritonitis
2. Control of the leak
3. Definitive management of the leak

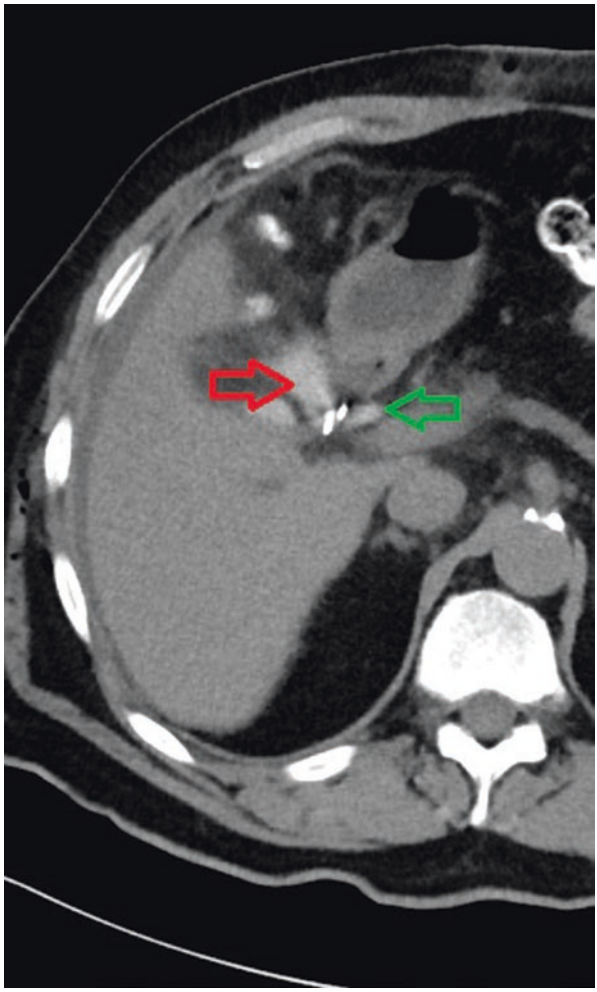

Fig. 4.30 CT cholangiogram in a 45-year-old man with severe abdominal pain 24 h after LC which demonstrates a leak into the gallbladder fossa from the cystic duct (red arrow) lateral to the cystic duct clips and the CBD (green arrow). The remainder of the CT cholangiogram revealed an intact biliary tree with no CBD stones. This was managed with an urgent laparoscopy and peritoneal lavage to manage the biliary peritonitis. The cystic duct stump was easily identified, and it was noted that the clips were not completely across the duct with bile leaking out. The clips were removed and an operative cholangiogram performed that confirmed normal biliary anatomy, no other leak and no CBD stones. The clips were replaced and a drain inserted into the gallbladder fossa. There was no further bile leak

Treatment of Bile Peritonitis The management of bile peritonitis requires an urgent laparoscopy and extensive peritoneal lavage. It is important to do this prior to controlling the bile leak with a drain or proceeding to definitive management. Placement of radiological drain into a bile collection does not necessarily manage the peritonitis. This often results in walling off of collections and ongoing sepsis. The additional advantage of re-laparoscopy and lavage are:

- Ensures optimal placement of the biliary drain
- Allows the site of the bile leak to be defined and confirmed, in most cases
- May allow an operative cholangiogram to be performed
- May offer the possibility of a definitive treatment of the bile leak

Control of the Leak At laparoscopy and following lavage, an intraoperative drain should be placed into the gallbladder fossa, if no definitive treatment is possible. This manages the leak, prevents further episodes of sepsis and can allow for planned definitive treatment which is usually endoscopic.

Definitive Treatment of the Leak The definitive treatment depends on the cause of the leak, the findings at laparoscopy and the skill of the surgeon at the time of laparoscopy. A bile leak from the gallbladder fossa may be confirmed with a repeat OC (Fig. 4.31a) and controlled with laparoscopic suturing of the gallbladder fossa

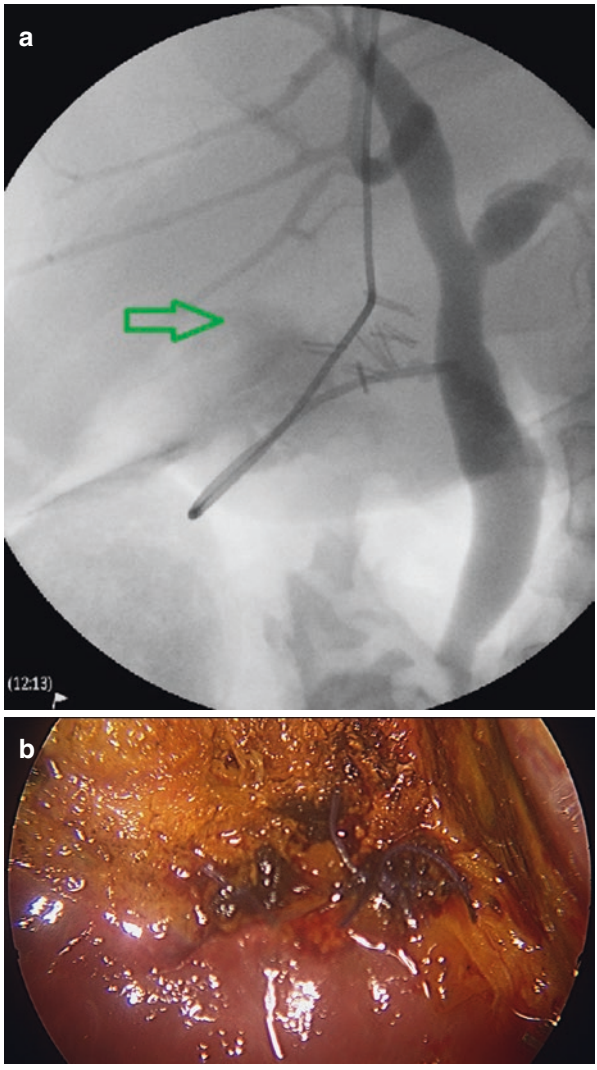

Fig. 4.31 (**a**) A 34-year-old man presented 48 h after discharge (72 h post-operatively) with a sudden onset of severe generalised abdominal pain. At the urgent laparoscopy after the peritoneal lavage, a bile leak from the gallbladder fossa was noted at laparoscopy and confirmed on operative cholangiogram. (**b**) The site of the leak was sutured with two figure-of-eight sutures and the leak controlled. This was confirmed on operative cholangiogram and a drain inserted. Post-operatively he was well with no bile leak and the drain was removed 48 h post-operatively

(Fig. 4.31b). A bile leak from the cystic duct may be visualised at laparoscopy. The clips, if safe to do so, can be removed, and an OC obtained. The OC will confirm the remaining ducts are intact and there is no other cause of the leak. If safe, the cystic duct can be dissected further and then closed by clips, a loop or a suture. A bile leak from a common hepatic duct or right hepatic duct may be noted visually at laparoscopy and either drained or when appropriate converted to open surgery and repaired (Sect. 4.8.3).

In patients where the leak from the cystic duct of the gallbladder fossa is not able to be definitively managed at the time of laparoscopy, the definitive treatment is to obtain drainage of the biliary tree with an ERCP, ES and insertion of a biliary stent (Fig. 4.32). This treatment overcomes the physiological obstruction (sphincter of

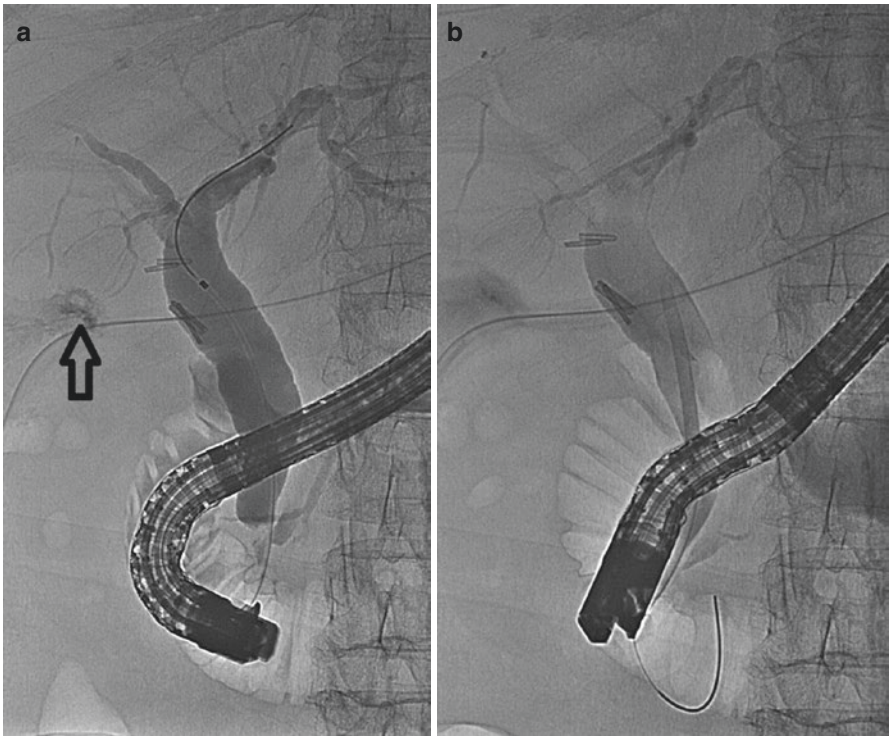

Fig. 4.32 (**a**) ERCP of a patient with post-operative bile leak following LC for gangrenous acute cholecystitis where there was a very difficult dissection getting the gallbladder off the liver. A cholangiogram was performed and the cystic duct noted to be very short (3 mm). It was carefully clipped and a drain inserted in anticipation of a possible bile leak from the cystic duct stump. The subsequent bile leak was controlled by the operative drain but did not resolve after 3 days. The presumed cause was a leak from the cystic duct, but the ERCP demonstrated a leak from the gallbladder bed (arrow). (**b**) A single 10 French stent was inserted after a sphincterotomy was performed. The leak resolved within 12 h and the drain was removed after 48 h. An ERCP to remove the stent was performed 10 weeks later as a day case

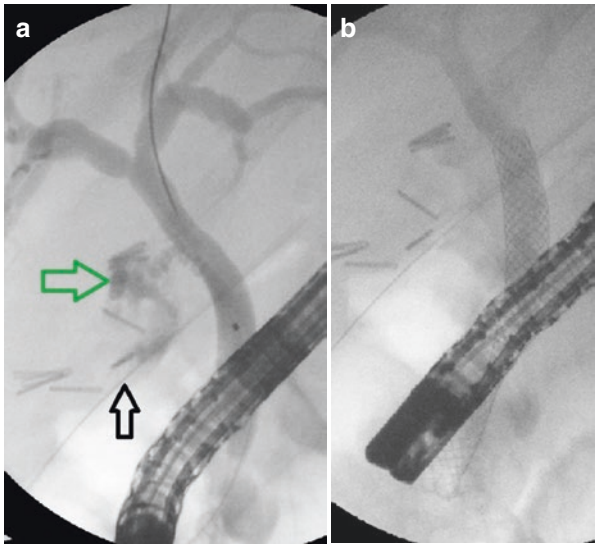

Fig. 4.33 (**a**) An ERCP with a high-volume bile leak (190 mL/24 h) 2 days after a subtotal cholecystectomy for gangrenous cholecystitis. As expected there is a free leak with a small residual component of the gallbladder neck. (**b**) An expandable, fully covered, removable metal stent was deployed. The leak resolved within hours. The stent was removed 3 months later

Oddi) that reduces the leakage of bile into the peritoneal cavity. As with any fistula, removal of the distal obstruction will usually lead to closure of the fistula. The success rate of ERCP sphincterotomy and stenting is between 92 and 100% [117–119]. A completely covered, removable metal stent may be used (Fig. 4.33) for those patients where there is failure to close after an initial ERCP and insertion of a plastic stent or where the risk of failure of closure is higher, for example, in a patient after a subtotal cholecystectomy where there is a residual neck of the gallbladder in situ.

4.8.3 Bile Duct Injury

Bile duct injury can vary in its extent and site and as previously noted has been classified by Strasberg (Fig. 4.29). The bile duct injury may be detected intraoperatively with visual identification or at routine cholangiography. Many, however, are identified post-operatively either as a result of a bile leak or with obstructive jaundice. Once identified, urgent early repair with a hepatico-jejunostomy by an experienced hepatobiliary surgeon provides the best outcomes. There is strong data to demonstrate that repair by an inexperienced surgeon or by the initial primary surgeon results in poorer outcomes.

A bile duct injury may present late as a CBD stricture.

4.8.4 ERCP and ES

The four most common complications associated with ERCP and ES for common bile duct stones are as follows.

4.8.4.1 Acute Pancreatitis

There is a wide range of the incidence of acute pancreatitis following ERCP (1.6–15% with an average of 3.5%) [120, 121]. The risk of post-ERCP pancreatitis is higher in patients with normal bilirubin, sphincter of Oddi dysfunction, multiple cannulations of the pancreatic duct, balloon dilatation of the ampulla and use of precut sphincterotomy [122]. Fortunately, many of these circumstances are less frequent in patients with symptomatic CBD stones, and therefore the risk of acute pancreatitis is lower in this cohort of patients. Treatment for post ERCP acute pancreatitis is the same as for most other causes of acute pancreatitis (Chap. 9).

4.8.4.2 Cholangitis

Incidence of cholangitis is low (less than 1%) [123, 124] following ERCP. When ERCP is for common bile duct stones, the occurrence of cholangitis is usually associated with either pre-existing cholangitis with ongoing poor drainage or subsequent poor drainage due to retained stones. Both of these causes can be predicted at the initial ERCP and managed expectantly with the insertion of a biliary stent at the initial procedure. If cholangitis does occur following ERCP for bile duct stones. It requires early recognition and consideration of an urgent ERCP and stent insertion in addition to antibiotic therapy to avoid 'failure to rescue'.

4.8.4.3 Haemorrhage

Haemorrhage following ERCP is most commonly associated with bleeding from the sphincterotomy site. This has an incidence of 1.3% although 70% of cases are considered mild, resolving spontaneously and not requiring any form of intervention [93]. Most bleeding that does require intervention can be managed endoscopically with a combination of adrenaline injection, diathermy, haemostatic clips or the insertion of an expandable metal stent which tamponades the bleeding point [121, 122].

4.8.4.4 Perforation

The incidence of perforation associated with ERCP and sphincterotomy ranges from 0.1 to 0.6% [122, 124, 125]. Most frequently the perforation occurs from the sphincterotomy extending beyond the lumen of the duodenum and bile duct into the retroperitoneal space. This will present with severe abdominal pain early after the ERCP with an elevated amylase and lipase and is frequently misdiagnosed as postoperative ERCP acute pancreatitis. The failure to recognise this complication may lead to incorrect treatment, delays in operative intervention and subsequent poor outcome. To avoid misdiagnosis and opportunity for early rescue, establishment of the presence of a retroperitoneal duodneal perforation with a CT scan to demonstrate the presence of retroperitoneal gas, with or without leakeage of contrast (Fig. 4.34). If the perforation is excluded, these patients can be managed as with acute pancreatitis. Where the perforation is confirmed, the management is dependent on the clinical assessment as well as the radiological findings. Post-ERCP perforation can be managed nonoperatively with nil orally and IV antibiotics when there is no sepsis, no clinical deterioration and no evidence of oral contrast

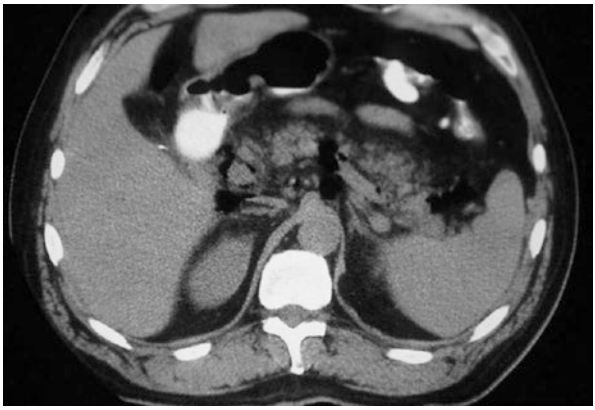

Fig. 4.34 A CT done 8h after an ERCP and ES to remove CBD stones. The patient had severe upper abdominal pain consistent with acute pancreatitis and elevated amylase (2,980) and lipase (5,030) consistent with a diagnosis of acute post-ERCP pancreatitis. The urgent CT revealed extensive retroperitoneal gas, but no contrast leak from the duodenum that was filled with oral contrast. This patient was managed nonoperatively with nasogastric decompression, nil orally and systemic antibiotics. By day 8, they were well and were discharged

leakage on CT scanning. This can occur safely in 63–66% of patients [126, 127]. However at least one-third of patients have sepsis, a clinical deterioration and/or contrast leak at CT scan require early surgical intervention to achieve early rescue. The best outcomes occur when a formal suture repair from within the duodenum is performed. The sphincterotomy located and the bile duct wall and duodenal wall sutured to close the defect in a similar fashion to an open sphincteroplasty [127]. This may be combined with duodenal, retroperitoneal and biliary drainage along with jejunal feeding.

Conclusion

Laparoscopic cholecystectomy (LC) and routine OC is the most frequent treatment for gallbladder stones. The safe dissection technique is based on principles outlined above. Operative cholangiography (OC) should be performed routinely. The main symptom for gallstones requiring an elective LC is biliary pain. Acute cholecystitis requires an urgent LC to achieve the best outcomes. All patients with possible or proven CBD stones, except those with severe cholangitis, should proceed to a LC first and the CBD stones found on OC be managed either with laparoscopic techniques or insertion of an antegrade biliary stent and post-operative ERCP. Patients with severe cholangitis (grade III) require an urgent ERCP and drainage of the CBD. If they have not had a cholecystectomy previously, this should be performed as early as practicable. Patients that have had a previous cholecystectomy with CBD stones should proceed to ERCP.

The complication of bile leak post LC requires early diagnosis and prompt treatment. The major strategy for the prevention of CBD injuries is good surgical

technique. In addition to good technique, CBD injuries are less frequent and less severe when routine OC is performed. Early detection and prompt treatment of CBD injuries is associated with better outcomes. Complications of ERCP and ES for CBD stone disease are acute pancreatitis, cholangitis, haemorrhage and perforation. Of these, perforation is frequently misdiagnosed leading to delay in definitive treatment. This is avoided by performing a CT scan in any patient with abdominal pain post ERCP and ES to exclude a perforation.

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Choledochal Cysts

5

Mark D. Stringer

Abbreviations

CBD	Common bile duct
CC	Choledochal cyst
CHD	Common hepatic duct
ERCP	Endoscopic retrograde cholangiopancreatography
GGT	Gamma-glutamyltransferase
MRCP	Magnetic resonance cholangiopancreatography
PBM	Pancreaticobiliary malunion

5.1 Introduction

A choledochal 'cyst' is a congenital dilatation of the bile duct(s). A better term would be congenital choledochal dilatation, but the 'cyst' nomenclature is so embedded in the literature that this chapter will refer to choledochal cysts (CCs).

5.2 Epidemiology

Choledochal cysts are particularly common among people from the Orient. It is estimated that pancreaticobiliary malunion (PBM), which is commonly associated with CCs, affects as many as 1 in 1000 Japanese [1]. The incidence of CCs was

M. D. Stringer
Department of Paediatric Surgery, Wellington Hospital, Wellington, New Zealand

Department of Paediatrics and Child Health, University of Otago, Wellington, New Zealand
e-mail: mark.stringer@ccdhb.org.nz

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previously reported to be about 1 in 100,000 live births in Western populations but may be increasing, either because of better detection or a genuine increase in incidence [2, 3]. More than two-thirds of CCs are diagnosed in children under 10 years, and girls outnumber boys by 3 or 4:1.

5.3 Classification

CCs are traditionally divided into five types (Fig. 5.1) [4]. Type I cysts are cystic or fusiform and account for at least 70% in most series [3, 5] (Fig. 5.2). Next in frequency are type IVa cysts, which consist of multiple cystic dilatations of the extra- and intrahepatic bile ducts (Fig. 5.2). Collectively, types I and IVa account for more than 90% of CCs. A type II diverticulum may affect the common bile duct but is most often seen at the level of the common hepatic duct [6]. A type III cyst (choledochocele) is a dilatation of the terminal common bile duct within the duodenal wall. Ziegler et al. suggest that type III cysts are not CCs because they may be acquired, may be lined by duodenal mucosa, are less prone to malignant change, have a more equal sex incidence and are not usually associated with PBM [7]. Type IVb (multiple extrahepatic duct cysts) and type V (single or multiple intrahepatic duct cysts) are rare. Multiple saccular dilatations of the intrahepatic bile ducts (Caroli's disease) may affect the liver diffusely or be localised to a lobe. When combined with renal anomalies and hepatic fibrosis, it is known as Caroli's syndrome. PBM can occur with minimal or no bile duct dilatation and has been termed a 'forme fruste' CC [8, 9] (Fig. 5.3). Isolated congenital cystic duct dilatation is exceptionally rare but should probably be included within the spectrum of CCs because of its association with PBM [10].

5.4 Pathology

There are three components to the pathology of a CC: the duct dilatation itself which may be complicated by inflammation, bile duct obstruction, infection, stones, perforation or malignancy; PBM, present in most but not all cases; and the potential for secondary liver disease (fibrosis, cirrhosis and abscess formation). Type Ic cysts typically extend from just below the origin of the common hepatic duct (CHD) to where the common bile duct (CBD) becomes embedded in the pancreas; at this level the CBD may be stenotic. Distal CBD obstruction is associated with higher intracholedochal pressures and more severe liver damage [11]. The gallbladder is often normal in size. Type If cysts are typically associated with PBM which may be further complicated by protein plugs within the common pancreaticobiliary channel. A stricture, or strictures, may involve the CHD or hilar ducts, particularly with type IVa cysts [12]. The epithelial lining of the CC may be ulcerated and exhibit metaplasia or dysplasia in older patients [13]. Hepatic histology may be normal or show

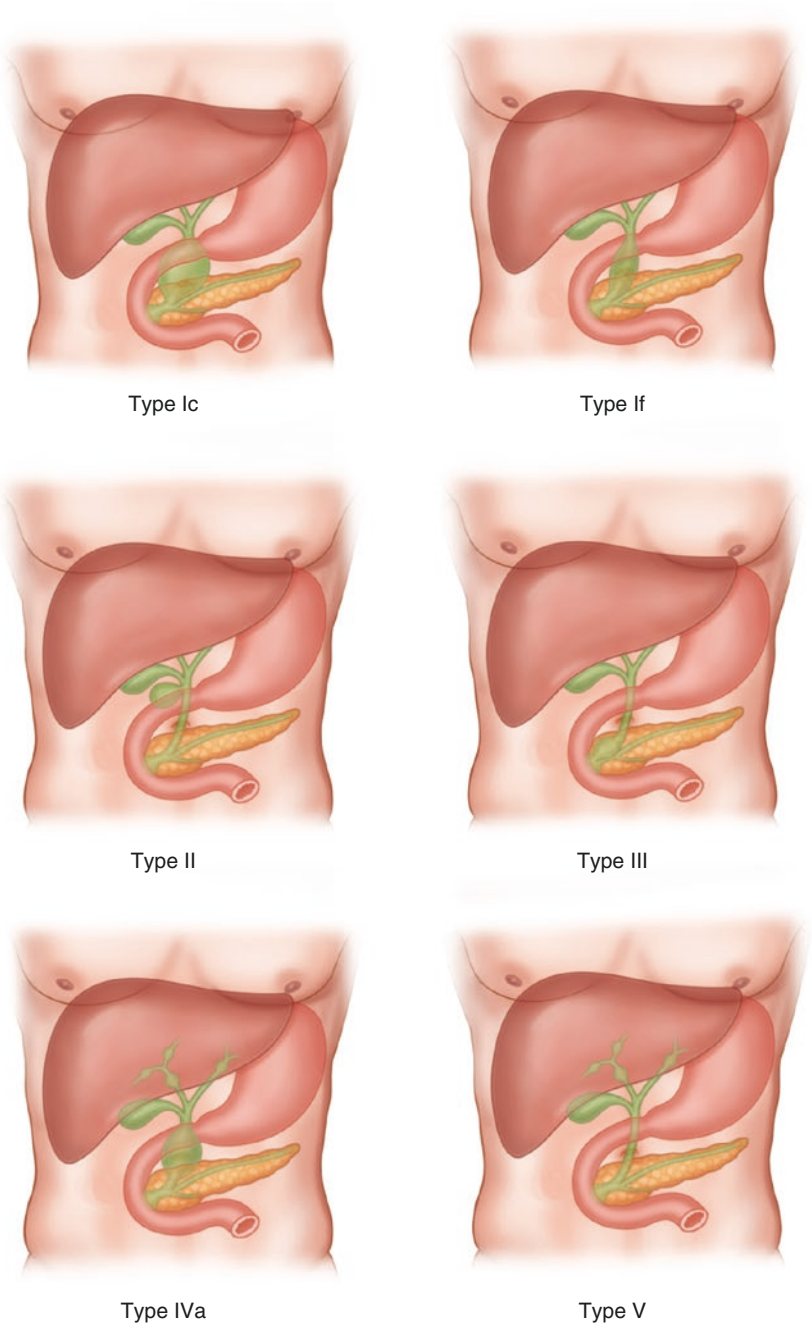

Fig. 5.1 Classification of choledochal cysts (based on Todani et al. 1977) [4]. Type I, cystic (Ic) or fusiform (If); type II, diverticulum of the extrahepatic bile duct, type III, choledochocele (dilatation of the terminal common bile duct within the duodenal wall); type IV, multiple cystic dilatations of the extra- and intrahepatic bile ducts (IVa) or multiple extrahepatic duct cysts (IVb); type V, intrahepatic duct cysts (single or multiple)

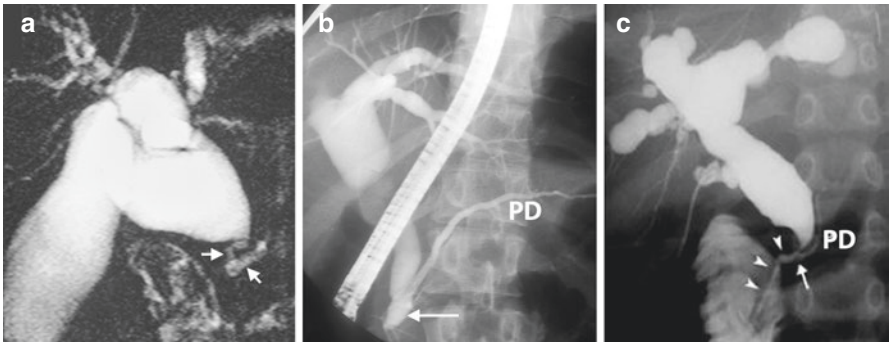

Fig. 5.2 (**a**) MRCP in an infant demonstrating a type Ic cyst with PBM (white arrows). (**b**) ERCP showing a type If cyst with PBM (white arrow). (**c**) Intraoperative cholangiogram of a type IVa cyst with PBM (white arrows). *PD* pancreatic duct

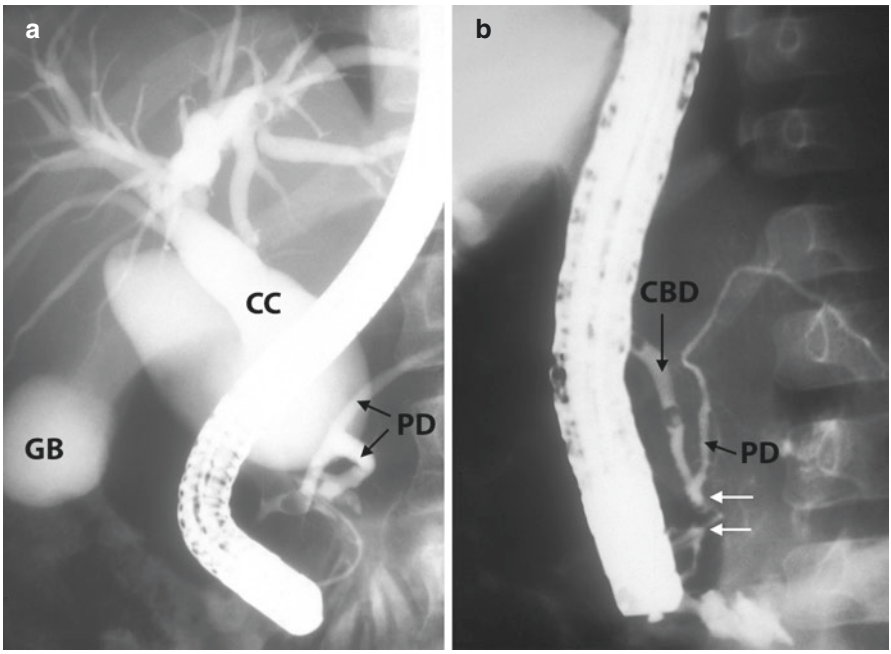

Fig. 5.3 (**a**) ERCP demonstrating complex pancreaticobiliary malunion associated with a fusiform CC. *GB* gallbladder, *PD* pancreatic duct, *CC* choledochal cyst. (**b**) ERCP showing pancreaticobiliary malunion (white arrows) with no CBD dilatation, the so-called 'forme fruste' CC. The filling defects in the CBD are air bubbles. *CBD* common bile duct

mild cholestasis and intrahepatic bile duct inflammation; periportal fibrosis and secondary biliary cirrhosis may develop in response to chronic bile duct obstruction [14]. The major duodenal papilla may be situated more distally in the second or even third part of the duodenum, particularly in the presence of PBM [15]. Other associated anatomical variants include an aberrant right sectoral or segmental bile duct joining the CHD or the cyst itself and a right hepatic artery crossing the cyst anteriorly [16]. Portal hypertension can develop as a result of portal vein compression by the cyst, hepatic fibrosis or cirrhosis.

5.4.1 Pancreaticobiliary Malunion

Choledochal cysts are frequently associated with an abnormal junction between the pancreatic duct and terminal CBD, such that the ducts join outside the wall of the duodenum and are not surrounded by a normal sphincter [17]. The anatomy of PBM (also known as anomalous pancreaticobiliary junction or a common pancreaticobiliary channel) varies depending on whether the CBD appears to join the pancreatic duct, or vice versa, or whether the junction is more complex [18] (Fig. 5.3). The abnormally long common channel often exceeds 5–10 mm in children [19] and 10–15 mm in adults. Because pancreatic ductal pressure normally exceeds that in the bile duct, PBM favours reflux of pancreatic juice into the biliary tract [20], leading to high concentrations of pancreatic enzymes within the bile. Reflux of pancreatic fluid into the bile duct has been observed by dynamic imaging during secretin-stimulated MRCP [21]. On occasions, bile enters the pancreatic duct [22] and may cause pancreatitis. PBM is present in about 70% of type I and IVa cysts [23] and in an even greater proportion of type If cysts [24]. It may also occur in the absence of choledochal dilatation [9, 25]. Chronic pancreaticobiliary reflux predisposes to the development of cancer in the gallbladder and CC [26].

Malformations outside the biliary tree in patients with a CC are rare. There are sporadic reports of associations with congenital cardiac disease, intestinal malrotation, duodenal atresia/stenosis, pancreas divisum and renal abnormalities [27–31].

5.5 Aetiology and Pathogenesis

Two main theories concern the origin of CC. The first of these suggests that a CC develops from an acquired weakness in the wall of the bile duct consequent on reflux of pancreatic juice and bile duct inflammation [32, 33]. However, PBM is not present in all patients with a CC, and it can occur in individuals without duct dilatation. Further, some CCs are detected prenatally or in early infancy before pancreatic enzyme secretion is mature [34–36]. The second theory states that a CC arises from distal obstruction of the CBD. In support of this, a stenosis is often seen immediately below a type Ic cyst. Ligation of the distal CBD in foetal lambs causes cystic

dilatation of the proximal bile duct [37]. Faulty development of the pancreaticobiliary junction and/or distal CBD may cause the obstruction. There is growing evidence to suggest that the cause of PBM is abnormal development of the ventral pancreatic anlage during embryogenesis [1]. Yet another theory suggests that a CC arises from a deficiency of interstitial cells of Cajal (the cells involved in regulating smooth muscle motility) in the wall of the bile duct [38]. However, any reduction in the density of these cells might be secondary to choledochal dilatation/inflammation. Such a mechanism has been postulated to explain the reduced density of ganglion cells in the wall of CCs [39]. None of these theories adequately explain the development of type IVa cysts.

In summary, whilst no individual theory is entirely convincing, the pathogenesis of a CC is probably related to faulty development of the pancreaticobiliary junction and/or distal bile duct leading to a variable degree of bile duct obstruction.

Genetic factors are presumably involved considering the ethnic variations and female preponderance of CC. However, familial CC is extremely rare [40], and twin studies have not identified an obvious genetic predisposition [41]. Gene sequencing suggests that CCs are genetically heterogeneous and mutations in several genes are probably necessary for their development [42].

5.6 Clinical Presentation

CC can present at any age, but approximately 80% are diagnosed before 10 years [27, 43]. Typical presenting symptoms include abdominal pain, vomiting, jaundice and/or fever. There are age-related variations in presentation:

5.6.1 Prenatal

A CC may be detected by prenatal ultrasound scan as early as 15 weeks of gestation [27, 44]. Most are type Ic although a few are type V. If a type Ic cyst is confirmed postnatally, early surgical treatment is advisable, particularly if the infant is jaundiced.

5.6.2 Infants

Infants are more likely than older children or adults to have a type Ic cyst and to present with obstructive jaundice [36, 45]. Vomiting, fever, failure to thrive and an abdominal mass are sometimes noted. In those with PBM, hyperamylasaemia is uncommon because the amylase concentration in bile is often low until about 1 year of age [34–36]. However, biliary concentrations of pancreatic lipase, elastase and trypsin are often significantly elevated [35, 46]. Liver fibrosis and cirrhosis from biliary obstruction can develop rapidly at this age but are reversible by early surgery [36, 47, 48]. Results of surgical treatment in infants are generally excellent [44, 49, 50].

An important differential diagnosis of a type Ic cyst in a jaundiced infant is a cystic variant of biliary atresia. If the cyst was detected prenatally, then enlargement of the cyst on serial scans favours CC pathology [51] as does the presence of dilated intrahepatic bile ducts postnatally [52]. A dynamic biliary radioisotope scan may help to distinguish the two conditions (there being no isotope excretion into the gut in biliary atresia), but if there is diagnostic doubt, the infant must be assumed to have biliary atresia until proven otherwise.

5.6.3 Older Children

Abdominal pain is a common presenting symptom in this age group [36, 45]. This may be accompanied by hyperamylasaemia [53]. If jaundice is present, it tends to be intermittent. The classic triad of jaundice, pain and a right upper quadrant mass is uncommon [27].

Diagnostic delay may be due to inadequate investigation of jaundice or pancreatitis or a failure to appreciate the significance of a dilated CBD [27]. A CC must be considered in the differential diagnosis of obstructive jaundice and/or pancreatitis. A child with recurrent or severe abdominal pain should have a plasma amylase checked. Hyperamylasaemia associated with a CC and PBM may be secondary to acute pancreatitis but is often a biochemical finding alone, with no clinical or radiological signs of pancreatitis [35, 46]. In these cases, hyperamylasaemia may be from diffusion of pancreatic amylase through the cyst epithelial lining or from pressure-induced cholangiovenous reflux of pancreatic amylase.

5.6.4 Adults

Most CCs in adults present with abdominal pain [3]. Adult CCs are more likely to be complicated by gallstones, cholangitis or pancreatitis than children [5]. Previous biliary intervention for stones or infection prior to diagnosis is not uncommon [3, 54]. In up to 10% of adults presenting with a CC, there may be complications such as hepatolithiasis, biliary malignancy or portal hypertension [5]. Malignancy at presentation is rare in patients younger than 30 years [3, 54]. Compared to children, adults have a greater proportion of type IV cysts [3, 54]. The relatively rare type II and III cysts are also more often seen in adults, and frequently present with pancreatitis [6, 7].

5.7 Complications

Choledochal cysts are associated with numerous complications (Fig. 5.4) which include:

- *Cholangitis*—This presents with jaundice, abdominal pain and fever. The causative organism is usually a Gram-negative bacterium.

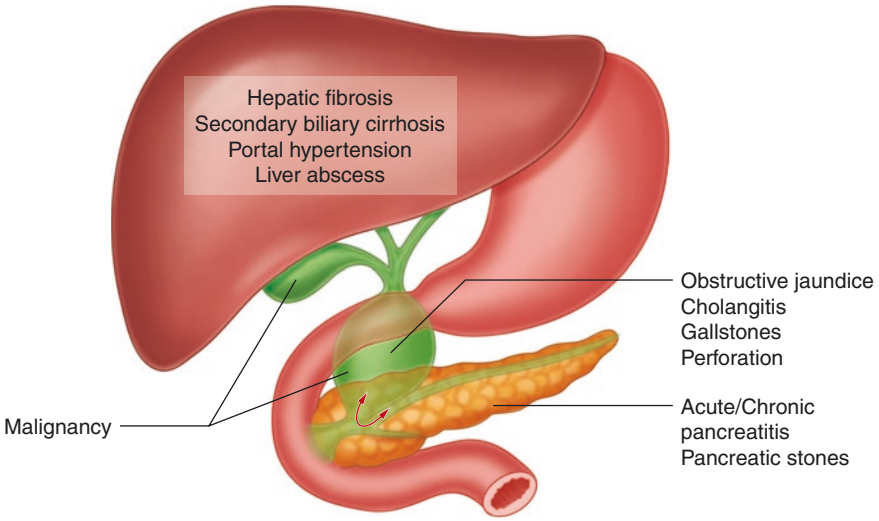

Fig. 5.4 Potential complications of choledochal cysts

- *Perforation/rupture*—This usually occurs spontaneously and mostly in children under 5 years [3, 27, 55, 56]. Perforation is the presenting feature in about 4% of paediatric CCs [3, 56]. The perforation may occur in any part of the wall of the cyst and is usually single (Fig. 5.5). Intraperitoneal rupture with biliary peritonitis is more common than retroperitoneal rupture, which presents more insidiously. Clinical symptoms and signs include abdominal pain, distension, vomiting, fever, mild jaundice and biliary ascites. Diagnosis is usually made by clinical assessment, abdominal ultrasound scan and a peritoneal tap [56, 57]. A biliary isotope excretion scan is occasionally helpful in diagnosis in atypical presentations. If the expertise is available, definitive surgery is associated with a good outcome [56]. In less-experienced centres or if the child is critically ill, temporary drainage of the cyst (e.g. repair of the perforation over a T-tube) followed by definitive surgery once the patient has recovered and the anatomy has been clearly defined is a safer option.
- *Pancreatic disease*—Recurrent acute or chronic pancreatitis may be caused by PBM, particularly if the common pancreaticobiliary channel is dilated or anatomically complex when it is more likely to contain protein plugs and calculi (Fig. 5.6).
- *Gallstones*—Gallstones or biliary sludge may develop from stasis within the biliary system. Yamaguchi (1980) reported an 8% prevalence among 1433 Japanese patients with a CC [43].
- *Portal hypertension*—This may develop from portal vein compression by a large CC, hepatic fibrosis/biliary cirrhosis from prolonged biliary obstruction or,

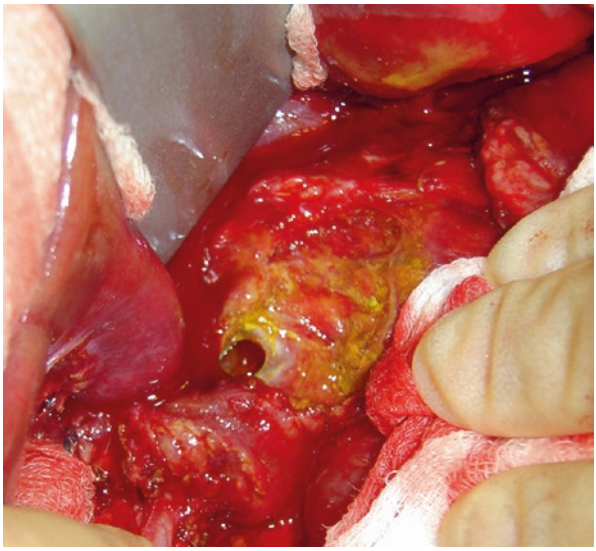

Fig. 5.5 Operative appearance of a perforated CC

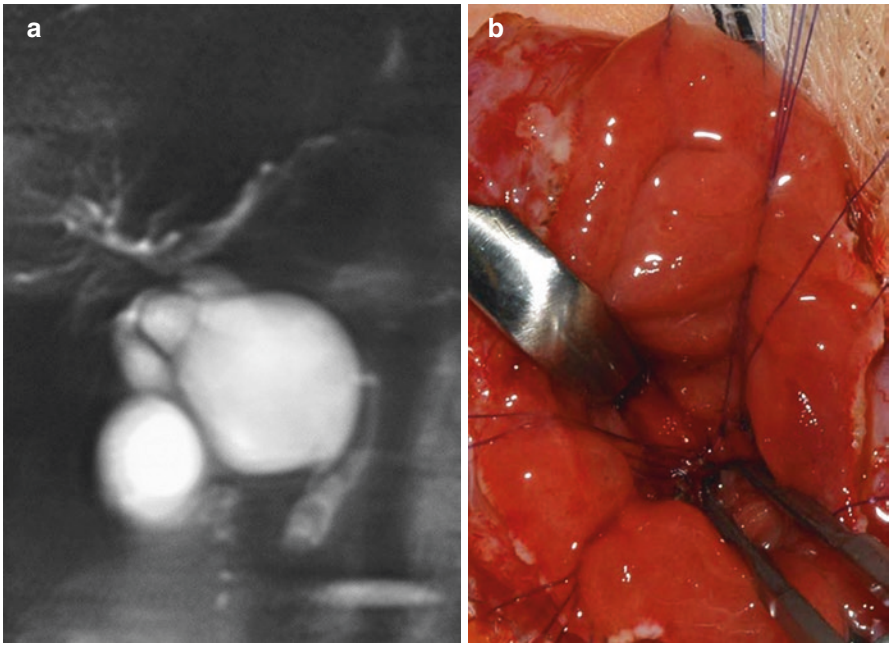

Fig. 5.6 (**a**) MRCP demonstrating a type Ic cyst with PBM in a child. The common pancreaticobiliary channel contained protein plugs and when the CC was excised a sphincteroplasty was performed (**b**) to enable clearance and drainage of the dilated common channel

rarely, portal vein thrombosis. Severe portal hypertension with large varices must be controlled prior to CC surgery [5, 58]. Transjugular intrahepatic portosystemic shunting is a useful approach unless the patient has advanced cirrhosis, when liver transplantation may be necessary.

- *Secondary biliary cirrhosis*—Liver fibrosis or cirrhosis arising from chronic biliary obstruction by a CC is more commonly seen in infants than in children and adults [14, 36, 59]. Liver fibrosis has been documented as early as 4 weeks of age [48] and cirrhosis within 2–3 months [48, 60, 61]. Liver fibrosis and early cirrhosis are potentially reversible if the obstructing CC is treated promptly and appropriately, although these patients may develop transient postoperative ascites [61] (author's unpublished observations). Liver transplantation is occasionally required for a CC with advanced liver disease [59, 61].
- *Malignancy*—This complication mainly affects adults although it has been described in a few children [43, 62]. In type Ic cysts, malignancy affects the cyst wall or gallbladder, whereas in type If, the gallbladder is the dominant site. In type IVa CCs, hilar or intrahepatic ducts may be affected. Histology of these cholangiocarcinomas or gallbladder cancers is usually that of an adenocarcinoma but squamous cell cancers have occasionally been reported [62–64]. The cancer risk increases with age. In a large retrospective Korean multicentre study, 10% of adults operated for a CC had a concurrent biliary tract malignancy [65]. Factors predicting malignancy were age >40 years and PBM. PBM without choledochal dilatation predisposes to gallbladder cancer in adults [66]. Reflux of pancreatic enzymes into the bile ducts causes inflammation, increases biliary epithelial turnover [67] and may induce oncogene mutations [25]; epithelial damage is further exacerbated by stones and infection. Malignant change may be preceded by epithelial metaplasia and/or dysplasia [68]. The risk of malignancy is particularly high in patients who have been treated inappropriately by internal drainage of a CC (cystenterostomy) [69].

5.8 Investigations

Biochemical liver function tests can be normal or may show obstructive jaundice. Hyperamylasaemia may be present during an episode of abdominal pain. Clotting disturbances must be excluded in patients with jaundice.

Ultrasonography is the initial imaging modality of choice. The position, size and contour of the CC, the calibre and morphology of the proximal bile ducts, vascular anatomy and hepatic echotexture can be evaluated together with any disease complications. Mild but abnormal dilatation of the CBD/CHD must not be overlooked or dismissed: the diameter of the normal CBD measured by ultrasound is up to 2 mm in infants, up to 4 mm in children under 12 years and up to 10 mm in adults [70–72].

Magnetic resonance cholangiopancreatography (MRCP) is the next imaging investigation (Figs. 5.2 and 5.6). Bile and pancreatic juice have high signal intensity on T2-weighted images. Adequate definition of the pancreatic duct and PBM was

previously a concern, but this is now increasingly possible, even in infants, if modern scanners and image acquisition techniques are used [73, 74]. Thin-slice maximum-intensity projections provide the surgeon with an anatomical road map. MRCP may also detect associated gallstones and cholangiocarcinoma [74].

Endoscopic retrograde cholangiopancreatography (ERCP) provides excellent visualisation of the cyst, bile duct anatomy and pancreaticobiliary junction (Figs. 5.2 and 5.3) but is associated with a small risk of complications including acute pancreatitis and biliary sepsis. ERCP is useful when the degree of biliary dilatation is minimal or if an MRCP has failed to clarify the anatomy of the pancreaticobiliary junction. These instances are becoming increasingly uncommon with modern MRI scanners and techniques.

Hepatobiliary scintigraphy may occasionally be useful in selected patients, e.g. the jaundiced infant with a suspected cystic variant of biliary atresia. Contrast-enhanced CT may be helpful in evaluating pancreatitis or a suspected tumour.

Distinguishing type I cysts with intrahepatic dilatation from type IVa cysts on preoperative imaging can be difficult, resulting in a tendency to overcall type IVa cysts [45, 75]. The intrahepatic ducts in type IVa are often irregular with sacculations and stenoses unlike the smooth intrahepatic duct dilatation seen with obstructing type Ic cysts (although type I cysts may be associated with hilar duct strictures). Resolution of the intrahepatic duct dilatation after successful treatment of the extrahepatic CC indicates a type I cyst [76].

A full blood count, liver function tests, plasma amylase, clotting studies and blood group are routinely checked prior to surgery and the imaging reviewed. In most cases the latter will be a high quality MRCP. The possibility of variant anatomy should be considered, e.g. an aberrant right sectoral duct joining the CHD or cyst and/or a replaced or accessory right hepatic artery [16].

5.9 Differential Diagnosis (Table 5.1) [3, 45, 77–80]

Table 5.1 Differential diagnosis of a choledochal cyst

Biliary atresia (with extrahepatic cyst)	In infants with obstructive jaundice
Embryonal rhabdomyosarcoma of the bile duct	In preschool children, this malignant tumour may masquerade as a CC [3, 77, 78]. Imaging evidence of intraductal solid tissue extending into the liver should prompt suspicion [79]
Primary sclerosing cholangitis with a dilated bile duct proximal to a dominant stricture	In older children and adults. Clues to this possibility include irregular intrahepatic ducts, a history of inflammatory bowel disease and/or abnormal immunological findings
Choledocholithiasis	A CC containing stones may be misdiagnosed as primary gallstone disease. In one series of children with CC, 11% had undergone cholecystectomy for gallstones prior to diagnosis [45]. It can sometimes be difficult to distinguish a dilated CBD with a distal obstructing stone/debris from a fusiform CC although the bile duct in a CC tends to be wider [80]. An MRCP usually provides the answer

CC choledochal cyst, *CBD* common bile duct

5.10 Surgical Management

Radical cyst excision and reconstruction by wide hilar hepaticoenterostomy is the optimum treatment for the more common types of CC, namely, types I and IVa [81, 82]. Surgery can be performed safely at all ages with minimal morbidity by experienced surgeons. Early surgery is advisable for infants with bile duct obstruction. Simple anastomosis of a loop of bowel to the CC (cystenterostomy) should never be performed because of the inevitable severe long-term morbidity (cholangitis, pancreatitis, cholelithiasis, anastomotic stricture, biliary cirrhosis and malignancy) [83]. Mild pancreatitis need not delay surgery [84], but severe pancreatitis, cholangitis or portal hypertension will require staged management [5].

Most types of choledochal cyst are best treated surgically by radical cyst excision and reconstruction with a wide hilar hepaticoenterostomy.

5.10.1 Preoperative Assessment and Preparation

A nasogastric tube is inserted intraoperatively but can be removed at the end of the operation in most patients. Broad-spectrum intravenous antibiotics are given at induction of anaesthesia and continued for up to 5 days postoperatively.

5.10.2 Operative Technique (Open Approach)

An oblique or transverse right upper quadrant incision affords adequate exposure. The duodenum and head of pancreas may be displaced anteriorly by the cyst. The appearance of the liver, spleen and pancreas should be recorded. If the anatomy of the bile ducts and pancreaticobiliary junction has not been adequately defined preoperatively, then an intraoperative cholangiogram is performed. Transcystic cholangiography provides good definition with small cysts. With large cysts, cholangiography is best performed by injecting contrast directly into the lower end of the CBD *and* into the CHD using a butterfly needle. Bile is aspirated from the cyst with a fine needle and sent for culture and biliary amylase concentration (often > 100,000 U/l).

A plane is developed between the anterior wall of the cyst and the overlying peritoneum. The dissection extends medially and laterally, staying on the wall of the cyst, and inferiorly between the cyst and duodenum; bipolar cautery provides safe and accurate haemostasis. Large cysts are best decompressed to facilitate dissection (Fig. 5.7). The gallbladder and cystic duct are mobilised but left in continuity with the cyst, and the cystic artery is ligated and divided. Where the bile duct narrows down inferiorly, it is dissected circumferentially and encircled with a silastic loop (Fig. 5.8). In this region, small blood vessels arising from the pancreas need careful cautery. The distal common bile duct is dissected along the retroduodenal area to within the head of the pancreas where it is transected. The cholangiogram gives a

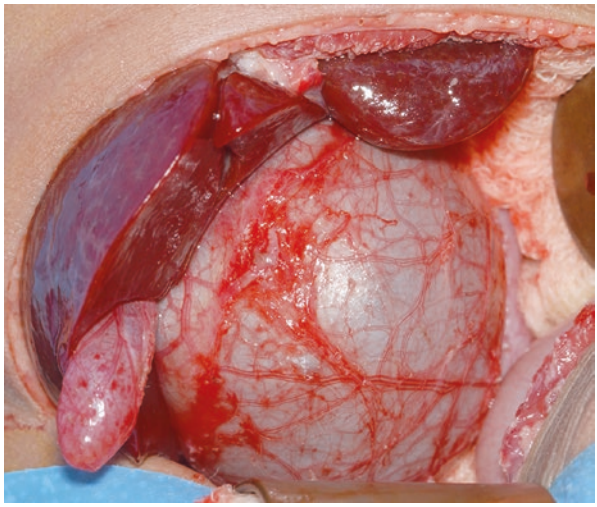

Fig. 5.7 A large type Ic cyst that was decompressed to facilitate further dissection

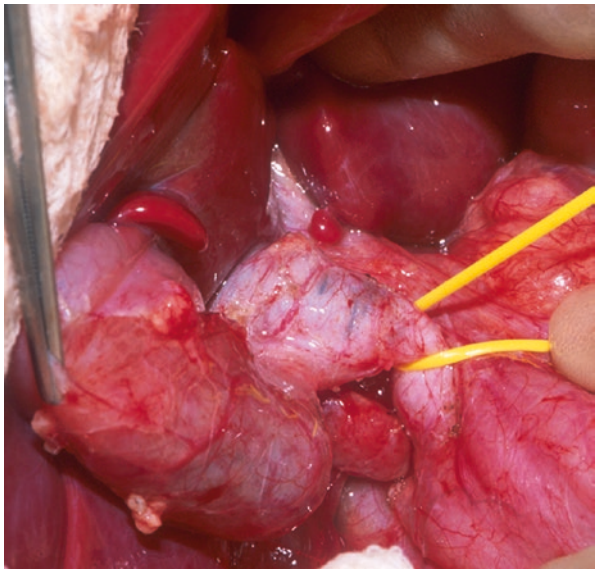

Fig. 5.8 The CBD has been slung prior to distal dissection to within the head of the pancreas

useful indication of the appropriate distal level of bile duct transection. Calculi or protein plugs within a dilated common channel should be cleared using saline irrigation, biliary balloon catheters and, in older children and adults, intraoperative endoscopy with a narrow irrigating endoscope. The stump of the distal bile duct is then ligated or oversewn with an absorbable suture.

The cyst and gallbladder are elevated forward, exposing the portal vein behind. Occasionally, the right hepatic artery crosses anterior to the cyst and is adherent to its wall, when it should be carefully freed and preserved (Fig. 5.9). The common hepatic duct is divided at the level of the bifurcation with scissors or scalpel rather than electrocautery; it should look healthy and well vascularised. The aim should be

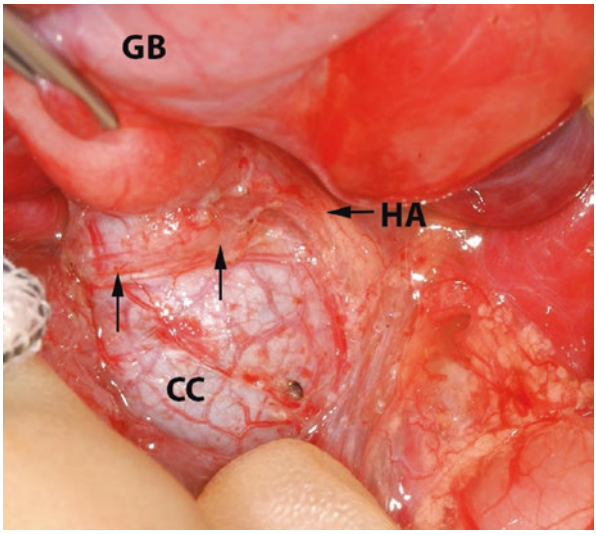

Fig. 5.9 Occasionally, the right hepatic artery crosses anterior to the CC and is adherent to its wall (arrows), when it must be carefully freed and preserved. *CC* choledochal cyst, *GB* gallbladder, *HA* hepatic artery

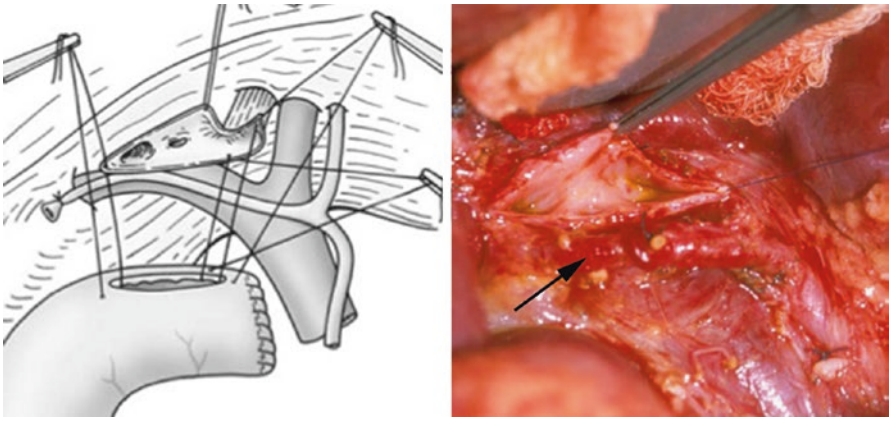

Fig. 5.10 Wide hilar hepaticojejunostomy (modified from Stringer 2007). The arrow indicates the right hepatic artery that was crossing posterior to the CHD

to excise all the CHD whilst preserving the hilar duct confluence. Debris is cleared from any dilated hilar or intrahepatic ducts by catheter irrigation with normal saline and, in larger ducts, with a choledochoscope [85]. The extrahepatic segment of the left hepatic duct is incised for a variable distance (5–10 mm) to enable a wide hilar hepaticoenterostomy (Fig. 5.10) [86, 87]. Anastomosis to the narrow common hepatic duct must be avoided because of the subsequent risk of stricture and malignancy. Opening the hilar duct confluence and left hepatic duct in this way allows identification and treatment of any associated hepatic duct stricture that may be part of the choledochal pathology [88].

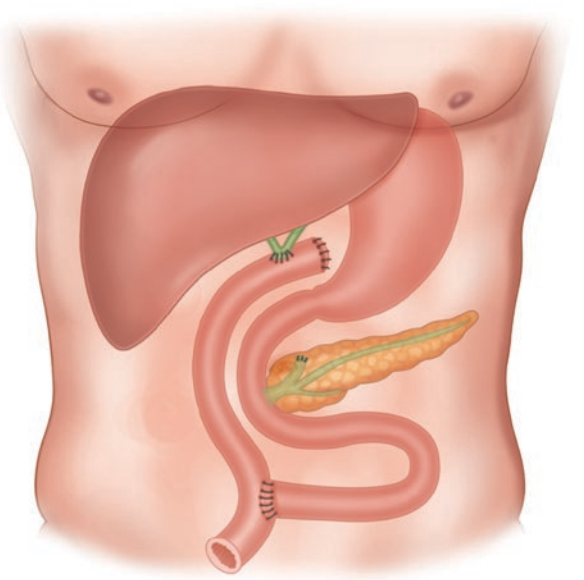

Fig. 5.11 Schematic representation of Roux-en-Y hepaticojejunostomy with a wide hilar anastomosis. Note that the bilioenteric anastomosis is fashioned close to the stapled end of the retrocolic Roux loop to avoid later redundancy

The duodenojejunal flexure is identified, and the jejunum divided approximately 15–20 cm downstream with a linear stapler, at a site where there is a suitable vascular arcade to fashion a Roux loop which will reach the hilum of the liver without tension. The stapled end of the Roux loop is oversewn with an absorbable suture and passed through a window created in the transverse mesocolon just to the right of the middle colic vessels. The jejunal Roux loop is widely anastomosed to the hepatic duct bifurcation at the liver hilum using fine interrupted monofilament absorbable sutures (e.g. 6/0 PDS) (Fig. 5.11). Magnifying loupes enable a precise anastomosis to be constructed. The width of the anastomosis should ideally be 2 cm or more in adults, 1.5 cm or more in children and a minimum of 6mm in neonates [87]. The anastomosis is fashioned a few millimetres from the end of the Roux loop to avoid the risk of developing a blind pouch or sump with future growth of the bowel. The author uses a 30 cm Roux loop in older children and a 20 cm loop in infants. Cholangitis after CC surgery is related to inadequate bilioenteric drainage (avoided by a wide hilar hepaticoenterostomy) rather than ascending infection via the Roux loop. Other authors have found no increased rate of cholangitis with Roux loops shorter than 40 cm [89].

The proximal jejunum is anastomosed in an oblique end-to-side manner to the Roux loop using a single layer of interrupted extramucosal absorbable sutures. Bowel handling and exposure are kept to a minimum to minimise the risk of adhesions. The mesenteric defects in the small bowel mesentery and transverse mesocolon are closed with fine interrupted sutures. A liver biopsy is taken at the end of the operation to document hepatic histology. The operative field is irrigated with warm saline, and, in straightforward operations, the abdomen is closed without drainage. If a drain is inserted, it is placed in Morison's pouch rather than in direct contact with the hepaticoenterostomy.

5.10.3 Laparoscopic Approach

After insertion of a urinary catheter and nasogastric tube and with the patient 30° head up, a 5 or 10 mm camera port is inserted at the umbilicus using an open Hasson technique. Three working 5 mm ports are inserted in the right and left flanks and right side of the abdomen, respectively. The pneumoperitoneum is set at 8–12 mm Hg. In children, a combination of 3 mm and 5 mm instruments is used. Operative steps are as follows: liver suspension by a suture around the round ligament close to the umbilical recess; needle puncture of the cyst and cholangiography if the anatomy has not been adequately defined preoperatively; needle decompression of larger cysts; ligation and division of the cystic artery; cholecystectomy; dissection of the lower part of the CC, opening it transversely; cautery dissection of the cyst staying close to its wall; division and ligation/clipping of the distal common bile duct; proximal dissection of the cyst; and transection of the bile duct at the hilar bifurcation. If a Roux-en-Y loop anastomosis is planned, this can be fashioned manually after exteriorising a segment of jejunum through an extended incision at the umbilical trocar site [90]. Alternatively, an entirely intracorporeal technique can be used [91]. The jejunum is anastomosed to the hepatic duct bifurcation with interrupted or continuous sutures. Hepaticoduodenostomy is a popular alternative since it is quicker and avoids an extracorporeal procedure [90, 92]. There have been recent reports of single-incision laparoscopic repair [93].

Additional/alternative operative techniques are shown in Table 5.2 [3, 15, 93, 94], and operative approaches to less common types of choledochal cyst are outlined in Table 5.3 [6, 7, 9, 25, 95].

Table 5.2 Additional/alternative operative techniques

Hepaticoenterostomy	An end-to-end hilar hepaticojejunostomy can be used instead of an end-to-side anastomosis. Some surgeons advocate hepaticoduodenostomy rather than hepaticojejunostomy, arguing that it is more physiological, is associated with a lower risk of adhesion obstruction and minimises the loss of absorptive mucosa, but there are concerns about bile gastritis and the long-term potential for anastomotic malignancy. The appendix should not be used as a conduit (hepatico-appendico-duodenostomy) because of a high incidence of biliary obstruction. An intussusception 'valve' offers no advantage in the Roux loop
Hilar ductal strictures	Can be managed by ductoplasty or an extended hilar anastomosis
Aberrant extrahepatic bile ducts	Should be incorporated into the bilioenteric anastomosis [16]
Dilated common pancreaticobiliary channel containing debris	The channel must be cleared of debris. A transduodenal sphincteroplasty may be considered
Portal hypertension or dense inflammation from previous infection/surgery	May make radical cyst excision hazardous. Intramural resection of the posterior wall of the cyst (excising only the mucosa and inner wall) reduces the risk of severe haemorrhage and injury to the portal vein [94, 114]
Severe cholangitis	Temporary preoperative endoscopic stenting and drainage may be useful in affected patients [5]
Possibility of malignancy	Intraoperative frozen section histology should be available [3]

Table 5.3 Operative approaches to less common types of choledochal cyst

PBM with minimal or no bile duct dilatation	Should not be treated by endoscopic sphincterotomy, transduodenal sphincteroplasty or cholecystectomy alone because these patients are at risk of recurrent pancreatitis and biliary tract malignancy. The extrahepatic bile ducts and gallbladder should be excised [9, 25]
Type II cysts	Excision of the diverticulum and repair of the bile duct are described but only really applicable to a CBD diverticulum. A type II diverticulum of the CHD or a diverticulum complicated by severe inflammation or malignancy is best treated by complete extrahepatic bile duct resection and bilioenteric drainage [6]. Laparoscopic excision of the diverticulum is challenging because of potential damage to native bile ducts [6]
Type III cysts	No consensus on surgical management [7]. Large choledochoceles have been marsupialised transduodenally or treated by extrahepatic bile duct excision and Roux-en-Y hepaticojejunostomy. Smaller choledochoceles have been treated by open sphincteroplasty or endoscopic sphincterotomy, but this is only appropriate if there is no PBM
Type IVa cysts	After treatment of the extrahepatic component, residual intrahepatic ductal disease may lead to recurrent cholangitis, stones, abscesses and cancer. Liver resection is an option for intrahepatic disease confined to one lobe [95]. For bilobar involvement, liver transplantation may eventually be required
Type V cysts	Solitary asymptomatic cysts can be left untreated. For multiple symptomatic cysts confined to one lobe, hepatic lobectomy may be curative. Diffuse bilobar disease not controlled by antibiotics and drainage procedures is an indication for liver transplantation

CBD common bile duct, *CHD* common hepatic duct, *PBM* pancreaticobiliary malunion

5.11 Results and Complications of Surgery

Radical cyst excision and wide hilar hepaticoenterostomy achieves consistently good results, particularly when performed in children with uncomplicated cysts [12, 87, 96]. Complications after CC resection are more common in adults than children [3, 97], and outcomes are distinctly worse in the small proportion of adults with concomitant liver disease, portal hypertension or malignancy.

After successful surgery, hepatic cholestasis, bile duct proliferation and inflammation resolve. Regression of hepatic fibrosis and early biliary cirrhosis have been documented by some [61, 98] but not all authors [14]. Biochemical liver function tests including gamma-glutamyltransferase (GGT) should become normal postoperatively. Early postoperative complications such as anastomotic bile leak, bleeding, acute pancreatitis, wound infection and intestinal obstruction are uncommon. A bile leak usually resolves with external drainage and intravenous antibiotics.

Late complications include bilioenteric anastomotic stricture (Fig. 5.12), stone formation (especially within dilated intrahepatic ducts in type IVa cysts), pancreatitis, adhesive bowel obstruction and malignancy. Chronic low-grade biliary obstruction can progress to secondary biliary cirrhosis. These long-term complications may present clinically (e.g. cholangitis) or with abnormal liver function tests or follow-up ultrasound scans. An anastomotic stricture may develop 10 years or more, postoperatively [99]. Todani reported a 10% reoperation rate among 103 children

followed for a median of 14 years, and Yamataka et al. noted a 9% major complication rate in another 200 Japanese children followed for a mean of 11 years [12, 97]. In both series, revisional surgery was required to treat cholangitis secondary to anastomotic or ductal strictures, ductal calculi, common channel calculi and adhesive small bowel obstruction. Complications were more common with type IVa cysts or after bilioenteric anastomosis to the CHD [96] (Fig. 5.13). Complications after wide hilar hepaticojejunostomy are rare [87].

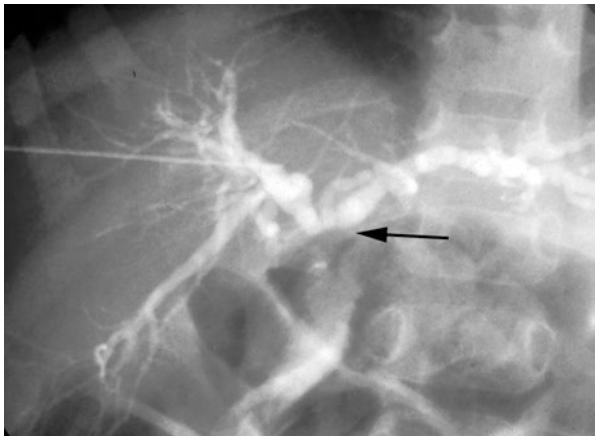

Fig. 5.12 A percutaneous transhepatic cholangiogram demonstrating dilated intrahepatic ducts proximal to a bilioenteric stricture (arrow) in a 14-year-old girl presenting 12 years after surgery elsewhere for a type I CC

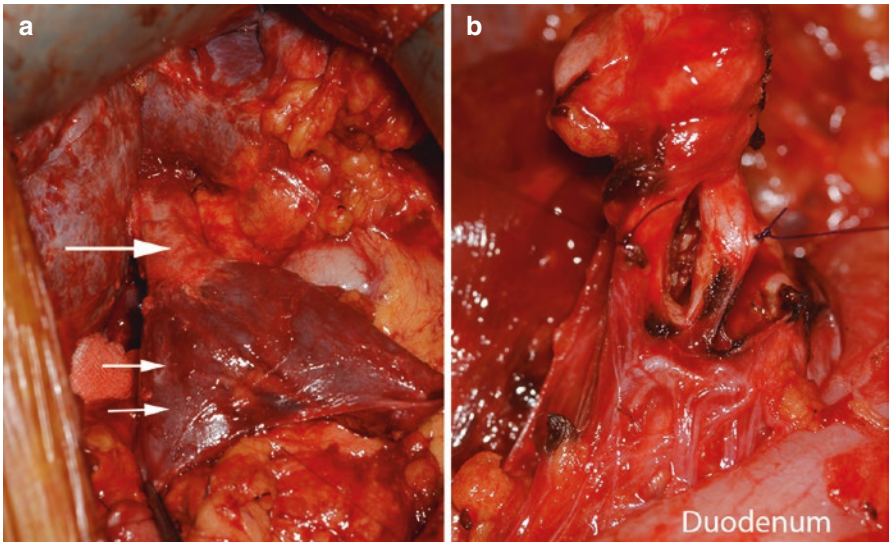

Fig. 5.13 (**a**) Redo surgery for an incompletely excised CC in an adult. Note the residual CHD (large arrow) and upper end of the previous Roux loop (small arrows) which has been divided and is therefore devascularised. (**b**) The residual CHD and attached end of the Roux loop have been elevated and opened to reveal contained debris. The right hepatic artery is visible crossing posterior to the CHD

Cholangitis may signify an anastomotic bilioenteric stricture, an intrahepatic ductal stricture or stone, debris/obstruction within the Roux loop or, rarely, a malignancy. Interventional radiology may enable stones to be cleared and strictures dilated and can also provide temporary percutaneous transhepatic biliary drainage of infected bile [100], but surgery is often required for definitive treatment of these problems.

Pancreatitis may develop years later in individuals with a residual complex or dilated common channel containing protein plugs or calculi or in patients with a significant residual distal bile duct remnant [101] (Fig. 5.14). ERCP is useful in assessment, and endoscopic sphincterotomy may be curative.

Malignancy can still develop after CC excision, particularly if the CC has been incompletely excised [65, 102–105]. Even after adequate cyst excision, malignancy can develop in residual extrahepatic ducts such as the intrapancreatic remnant of the distal CBD or in abnormal intrahepatic ducts, particularly in type IVa cysts [106–109]. Lee and Jang reviewed 54 cases of malignancy following CC excision (60% type IVa and 40% type I): the most frequent site of involvement was the hepatic duct at, or near, the bilioenteric anastomosis, followed by the intrahepatic ducts and the

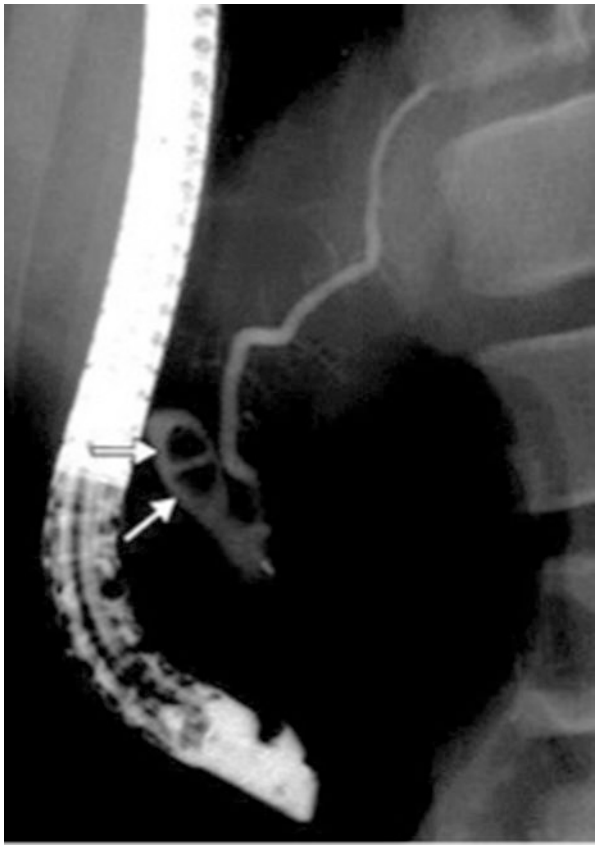

Fig. 5.14 Intrapancreatic remnant of distal CBD containing gallstones following CC excision many years previously. The patient represented with acute pancreatitis. This can usually be avoided by adequate primary surgery

distal remnant CBD [104]. The mean interval between initial surgery and the cancer was 10 years (range 1–32 years). The authors concluded that '… wide anastomosis with free drainage of bile as well as complete excision of dilated bile duct(s) appears essential to prevent development of carcinoma'. Malignant change typically carries a poor prognosis, even worse than cholangiocarcinoma in general, largely due to late-stage tumours [64, 104, 108]. Type IVa cysts and adults >30 years are at greater risk of long-term complications [110]. Outcomes may be improved by earlier tumour detection using routine surveillance imaging, liver function tests and tumour markers such as carbohydrate antigen 19-9 (CA19-9) [104] and by appropriately investigating patients with cholangitis or hepatolithiasis after cyst excision [65]. Currently, there is no consensus on how best to follow up patients after CC excision [111].

5.11.1 Should Choledochal Cysts Be Treated by Specialist Hepatobiliary Surgeons?

Excising a CC is usually straightforward. However, a good long-term outcome requires radical cyst excision and a wide hilar hepaticoenterostomy. A survey of Dutch paediatric surgeons found that two-thirds encountered a CC no more than twice a year; evidence-based management was less likely when compared to those with greater experience [112]. Surgical complications are probably more likely if the operation is performed occasionally. In a recent series from the USA, seven surgeons managed 62 paediatric CC over 22 years [45]. Complications occurred in 31% of patients during a median follow-up of only 2 years: these included anastomotic leaks requiring revision, laparotomies for adhesion obstruction, residual cysts, cholangitis, pancreatic duct stones and anastomotic stricture.

The need for hepatobiliary expertise is also highlighted by the laparoscopic literature. Laparoscopic excision of a CC was first reported in 1995 [113]. Since then, numerous articles have described the results of surgery using minimally invasive techniques (including robotic surgery) in children and adults [90, 114–128]. Purported benefits of laparoscopic approaches include reduced postoperative pain, shorter length of hospital stay, fewer postoperative adhesions, better cosmesis and earlier return to activity, but most reports have been retrospective with historical controls, ignoring the fact that open surgical techniques have improved. Operative times have generally been longer with laparoscopy. Other major concerns about current laparoscopic results are:

1. The bilioenteric anastomosis is frequently at the level of the CHD rather than a wide hilar hepaticoenterostomy [90–92, 114, 121, 122]. This has led to a high incidence of bilioenteric stricture and redo surgery within relatively short follow-up periods [90, 129, 130].
2. The level at which the distal CBD is transected is often poorly described [116, 118, 119, 121, 128] raising concerns about the length of the remaining intrapancreatic bile duct remnant.

3. Intraoperative injuries to the portal vein [90, 131], right hepatic artery [117] and hepatic duct [90, 92] have been reported. In some series, blood transfusion has been necessary in 5–13% of patients [116, 119, 121].
4. Hepaticoduodenostomy has been promoted over hepaticojejunostomy predominantly because it is technically quicker and easier to perform laparoscopically and can be completed without the need for an extracorporeal enteric anastomosis [92, 132]. Issues related to duodenogastric bile reflux and gastritis [133] have been downplayed. Concerns have been expressed about the long-term risk of cholangiocarcinoma and gastric cancer after hepaticoduodenostomy [134, 135].

Laparoscopic techniques continue to be refined. Examples include using a ureteroscope to gauge the length of intrapancreatic bile duct [136] and to clear the common channel of any protein plugs [137] and performing a ductoplasty to widen the bilioenteric anastomosis [138].

In summary, CCs are relatively rare and complex and should ideally be managed by hepatopancreaticobiliary surgeons. For most types of CC, the goal of surgery is to achieve radical cyst excision and wide hilar hepaticojejunostomy. Surgeons must avoid the short-term attractions of laparoscopic approaches (principally cosmetic with a potentially faster recovery) if the long-term results of best practice open surgery cannot be replicated using minimally invasive techniques [139]. It is crucial to understand that the outcomes of CC surgery in young individuals are not fully evident for decades. In the future, it will be important to develop optimum follow-up protocols such that late complications after surgery are detected early and cost-effectively.

Conclusion

Congenital dilatation of the bile duct(s), otherwise known as a choledochal cyst, may affect the extrahepatic or intrahepatic bile ducts or both. It is frequently associated with an abnormal union between the pancreatic and bile ducts, which allows reflux of pancreatic juice into the bile duct and predisposes to pancreatitis. Most patients with a CC present with abdominal pain and/or jaundice in childhood. The condition is more common in females and Orientals. Potential complications of the malformation include obstructive jaundice, cholangitis, cyst rupture, gallstones, pancreatic disease, secondary biliary cirrhosis and bile duct malignancy. For most types of choledochal cyst, optimum management involves accurate imaging of the bile and pancreatic ducts and associated pathology followed by radical excision of the extrahepatic bile ducts and reconstruction by wide hilar hepaticoenterostomy. Long-term follow-up is essential to detect late complications such as bilioenteric strictures and malignancy which are more likely to occur if the original excision and reconstruction was insufficiently radical or if the original bile duct pathology involved both the intrahepatic and extrahepatic bile ducts.

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External Biliary Fistula (EBF): The Bare, Prepare and Repair (BPR) Approach to Management

6

Rajan Saxena, Selvakumar Balakrishnan, and Ashish Singh

6.1 Introduction

An external biliary fistula (EBF) is an unwelcome, complex and devastating problem faced by surgeons globally and is associated with severe physical and mental trauma to the patient [1]. It is also associated with considerable morbidity and mortality [2] (Fig. 6.1).

EBF is most commonly iatrogenic in origin, with post-cholecystectomy injuries of the bile duct being the front runner. Major bile duct injury occurs in 0.1–0.2% of open cholecystectomies and 0.3–0.5% of laparoscopic cholecystectomies [3, 4]. At the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), a tertiary care referral centre in North India, we have managed more than 600 bile duct injuries in the last 25 years. Of these, more than 70% were associated with EBF (unpublished data).

External biliary fistulas can be classified:

1. Based on the presence or absence of an intra-abdominal collection—uncontrolled or controlled
2. Based on the nature of discharge and extent of associated injuries—purely biliary or complex bilio-pancreatic-visceral
3. Based on the presence or absence of an associated vascular injury

Technically, external biliary drainage done with therapeutic intent either as a part of staged management or as a permanent option (e.g. percutaneous transhepatic biliary drainage [PTBD], endoscopic nasobiliary drainage [ENBD], tube cholecystostomy) may also be considered to be an EBF. These fistulas are usually well controlled and well managed as the treating physician would take precautionary measures to

R. Saxena (✉) · S. Balakrishnan · A. Singh
Department of Surgical Gastroenterology & Liver Transplant Unit,
Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

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Fig. 6.1 Clinical image of a patient of post-cholecystectomy bile duct injury with a long-standing uncontrolled external biliary fistula (EBF)

prevent tube slippage and the consequences of chronic loss of bile. As a result, these entities will not be discussed in this chapter as the present discussion is intended to focus purely on EBF following biliary surgery. The discussion on 'ravages' of EBF (see below) is equally applicable to the management of these patients, as well.

6.2 Aetiology

EBF may result:

1. After cholecystectomy with or without common bile duct exploration (CBDE)
2. After bilio-enteric anastomosis
3. After surgery for hydatid disease of the liver
4. After liver trauma—blunt/penetrating
5. After liver resection for disease or as part of organ donation
6. After liver transplantation
7. Following radiological intervention (liver biopsy, abscess drainage, etc.)
8. Due to spontaneous perforation in the biliary tree, e.g. rupture of a choledochal cyst or spontaneous cholecysto-cutaneous fistula due to stone disease or malignancy

An EBF, over time, results in significant physiological alterations in the patient, which we have broadly referred to as the 'ravages' of EBF.

6.3 The 'Ravages' of EBF

The 'ravages' of EBF are a function of:

(a) The volume of daily bile loss
(b) The duration of fistula

(c) The presence of associated sepsis
(d) The degree to which bile is diverted from the gastrointestinal (GI) tract and whether this diversion is complete or partial

The 'ravages' of EBF include:

1. *Collection*: In all uncontrolled fistulas, the intra-abdominal collections may be localised (bilomas or abscesses, if infected) or generalised (bile ascites or peritonitis, when infected). Infected collections can get complicated by septicaemia, ileus or multi-organ failure. Infected collections, if present for prolonged periods, may eventually lead to internal fistulisation.
2. *Sepsis*: Secondary infection of bilomas leads to severe sepsis. Additionally, most of these patients have a partially or completely obstructed biliary system, which is an associated risk of cholangitis. Patients with recurrent cholangitis, not managed with early biliary drainage, may progress to develop cholangiolitic abscesses, which further perpetuate sepsis. These abscesses are more often seen in bilio-vascular injuries, with ischaemia contributing to impaired clearance of bacteria by the liver and resultant abscess formation in the ischaemic liver.
3. *Deficits*:
   (a) *Dehydration and dyselectrolytaemia*: Long-term total EBF results in fluid and electrolyte disturbances if refeeding of bile or timely replacement therapy is not instituted. Sodium loss is usually greater than the chloride loss, leading to metabolic acidosis [5]. The serum potassium level is initially low, but the accompanying fluid loss may lead to a decrease in plasma volume, low-output renal failure, and consequent hyperkalaemia [6].
   (b) *Anaemia*: The anaemia encountered in these patients could be due to pre-existing factors, chronic sepsis and resultant catabolic state, and/or at times due to blood loss secondary to the associated vascular injury and its consequences like haemobilia, bilhemia, associated pseudoaneurysm formation and associated bleed.
   (c) *Coagulopathy*: It is related to impaired production of vitamin K-dependent coagulation factors. Complete diversion of bile from the intestine contributes to fat-soluble vitamin malabsorption. Associated sepsis may also contribute to the development of coagulopathy.
   (d) *Bleeding*: It may be the effect of a generalised mucosal bleed or a disseminated intravascular coagulation (DIC) like situation owing to coagulopathy (related to vitamin K malabsorption or associated sepsis) or due to bleeding from a focal point such as a hepatic artery pseudoaneurysm or fistula tract granulation tissue bleed or both.
   (e) *Nutrition defects*: EBF can also lead to severe protein energy malnutrition, due to loss of protein-rich bile with bile salts, fat malabsorption due to bile diversion from gut, poor intake and a catabolic state due to ongoing sepsis. In neglected cases, deficits of other fat-soluble vitamins like vitamins A and D are also apparent in the form of night blindness and osteoporosis.

(f) *Skin excoriation*: EBF-associated skin problems are more often a sign of complex biliary fistulas (and associated activation of pancreatic enzymes), rather than a pure biliary fistula. Whenever it does occur, it is due to epidermal loss around the surgical wound or the drain site. This contributes further to catabolism, leading to protein and blood loss contributing to further morbidity in the form of pain and a reduced quality of life.
(g) Total diversion of bile may also result in disruption of the intestinal barrier function, bacterial translocation and sepsis [7].

These 'ravages' determine the patient's clinical presentation. Generally, patients present with sepsis due to an undrained collection or generalised biliary peritonitis or cholangitis due to an obstructed biliary system. The less common presentation would include lack of sepsis and a controlled biliary fistula.

6.4 Principles of Management: The 'BPR' Approach

A multidisciplinary approach is essential for success in the management of these patients and involves the surgeon, endoscopist and intervention radiologist working together [8] (Fig. 6.2). The general principles of management of all EBF are the same and include fluid resuscitation, correction of dyselectrolytaemia, control of sepsis, replenishment of deficits, investigational workup to delineate the type and extent of bile leak leading to fistula, relieving any distal biliary obstruction, allowing a period of conservative management for fistula closure and delayed definitive surgery.

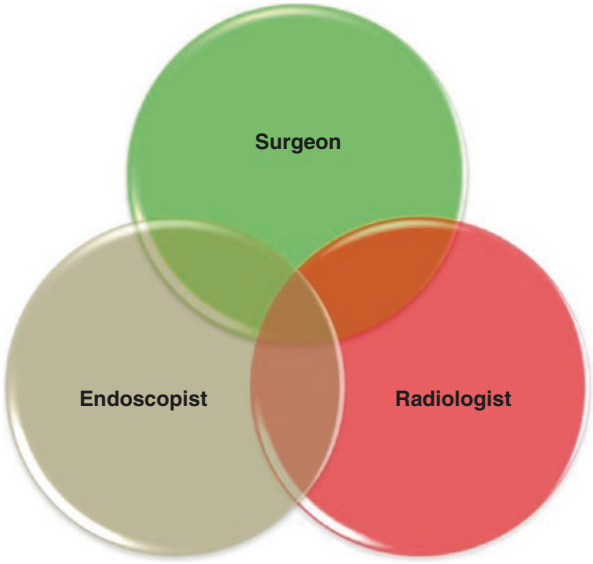

Fig. 6.2 The multidisciplinary team in the management of an external biliary fistula (EBF)

The *bare, prepare and repair (BPR) approach* is a staged approach to the management of EBF. In the following account, we will deal primarily with post-cholecystectomy bile duct injuries as they constitute the most common cause of EBF in our practice. Management of other conditions will be detailed in individual sections thereafter.

The exception to the staged (BPR) approach is patients referred early (within 72 h) following a bile duct injury, where an early attempt at repair can be feasible in the absence of sepsis. Although the 'ravages' of EBF are absent in this subset, the drawback for a surgeon is operating on a non-dilated duct. The staged approach detailed here is a universal approach applicable even in this situation, and it provides the added comfort of operating on a dilated duct at a later date. However, in the current context of an increasing experience with liver transplantation and biliary reconstruction in an undilated system coupled with the ability to deliver satisfactory long-term results, the impact of duct diameter on long-term success is questioned especially in high-volume biliary and transplant centres so long as a sepsis-free environment can be assured. This further reinforces the need for referral to and the management of such patients at high-volume centres with surgeons specialised in hepato-biliary surgery [9].

6.5 'Bare, Prepare and Repair'

6.5.1 Bare

The term 'bare' encompasses the attempt at obtaining a complete understanding about the patient with EBF. It represents a holistic approach and involves assessing the patient's general condition, comorbidities and consequences of the EBF (the 'ravages' listed above) and understanding the precise biliary anatomy accounting for every segmental and aberrant duct and whether they are dilated or not. The 'bare' phase is vital to the subsequent stages of management. This understanding leads to better patient optimisation and development of a sound definitive management strategy including either endoscopy, surgery or both, aimed at achieving the best possible outcomes in both the short and long term. It also helps to prognosticate the patient.

In summary, 'bare' aims to understand:

1. The ravages of the injury
2. The status of the biliary tree and its detailed anatomy (up to the subsegmental ducts)

6.5.1.1 Evaluation of 'Ravages'

1. History taking and reviewing old records:
   The first step involves taking a detailed and relevant history. A good history, especially in postoperative EBF, enables an understanding of the biliary pathology (that led to the index surgery), the nature and extent of the surgery and the cascade of ensuing events. Serious effort must be made to retrieve all prior records including preoperative blood results (e.g. complete haemogram, liver

function tests), preoperative imaging (abdominal ultrasound/USG, computed tomography/CT scans, magnetic resonance imaging/MRI) and the operative notes. These documents provide an insight into the events that led up to the surgery and that could have contributed to the biliary injury and resultant EBF.

It is vital to contact the surgeon involved in the operation and to go over the sequence of events that led to the injury (including intraoperative findings such as aberrant anatomy, presence of adhesions, ease of surgery, whether bile was noted in the porta, any untoward bleeding that may have led to a hasty attempt at controlling the bleed, any attempt at repair and the type of suture used, 'two openings' at cystic duct of the gall bladder specimen, etc.) and its aftermath. This information must be diligently recorded in the patient's notes.

2. Clinical examination:
   (a) Assessment of vital functions, level of hydration, as well as the nature and damage to the skin at the site of fistula
   (b) Features suggestive of dyselectrolytaemia
   (c) Clinical evidence of sepsis—altered sensorium, fever, tachycardia, tachypnoea, and acidotic breathing
   (d) Clinical signs of peritonitis
   (e) Monitoring of urine output
   (f) Indwelling drains—number, ensuring their secure fixation, drain output and nature of effluent

In patients with a long-standing history of EBF, additional features that need to be assessed clinically include:

(g) Evidence of protein-calorie malnutrition—pedal oedema, temporal /buccal hollowing, skeletal muscle wasting, low body mass index (BMI), lack of skin tone and turgor
(h) Evidence of fat-soluble vitamin deficiency—Bitot's spots and acanthosis of the skin (vitamin A deficiency), pathological fractures (vitamin D deficiency), petechiae and signs of easy bruising (features supportive of a coagulopathy due to vitamin K deficiency)
(i) Evidence of micronutrient and other vitamin deficiencies including angular stomatitis, beefy red tongue, etc.

3. *Laboratory tests*: These include a complete haemogram, renal function tests and electrolytes, liver function tests, albumin and coagulation profile (prothrombin time, international normalised ratio/INR, activated partial thromboplastin time/APTT). In addition, levels of serum calcium, magnesium and phosphate are also assessed. These tests may have to be repeated serially depending on the clinical condition of the patient.
4. *Cross-sectional imaging*—to look for collections:
   (a) USG
   (b) Triple-phase contrast-enhanced CT (CECT) scan of the abdomen and pelvis
   (c) MRI of the abdomen and pelvis

An abdominal USG is usually the first investigation done to look for collections in a patient with EBF. It is simple and non-invasive, can be performed at the patient's bedside, can guide placement of percutaneous drains and can be repeated serially to look for resolution of collections. The USG needs to focus on common locations for collections following EBF such as the subhepatic, subphrenic, pleural effusion and pelvic spaces. It can easily pick large bilomas, but it is not sensitive for smaller collections and collections at other locations, especially near bowel. A bedside USG is all that may be possible in a sick patient admitted to the intensive care unit (ICU).

Triple-phase CECT scan of the abdomen and pelvis with oral contrast is the most sensitive investigation to pick all intra-abdominal collections in a patient with EBF. For a given collection, a CT scan provides a good spatial orientation, insight into the morphology of the collection, its relation to adjacent structures, presence of air within it as well as best possible routes to target the collection for CT-guided percutaneous drainage (Fig. 6.3). In addition, a CT scan can detect bowel injuries (manifesting as contrast leak), vascular injuries, liver abscesses, etc. [10]—all of which are of relevance in the management of a patient with EBF. CT scan has the added advantage of being a more widely available modality and hence presents a more familiar interface with ease of interpretation for the treating surgeon. Care should be taken to ensure that the patient is adequately hydrated and possesses normal renal functions prior to the scan to prevent contrast-induced nephrotoxicity. In patients with renal dysfunction, an MRI of the abdomen with MR cholangiopancreatography/MRCP is a good substitute for the 'bare' phase. The new generation rapid sequence MRI, if available, obviates several disadvantages of commonly available conventional MRI scans (vide infra) and could be a one-stop-shop in the management of EBF.

MRI of the abdomen has an accuracy similar to CT scan for locating collections, with the added benefit of the MRCP for delineating the biliary anatomy. However,

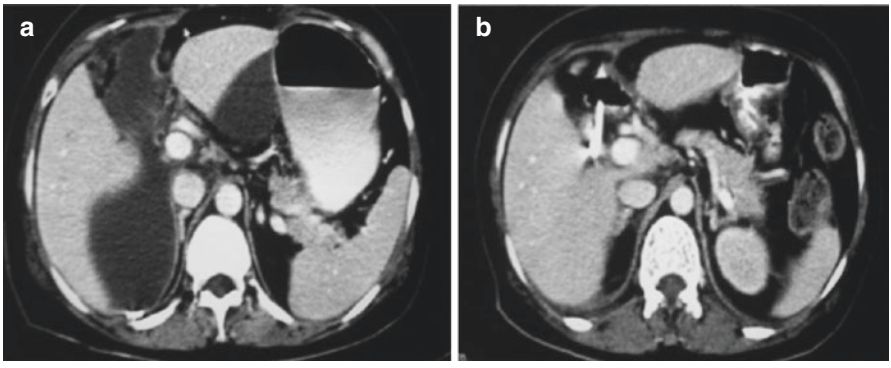

Fig. 6.3 Utility of a contrast-enhanced computed tomography/CT scan in the management of intra-abdominal collections. (**a**) Post-cholecystectomy biloma. (**b**) Post-percutaneous drainage (PCD) axial section in the same patient demonstrating a complete resolution in the collection

there are a few disadvantages of conventional MRI. In some parts of the world, MRI is not widely available with the attendant limitation in expertise to interpret the scan. Besides, it is time-consuming, which bears significance in a sick patient with sepsis and suspected collections. The priority in such a patient is detection and drainage of collections. The information on the biliary anatomy is of secondary importance. MRI also has limitations in guiding therapeutic interventions. Also, MRCP in the presence of perihepatic collections can be inaccurate in delineating the biliary anatomy.

Hence, CECT scan remains the investigation of choice for biliary collections in a patient with EBF. MRI may be considered in an EBF patient with renal failure.

6.5.1.2 The Biliary Map

In a patient with EBF, once control of sepsis is achieved, a clear road map with exact biliary anatomy is mandatory for formulating a definitive management plan, especially in the subgroup of patients with post-cholecystectomy bile duct injuries where immediate repair is being contemplated.

The 'biliary map' is directed at revealing the following:

1. Exact site and extent of injury
2. The status of bilio-enteric continuity
3. Any distal biliary obstruction
4. Any underlying biliary disease, particularly malignancy
5. Visualising the entire biliary tree

To obtain a complete map of the entire biliary tree, a single imaging modality may be insufficient, and a combination of imaging modalities may need to be resorted to achieve the goal. The following modalities, used in combination, may be required:

(a) MRCP
(b) Triple-phase CT scan
(c) Endoscopic retrograde cholangiopancreatography/ERCP
(d) Percutaneous transhepatic cholangiography and biliary drainage/PTC and PTBD
(e) Fistulogram
(f) Hydroxyindolediacetic acid/HIDA scan
(g) Abdominal USG

MRCP can detect the presence and delineate the level of biliary obstruction with an accuracy approaching 85–100% [11, 12]. It is a simple, non-invasive modality to map the biliary tree in the absence of bilio-enteric continuity. While it is capable of delineating an isolated biliary system, MRCP is fraught with the risk of overestimating the level of injury.

Triphasic CT scans permit a detailed assessment of the hepatic anatomy; atrophy-hypertrophy complex; biliary, arterial, and portal venous anatomy; and changes

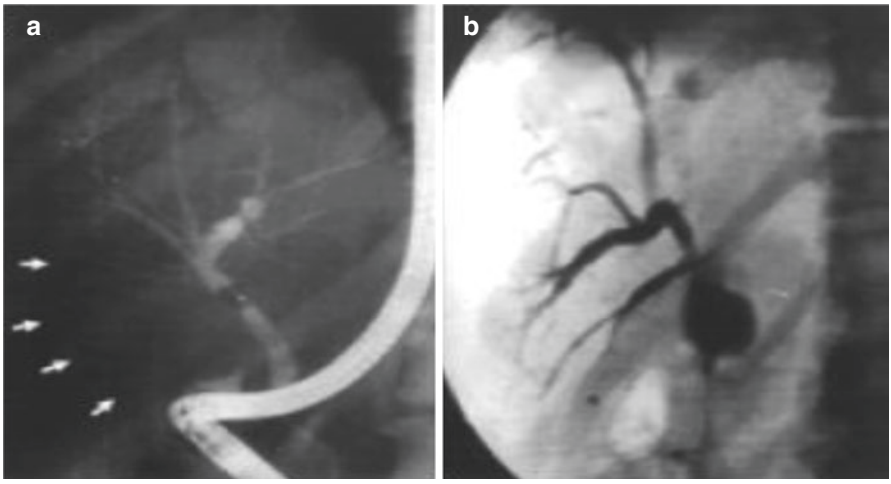

Fig. 6.4 BARE: Accurate biliary map using complementary investigations. (**a**) Endoscopic retrograde cholangiopancreatography/ERCP—balloon occluded ERC showing non-filling of the right posterior sectoral duct (arrows). (**b**) Percutaneous transhepatic cholangiogram/PTC demonstrating a dilated disconnected right hepatic duct/RHD with leak into a subhepatic biloma

indicative of cirrhosis. CT fistulography can be used to assess a fistulous tract as well as an isolated segmental/sectoral biliary system.

ERCP is a useful diagnostic and therapeutic modality where bilio-enteric continuity is maintained, at least in part [13] (Fig. 6.4), after bile duct injuries [14] and after liver transplantation with duct-to-duct reconstruction. It can provide an accurate biliary map but is rarely used nowadays solely as a diagnostic modality with the availability of non-invasive techniques like MRCP. It cannot delineate isolated biliary systems, and its use is restricted in the absence of bilio-enteric continuity.

In the present era, PTC has been replaced by MRCP which demonstrates biliary anatomy equally well even in a separated system. Chaudhary and colleagues [15], in a prospective study, demonstrated that PTC was comparable to MRCP in regard to image quality, assessment of the level of strictures, detection of intraductal calculi, cholangitic liver abscesses and atrophy of liver lobes. The need for multiple punctures at PTC to opacify all the biliary radicles, the risk of post-procedure cholangitis and the risk of vascular injury are some of the major drawbacks of PTC which render MRCP a preferred investigation.

A cholangiogram through a PTBD catheter/PTBD gram should always be performed whenever a PTBD has already been placed for biliary decompression, as it is a simple and cost-effective way of accurately delineating the biliary anatomy. Likewise an indwelling cholecystostomy or T-tube choledochostomy should be used for a direct contrast cholangiogram. Contrast injection at the time of these tubograms should be gentle with the patient in head-low position for adequate filling of intrahepatic biliary radicles under the cover of appropriate antibiotics. At our centre, we

prefer to use gravity-aided injections into these tubes rather than push injections, as we believe this reduces the risk of post-procedure cholangitis. Cholangiograms through tubes must be performed when the patient is out of sepsis.

Fistulography, too, may be attempted through a percutaneous drain (PCD) tube placed for drainage of perihepatic collections, once the fistula is controlled, under cover of appropriate antibiotics, and once the patient gets rid of sepsis. This provides a direct cholangiogram which effectively delineates the site of biliary fistula and the biliary anatomy (Fig. 6.5). It also determines whether a fistulous cavity has converted to a fistulous tract. However, fistulography is not useful in the early post-injury phase. In the absence of a matured tube tract in the early phase, the contrast will spill into the peritoneal cavity and is more likely to mask the site of injury rather than delineate the biliary tree.

HIDA scan is a useful non-invasive method of evaluating liver function and bile secretion to confirm the biliary enteric continuity, the presence of a fistula and the adequacy of drainage [16]. It is not useful for biliary tract mapping as it does not demonstrate the accurate anatomic details owing to limits in spatial and anatomical delineation.

USG abdomen is rarely done for biliary mapping as it cannot delineate the entire biliary anatomy nor define segmental biliary injuries. However, it can reveal the level of CBD block, formation of primary or secondary confluence and help in discerning features of cirrhosis. Its primary role is in the management of undrained collections.

The incidence of vascular injuries associated with BDIs ranges from 18 to 47% [17–19]. Although delineation of the vascular anatomy may not be considered routine practice at most centres as they do not change the management plan, it might be prudent to evaluate for vascular injuries as this helps in prognosticating the patients

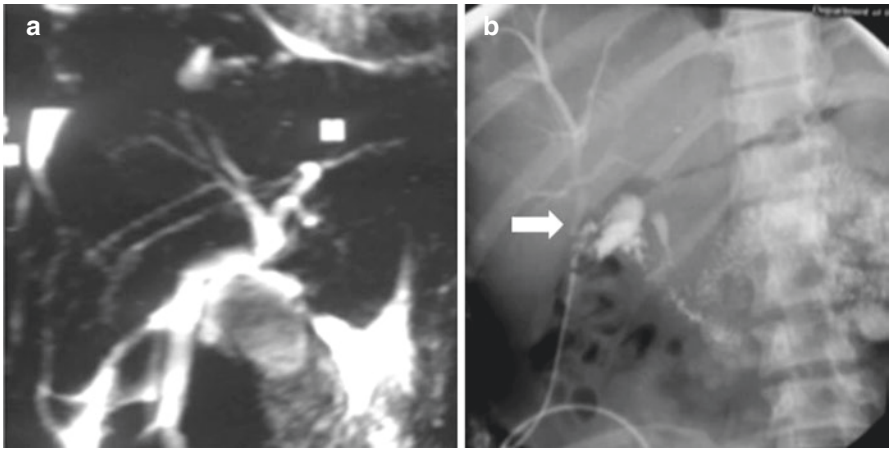

Fig. 6.5 Complementary imaging to bare the biliary tree. (**a**) MRCP, (**b**) Fistulogram The MRCP shows bile extravasation from the hilum without providing any segmental detail. Complementary use of imaging (fistulography) reveals an isolated injured to the right anterior sectoral duct (white arrow) as the source of biliary fistula

and from a medicolegal standpoint. Patients with a concomitant arterial injury with BDI tend to have a poorer outcome following repair [20]. Associated vascular injury complicates healing as the ischaemic biliary tissue converts to fibrotic tissue resulting in poor outcome of an apparently successful repair of biliary injury. Similarly, patients with concomitant portal venous injury run the risk of atrophy of the liver, warranting hepatic resection with a hepaticojejunostomy with the remnant segment of the liver to correct the problem [21].

No single imaging modality may be able to provide all the answers in a given patient with EBF. Thus, using a combination of complementary imaging modalities may enable the surgeon to develop a complete picture of the problem. MRCP is the most common modality used in the clinical setting with the addition of CT angiography for suspected bilio-vascular injuries.

6.5.2 Prepare: The Three 'C's

The 'bare' and 'prepare' phases of management proceed simultaneously. While in the 'bare' phase we try to understand the patient and the injury in their entirety, in the 'prepare' phase we optimise the patient's condition to provide their best chance at healing and a successful long-term result after repair of the fistula.

This phase can be outlined by *the three* '*C*'*s*:

1. **C**orrect the ravages of EBF by focussing on the following aspects that merit attention (acronym: **CHARN**):
   (a) **C**oagulation
   (b) **H**ydration
   (c) **A**naemia
   (d) **R**enal function
   (e) **N**utrition
2. **C**ontrol the fistula—draining collections and the biliary tree, if possible, by:
   (a) Insertion of PCD(s)
   (b) Surgical drainage—laparoscopy/laparotomy
   (c) Endoscopic biliary drainage (ENBD)/endoscopic stenting
   (d) Percutaneous transhepatic biliary drainage (PTBD)
3. **C**ontrol infection/sepsis:
   (a) PCD for liver abscesses
   (b) Biliary drainage for cholangitis (ENBD/PTBD/endoscopic stenting)

6.5.2.1 Correct: The Ravages of EBF: 'CHARN'

The consequences of chronic bile loss are the following:

1. Fat-soluble vitamin malabsorption—vitamins K, A, D and E
2. Protein energy malnutrition due to lack of digestion/absorption of dietary fats
3. Dehydration and a volume contracted state—due to chronic fluid loss

4. Potassium and bicarbonate depletion due to loss of electrolyte-rich bile
5. Acute kidney injury—due to volume contraction
6. Anaemia—due to chronic illness and sepsis
7. Breakdown of intestinal mucosal barrier with bacterial translocation
8. Immunosuppressed state—due to malnutrition and chronic illness

It is not uncommon to see a patient with EBF present nutritionally depleted and in a state of sepsis with anaemia, dehydrated and in renal failure, with a distended abdomen and multiple tubes draining bile exiting from the abdomen. EBF, despite being a benign condition, can reduce the patient to a state no different from a terminal malignancy.

Hence the first steps in management are resuscitation and stabilisation of the patient. This is followed by correction of the deficits and restoration of bile physiology as close to normal as feasible. These measures are carried out simultaneously rather than in a sequential manner and pari passu with 'bare'.

1. *Coagulation*: Coagulopathies manifest in the form of deranged prothrombin time/PT and INR. They are usually due to vitamin K deficiency and sepsis and are easily corrected by parenteral administration of vitamin K. In case the patient is too sick and needs an emergency intervention (PCD), transfusing the patient with fresh frozen plasma (FFP) for immediate correction of coagulopathy is an option.

   After normalisation of the PT and INR, other fat-soluble vitamin deficiencies need correction by intramuscular depot injections. Administration of depot injection before correction of coagulation deficits may cause a large injection site hematoma. Oral administration of fat-soluble vitamins is futile at this stage.
2. *Hydration*: Hydrate the patient by securing adequate venous access. Prior to attempting gaining central venous access, it is prudent to correct coagulopathy.

   Crystalloids are the preferred solutions for hydration, with the target to maintain a mean arterial pressure (MAP) >60 mmHg and a urine output >0.5 mL/kg/h. Initial fluid supplementation should be generous to take into account the accumulated fluid deficits over the past many days. Thereafter, fluid supplementation involves maintenance fluids and replacement for daily bile loss. Infusing albumin serves as a useful adjunct in severely malnourished patients with low plasma oncotic pressures.

   Hypokalaemia, hypocalcaemia and hypomagnesaemia are commonly encountered. Potassium, calcium and magnesium levels need to be monitored regularly, and supplements provided accordingly. Using a venous blood gas analysis to monitor metabolic derangements like bicarbonate deficit is advisable. Good hydration, as evidenced by a satisfactory urine output and correction of electrolyte deficits, generally ensures a gradual correction of bicarbonate with the need for a bicarbonate infusion being uncommon. Renal replacement therapy (RRT) may be required in patients with severe acidosis.
3. *Anaemia*: In a frail patient with EBF, anaemia creates an additional stressful hyperdynamic state and also hampers healing. Transfusing packed red blood

cells (PRBCs) to maintain a haemoglobin level of at least 9 g% is advisable. In addition, to promote healing, supplementation of vitamin C is warranted.

4. *Renal dysfunction*: Renal dysfunction in EBF patients is generally prerenal (due to a volume contracted state) and tends to get corrected with satisfactory hydration. In case of renal shutdown, RRT may need to be instituted, while other corrective measures are undertaken. A slow low-efficiency dialysis (SLED) or continuous renal replacement therapy (CRRT) is better tolerated by patients with hemodynamic instability in comparison to routine haemodialysis.
5. *Nutrition*: While the other deficits are being corrected, nutritional therapy is initiated. Usually these patients are in a severe catabolic state due to ongoing sepsis. This is compounded by intestinal fat malabsorption due to bile loss. A two-pronged approach—instituting supervised nutritional therapy (enteral or parenteral) and bile refeed (so long as enteral feeding is tolerated)—is the right way to go.

   Nutritional therapy may be enteral or parenteral, depending on the clinical condition of the patient, bowel motility and associated bowel injuries. These patients usually need 30–35 Kcal/kg/day and 1.5–2 g/kg/day of proteins. Whenever possible, enteral nutrition is preferred as it is cheap, is easy to administer and has associated immunological benefits. In cases of severe malnourishment, parenteral nutrition for the initial 7–10 days may need to be initiated until adequate enteral feeding is established.

   A useful approach is to devise a dietary chart for every patient based on easily available dietary items with dietary counselling and monitoring of daily intake. While oral feeds are preferred, in patients who are unable to tolerate or maintain adequate oral feeds sufficient to meet their daily requirements, placement of a fluoroscopically guided nasojejunal tube (NJ) for enteral feeding is another option. The advantages of NJ feeding are manifold including controlled delivery of calories and proteins, easy bile refeeding without the problem of bile-reflux gastritis and overall better patient tolerance as compared to nasogastric feeding.

   Every effort must be made to refeed the bile lost from drains, PTBD or ENBD. Bile refeeding corrects fat malabsorption and enhances the success of nutritional therapy. Besides, it restores gut mucosal integrity and gut immunity. Prior to commencing bile refeed, sending of serial bile cultures to guide appropriate antibiotic therapy for 5–7 days helps to avoid infective diarrhoea. While studies describe the refeeding of bile via enteric tubes (NG, NJ or feeding jejunostomy/FJ) [22], the authors do not resort to placing a feeding tube solely for the purpose of bile refeed. Refeeding bile orally prevents tube complications and makes it easy for feeding to be carried out at home. To improve the palatability for patients on oral nutritional therapy, the authors advise mixing the bile with a soft drink that the patient prefers or adding a flavouring agent. This practice not only masks the colour of bile but also helps to improve its acceptance. The addition of fat dense foods like cream or butter not only increases the palatability of bile but also its caloric value. Patients usually tolerate bile refeed well with an improved sense of well-being, except for occasional bile gastritis which is managed easily with the use of metoclopramide and sucralfate suspension. The authors have successfully used long-term oral bile refeeding in a liver transplant

recipient who had a tube hepaticostomy for 3 months followed by a delayed Roux-en-Y hepaticojejunostomy (*Manuscript in press*).

6.5.2.2 Control the Fistula

As discussed earlier, a 'controlled' EBF is a fistula with direct egress of bile to the exterior in the absence of any intra-abdominal collection. The strategic aim is to convert an uncontrolled fistula to a controlled one by draining all collections.

Initially in a patient with uncontrolled fistula and sepsis, empirical broad-spectrum antibiotics are initiated that cover the common spectrum of enteric organisms. Every available bile/pus sample should be cultured and antibiotic sensitivity analysed so that antibiotics can be changed depending on the culture reports.

Based on the mapping of the collections during the 'bare' phase with USG or CECT abdomen, these collections and the fistula may be tackled as follows:

1. Percutaneous drainage (PCD)
   After instituting a PCD where possible, the size of collections is monitored by serial USG or CT, and the PCDs may be gradually upsized or repositioned until complete resolution of all collections. In appropriately selected patients, PCDs usually achieve control of biliary fistulas with low morbidity, obviating the need for surgery.

   PCDs are usually successful in controlling the fistula of patients with even large but 'walled-off' collections in the absence of an associated bowel fistula. In a relatively stable patient without peritonitis, PCDs usually achieve control of the fistula but may require multiple sessions of intervention and prolonged hospitalisation. Besides, PCD may be all that is feasible in a patient who is too sick for surgery or who is admitted in the ICU with multi-organ failure, as it is possible at the bedside under USG guidance.

   PCDs may not be successful in patients with multiple collections at inaccessible locations or associated bowel injury. In such cases, surgery is a better option.
2. Surgical drainage
   Surgical drainage has been the traditional 'gold' standard and aims to achieve satisfactory drainage of all biliary collections in a single sitting. However, surgical drainage requires a general anaesthesia and a relatively fit patient to tolerate the insult of a major surgery. Hence, it may not be feasible in a severely moribund patient.

   In the present time, the indications of surgery for control of an EBF are limited to two scenarios - the low likelihood of a successful PCD placement or after failed PCD and in the presence of an associated bowel injury. It may be the only option at a centre lacking expertise in intervention radiology.

   The only goal of surgical exploration is to convert an uncontrolled situation into a controlled one by carrying out a peritoneal lavage and securing adequate and complete drainage. No attempt should be made at delineating or repairing the injured biliary anatomy as it is likely to result in more harm than good. A wide-bore drain with a terminal hole must be placed in the subhepatic space and as close to the hilum as possible.

3. Endoscopic drainage of the biliary tree
   After the fistula has been controlled, if the output is very high or the fistula has become persistent owing to a distal obstruction, endoscopic biliary drainage is considered. But it can only be attempted in the presence of a maintained bilio-enteric continuity. Additionally, in type A Strasberg injuries [23], endoscopic drainage may result in the definitive healing of the fistula.
   While some centres recommend a routine ERCP in every case of bile duct injury to look for bilio-enteric continuity and intervention, if warranted, in the same setting, the authors reckon that ERCP is too invasive and costly a procedure to be used routinely for establishing bilio-enteric continuity. ERCP is useful if there exists the possibility of a therapeutic benefit in the given patient.
   In the presence of bilio-enteric continuity, endoscopic drainage of the biliary tree may decrease the output of the EBF and hasten fistula closure. Endoscopic drainage is specifically indicated in the following situations:

(a) Distal biliary obstruction leading to persistent high-output fistulas, e.g. cystic duct stump blowout with choledocholithiasis (Fig. 6.6)
(b) Peripheral injuries such as the Strasberg type A injury
(c) Lateral injuries such as the Strasberg type D injury or lateral injury to the RHD, e.g. during extended cholecystectomy for carcinoma gallbladder (Fig. 6.8)
(d) Bile leak following liver transplant with duct-to-duct reconstruction

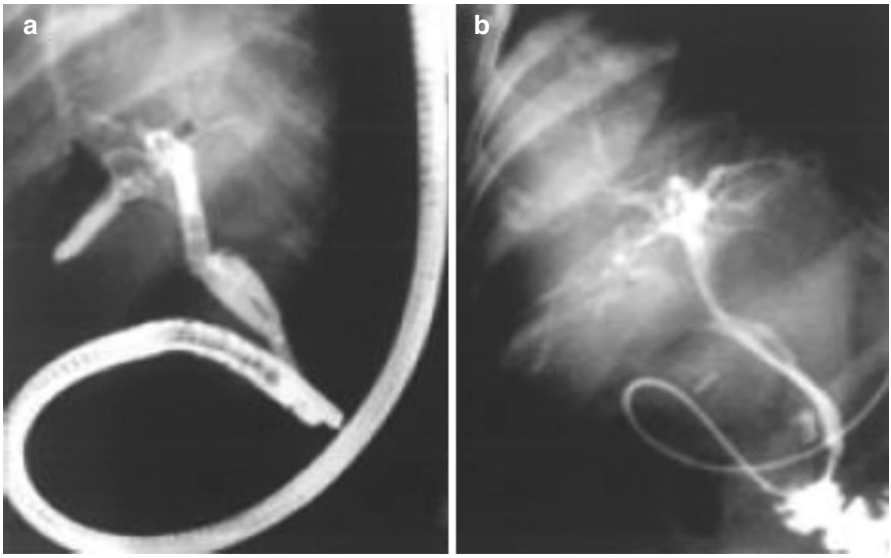

Fig. 6.6 PREPARE: EBF due to cystic duct stump blowout with missed common bile duct/CBD stones. (**a**) Note is made of leak of contrast on ERCP from the cystic duct stump and the presence of CBD stones. (**b**) Closure of the fistula 7 days after CBD clearance and endoscopic nasobiliary drainage/ENBD

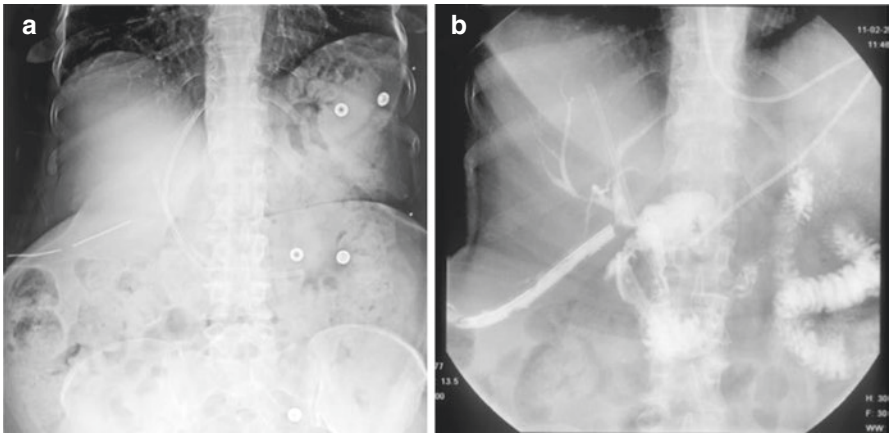

Fig. 6.7 Endoscopic intervention in EBF. (**a**) Right hepatic duct injury during extended cholecystectomy requiring multiple stents noted on a plain X-ray abdomen. (**b**) Placement of ENBD for control as seen on the ENBD gram. The fistula healed in 2 weeks

(e) Bile leak from cystobiliary communication (CBC) following hydatid cyst surgery
(f) Bile leak from the cut surface of the liver after hepatectomy

Endoscopic drainage may be achieved by one of the following procedures:

(a) Endoscopic sphincterotomy (ES)
(b) ES+ stenting across the defect
(c) ENBD used alone, or in combination, with stents (Fig. 6.7)

Although for a type A Strasberg injury ES is all that may be necessary, most endoscopists would place a stent as well. For a type D Strasberg injury or bile leak following a liver transplant, stenting across the defect definitely helps in the healing of the EBF. ENBD has its several advantages over stenting in that it permits bile sampling for culture, repeated flushing to prevent blockage, with the additional option to obtain a cholangiogram to check for closure of the fistula. In the long term, however, ENBD is uncomfortable for the patient and may contribute to significant fluid and electrolyte losses. The fluid and electrolyte losses following high output from the ENBD can be managed with bile refeeding.

4. Percutaneous transhepatic biliary drainage (PTBD)
PTBD is indicated for biliary decompression and control of a fistula in patients with bilio-enteric discontinuity, where endoscopic drainage is not possible. In persistent high-output fistulas, PTBD is used to divert bile from the fistula site to promote healing, thereby 'drying up' the fistula site and aiding future attempts at repair.

As with ERCP, PTBD is an invasive procedure with risk of complications and must hence be used judiciously.

6.5.2.3 Control Infection/Sepsis

Following drainage of collections, most patients with an EBF become sepsis-free, although, there remain some patients who will continue to remain septic. The causes for sepsis in these patients could be cholangitis and cholangitic abscesses or foci outside the abdomen such as pneumonia. In these patients, the causes of sepsis have to be specifically looked for and managed appropriately.

Cholangitis in the setting of EBF is usually associated with an obstructed biliary system. Based on the presence or absence of bilio-enteric continuity, an endoscopic or percutaneous biliary drainage usually helps to relieve cholangitis (Fig. 6.8).

Cholangitic liver abscesses may occur in neglected patients of EBF with recurrent cholangitis or in patients with bilio-vascular injuries. Most patients respond to biliary drainage and a prolonged course of appropriate antibiotics. For patients with persistent sepsis despite biliary drainage, or for those with large cholangitic abscesses or associated vascular injuries, PCD placement into these abscesses may be required to rid the patient of sepsis.

6.5.3 Repair

This is the last phase of the patient management and comes after all goals in the **bare** and **prepare** phases are achieved. For a successful repair and long-term outcome, there are three prerequisites:

1. An optimised patient
2. Appropriate timing and procedure
3. An experienced surgeon

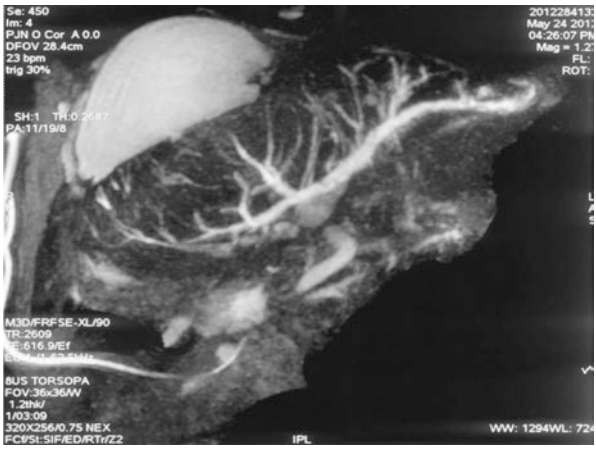

Fig. 6.8 MR cholangiopancreatography/MRCP with MRI abdomen in a patient of EBF with a subphrenic collection and cholangitis. This patient required a PCD and a percutaneous transhepatic biliary drainage/PTBD to become sepsis-free prior to repair

Repair is considered in a patient with EBF after the following are achieved by the principles outlined in the 'prepare' phase:

1. A sepsis-free patient
2. Optimised liver and renal functions, electrolytes and haemoglobin
3. Good nutrition and functional performance
4. A healed fistula and a desirably dry right upper quadrant
5. An accurate biliary map

Once the patient is sepsis-free and in the anabolic phase of recovery, most EBFs would dry up in 2–3 months. Some, however, may persist and warrant further steps. The various scenarios that may arise in patients presenting with EBF include:

1. Patient presenting within 72 h of injury with EBF
2. Patient presenting after 72 h of injury with EBF:
   (a) Persistent fistula even after waiting period of 2–3 months
   (b) Healed fistula without scarring and stricture
   (c) Healed fistula with stricture formation

6.5.3.1 The Patient Presenting Within 72 h of Injury with EBF

A patient presenting within 72 h with an EBF, to a high-volume hepato-biliary centre, may be considered for definitive repair if there are no intra-abdominal collections or associated vascular injury. The 'ravages' of EBF are absent in these patients as the interval following injury is very short. The hilar tissues are usually not inflamed or oedematous, and the results of repair appear seemingly similar to those of a delayed repair. Therefore, if the patient is not septic, the authors advise immediate repair after initial stabilisation of the patient and evaluation of the complete biliary tree. In the authors' centre, a patient referred without bile contamination and sepsis, and who is haemodynamically stable, undergoes an MRCP along with other evaluations (listed above) and is taken to the operating room straight from the MRI console for the surgical repair (Fig. 6.9; [24]). Timing is crucial to the outcome.

Early repair can result in minimum morbidity, short hospital stay and low hospitalisation cost, with good long-term results in the hands of expert hepato-biliary surgeons. Sahajpal and colleagues [20] classified repair of BDI based on timing of repair, namely, on table, or within 72 h of injury, as immediate repair, 72 h to 6 weeks after the injury as intermediate repair and more than 6 weeks after the injury as delayed repair, and demonstrated satisfactory results in 13 patients who underwent repair in <72 h. Perera and colleagues [9], too, showed that results of the early repair were comparable to delayed repair when performed by expert surgeons. At the authors' centre, they have undertaken eight early repairs over 6 years with an excellent MacDonald A outcome (unpublished data).

However, only a minority of BDIs with EBF are referred so early, and among them, only a subset of patients are free of sepsis and fit for such an early repair. The vast majority present in sepsis and with collections necessitating the BPR approach outlined above.

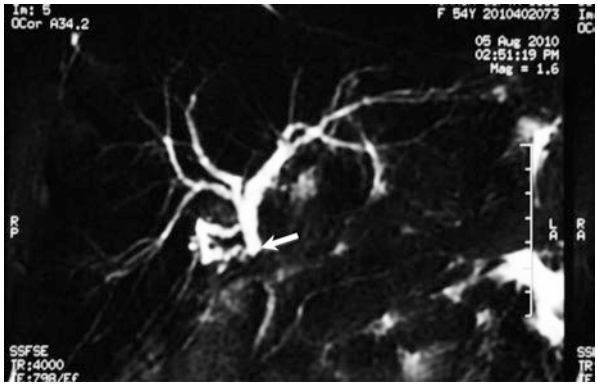

Fig. 6.9 Coronal reconstruction of MRCP depicting a Hannover D2 or Stewart-Way Class 3 injury (white arrow), in a patient presenting 60 h post-cholecystectomy. The patient underwent an uneventful immediate repair

6.5.3.2 Patients Presenting After 72 h of Injury with EBF

Most patients who present after 72 h with EBF (late referrals) have significantly inflamed and friable hilar tissues. Hilar dissection may lead to further damage, and friable tissues may not hold sutures well, both of which contribute to high chances of anastomotic leak and long-term failure.

In a nationwide review from France of 543 BDIs, 194 patients underwent immediate repair of the BDI, 216 repairs were performed within 45 days and 133 repairs after 45 days. Early repair, in comparison to delayed repair, had a higher complication (29% vs 14%, $p < 0.001$) and failure rate (43% and 8%, $p < 0.001$) [21]. Stilling and colleagues [25] from Denmark, in a review of 139 repairs done at a median of 5 days following BDI, reported a 4% mortality rate, 36% morbidity rate and 30% re-stricture rate at a median follow-up of 102 months. Similarly Sahajpal and colleagues [20] noted a worse outcome ($p < 0.03$) with repair done after 72 h and before 6 weeks from the injury.

In contrast, a delayed repair (more than 6 weeks after the injury) produces excellent long-term results. The authors operated 300 patients in a delayed fashion between 1989 and 2004. In 149 patients with more than 5 years of follow-up, excellent to satisfactory outcomes were seen in 91% patients with poor outcome requiring re-intervention that was noted in only 5% patients [26]. Lillemoe and colleagues [27] reported on 156 patients with delayed repair with a 91% success at a mean follow-up of 58 months and 98% success with the addition of re-intervention.

Hence in this group of patients presenting after 72 h, even when sepsis-free, it is not recommended to do early definitive repair at presentation. These patients need to be managed according to the BPR approach outlined in Fig. 6.10, with a 4–6 weeks conservative trial at fistula healing while being sepsis-free and in a state of anabolism. The authors follow a policy of delayed repair after such a trial period, at the end of which, these patients may evolve into one of the following scenarios:

Persistent Fistula Even After Waiting Period of 2–3 Months

It is desirable to operate once the inflammation at the hilum has resolved as this offers the potential for firm tissues for a satisfactory repair. But, sometimes even

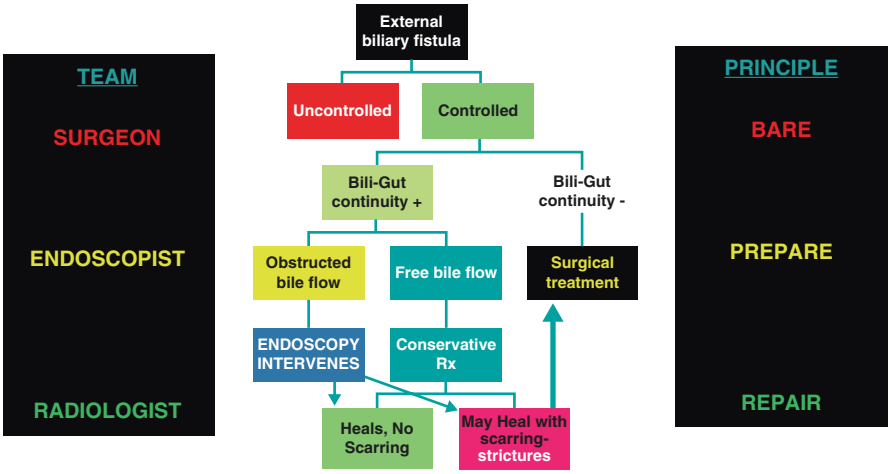

Fig. 6.10 Algorithm demonstrating the 'BPR' approach to the management of EBF

after waiting for 2–3 months, the EBF may not heal. In this situation, a proximal biliary diversion with PTBD may be done to reduce the volume of fistula output, which may help healing of the fistula.

Rarely, even after all these measures, the fistula may persist necessitating surgical repair. In a study from the authors' institute [28], 110 patients out of 364 who underwent biliary repair had an EBF at the time of surgery. Of the 110 patients, 92 (84%) had a successful outcome, while 18 (16%) had a failed repair (MacDonald's C and D). Although the success of repair in this setting is inferior to that achieved in a dry system (>90%), it may be the best outcome for the given scenario.

Healed Fistula Without stricture

A few patients with bilio-enteric continuity can be managed with definitive endoscopic management, which may lead to healing of the EBF without a stricture. These include patients with Strasberg type A and D injuries. These patients do not require any further intervention, although they need to be kept on regular follow-up as some of them, especially those with Strasberg type D injuries, may go on to develop benign biliary strictures (BBS) necessitating definitive surgery at a later date.

Healed Fistula with Stricture Formation

Various classifications for BBS have been published over the years. However, the time-tested and commonly used system is the Bismuth classification [29] described in 1982. The authors have further subclassified Bismuth type III into IIIa and IIIb based on the presence or absence of floor of the primary confluence [30]. This distinction helps plan further surgical strategy.

Patients with expected difficult access to hilum (Bismuth type IV–V strictures, atrophy-hypertrophy complex, etc.) benefit by a pre- or intraoperative percutaneous

catheterisation of biliary ducts. These catheters may be used to pass a guide wire or flush with saline or to obtain a cholangiogram and thus guide in the intraoperative identification of ducts at the hilum. Strasberg and colleagues [31] showed that such an approach is associated with an increased chance of success at repair.

In the authors' experience, about 70% of BDIs go on to develop BBS. The factors associated with the risk of development of a BBS were female gender, open cholecystectomy as the index operation, delay in the referral from identification of injury, persistence of an EBF beyond 4 weeks, EBF output >400 mL/day and a complete BDI [32].

With no bilio-enteric continuity, operative treatment is the only option. On the basis of the type of BBS and presence of associated vascular injury and atrophy-hypertrophy complex, the type and extent of surgery are decided. It may range from a hepaticojejunostomy/HJ to hepatic resection and even liver transplantation after multiple failed attempts at repair.

Hepaticojejunostomy: Principles of Surgical Repair

Long-term success of surgical repair depends on a variety of factors. The most crucial and controllable factor is sound surgical technique. The basic tenets of a good technique leading to successful repair are:

1. Using healthy, non-oedematous duct mucosa and wall
2. Mucosa to mucosa approximation
3. Minimal inflammation of the hilar plate
4. Sepsis-free environment at the hilum (as far as possible)
5. Good vascularity
6. Tension-free repair
7. Wide anastomosis to achieve a stoma size of >2 cm
8. Incorporation of all sectoral ducts in high strictures

The Hepp-Couinaud approach to the left duct involves lowering of the hilar plate beneath segment 4b to ensure a good exposure of the hilum [33, 34]. This greatly facilitates extension of the stoma to the left duct and the performance of a wide mucosa to mucosa anastomosis ensuring excellent long-term outcomes [35].

The bile duct heals by the mechanism of over-healing and ring fibrosis after an injury leading to a reduction in stoma size in the long term in comparison to what was crafted at surgery [36]. Hence a wide stoma with good vascularity and mucosa to mucosa approximation are needed to promote primary healing with limited fibrosis which will lead to satisfactory long-term outcomes [37].

Long-Term Results of Repair

The best long-term outcomes are achieved by following a stepwise approach with good technique as enumerated above. Good long-term results with HJ can best be achieved by experienced hepato-biliary surgeons. The authors have reported a >90% long-term success rate [26].

The predictors of long-term outcome are preoperative bilirubin, previous attempts at repair, cirrhosis, portal hypertension, repair in the presence of EBF, bilio-enteric fistula, atrophy-hypertrophy complex and anastomotic leak [28]. Injury-repair interval, preoperative stenting and duration of postoperative stenting have not been found to influence the outcome of repair [28, 35].

Repair in patients with strictures at, or above, the level of confluence of the left and right ducts (Bismuth's types III, IV and V) has been found to be another risk factor for failure in some series [38, 39]. In the authors' experience, however, no such difference in the outcome of repair between low (Bismuth's type I and II) and high (Bismuth's type III, IV and V) strictures was noted [26, 28].

6.6 Special Situations

6.6.1 External Chronic Refractory Biliary Fistula (ECRBF)

ECRBF is a rare situation, where the fistula becomes chronic and persistent for more than 5 months, even after all conservative measures at biliary decompression (ES and/or stenting or PTBD) have been attempted [40]. The reported incidence of such an entity is 0–5% [28, 41–43]. It may occur following any liver or biliary surgery although it has most commonly been noted following conservative surgery for hydatid cyst of the liver.

Some ECRBF following liver trauma or isolated sectoral duct injury or bilio-vascular injuries with atrophy-hypertrophy complex may require liver resection to control the fistula (Fig. 6.11).

Fistulojejunostomy remains another viable option, with good results being obtained in EBF [40]. Recent reports have suggested varying degrees of success with glue injections (N-butyl cyanoacrylate) for refractory fistula management [44]. However, such techniques run the risk of spill of the glue into the biliary tree with consequent disastrous consequences for the patient. Until further convincing evidence is available with such techniques, they can at best be regarded as experimental.

6.6.2 EBF Following Bilio-Intestinal Anastomosis: The 'Leak' Fistula

Anastomotic leak is a serious problem in the postoperative setting with broad-reaching long-term repercussions. Initial management is according to the BPR approach. Most minor leaks heal spontaneously provided there is no ischaemia or disease at the suture line and no distal obstruction, but major or persistent leaks may require biliary diversion with PTBD for healing.

Once healing occurs, these patients need to be kept under close surveillance. If an anastomotic stricture develops, further management depends on the level of block and sectoral separation on biliary mapping. Options include PTBD with balloon dilation of the stricture, a revision HJ or a hepatectomy with revision HJ.

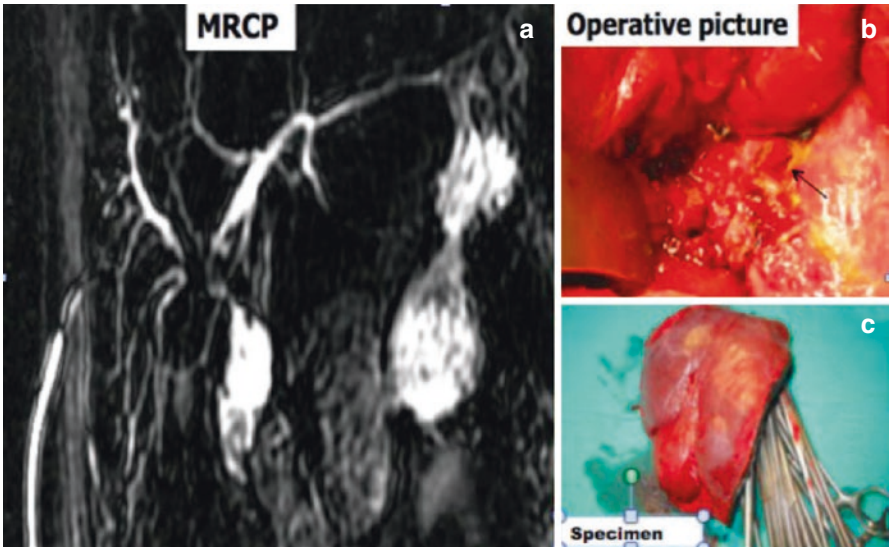

Fig. 6.11 EBF after hilar injury with right portal venous/RPV thrombosis. (**a**) Coronal reconstruction of the MRCP demonstrates bile leak from the hilum closer to the left duct with crowding of ducts in the right lobe secondary to atrophy induced by the RPV injury. (**b**) Intraoperative photograph demonstrating the site of bile leak from the left duct (black arrow). The patient underwent a right hepatectomy with left duct hepaticojejunostomy. (**c**) Photograph of the right hepatectomy specimen

If the stricture is well below the confluence with an intact left duct, a revision HJ at the hands of an expert hepato-biliary surgeon offers the best chance of a successful long-term outcome. However, if the stricture is high involving the hilum and left duct or the strictured HJ was originally performed at a high-volume hepato-biliary centre, PTBD with balloon dilation is usually the first option. In case of failed percutaneous intervention with atrophy-hypertrophy complex, a right hepatectomy and a revision left duct HJ may be the next option.

6.6.3 EBF Following Liver Trauma

Blunt or penetrating grade III or IV liver trauma may be complicated by bile collections and biliary fistulas in 0.5–14% of patients [45–50]. EBF may result from a direct biliary tree injury, following nonoperative management of liver trauma or sometimes after operative intervention for trauma.

At the present time, nonoperative management is the preferred modality to treat patients with liver trauma who are haemodynamically stable, with an associated 85–97% success rate [51]. However, the drawback of such an approach is delayed presentation of complications like bile leaks with biloma formation, haemobilia, and development of liver abscesses. Bilomas and liver abscesses need PCD placement, while haemobilia necessitates selective embolisation of the involved artery.

Most post-traumatic biliary fistulas are from peripheral ductules (like Strasberg type A injury) and heal spontaneously [49]. Healing may be hastened by endoscopic intervention to decompress the biliary system. Major biliary injuries such as complete transection of the CBD require an approach similar to that for any BDI, as described in the BPR approach.

A segment of the liver isolated by the injury may atrophy with healing of the EBF, or it may result in a persistent EBF. Management of persistent EBF in an isolated segment is difficult—a cholangiojejunostomy may be required if a large segment is involved or a partial hepatectomy if a small segment is involved.

A small subset of liver trauma patients treated primarily surgically (debridement/resection/hepatorrhaphy) may present with a persistent biliary fistula despite endoscopic intervention. The approach is dictated by the BPR strategy. Surgery, if at all warranted, would include a formal liver resection or a fistulojejunostomy or hepatotomy followed by cholangiojejunostomy, depending on the clinical scenario.

6.6.4 EBF Following Liver Resection (Including Donor Hepatectomy)

The incidence of bile leak following hepatic resection ranges from 1.7% to 12% [52–57]. Yamashita and colleagues [57] identified operative procedures exposing the major Glissonian sheath and including the hilum, such as anterior sectorectomy, central hepatectomy and caudate resections, to be associated with a high risk for development of postoperative bile leak.

In most patients, the bile leak is from the cut surface of the liver. These cease spontaneously or after biliary decompression with endoscopic or percutaneous intervention [55]. At times, a persistent fistula requires resurgery [58], especially when associated with a major BDI or arising from an injured caudate lobe duct.

Sometimes, if a simultaneous bilio-enteric anastomosis has been performed as part of the hepatectomy, this may be the site of the bile leak. While it may be difficult to pinpoint the exact site of leak (anastomosis or liver cut surface), using a dynamic scintigraphic study may help resolve the issue. It is managed as in the case of any other leak, as described above.

6.6.5 EBF Following Liver Transplantation

The reported incidence of biliary leaks following liver transplantation varies widely from 10% to 50% [59–61]. The potential sources of bile leak include the site of biliary reconstruction or the cut surface of the graft in reduced, split or living donor liver graft. The leak rates following a choledocho-choledochal reconstruction or a Roux-en-Y HJ/RYHJ are similar [62].

The management principles of bile leak even after liver transplantation remain the same, namely, drainage of collections for control of sepsis and biliary decompression (endoscopic intervention in choledocho-choledochal reconstruction or PTBD in RYHJ) [63].

The leak from cut surface generally settles with conservative approach. In the absence of hepatic artery thrombosis/HAT, a PCD into the bile collection and endoscopic stenting (in duct-to-duct reconstruction) generally resolves the problem.

A leak from the choledocho-choledochal anastomosis which cannot be controlled by endoscopic intervention in a patient with patent hepatic artery may require conversion to a RYHJ. If the bile leak is associated with HAT, with a sloughed out graft bile duct, re-transplantation may be required.

Anastomotic leaks are related to technical errors, tension at the anastomotic site or ischaemic necrosis after HAT. As HAT is a devastating problem, requiring even re-transplantation, it should always be ruled out in any patient presenting with bile leak post liver transplant. Leaks associated with ischaemic necrosis require surgical revision with RYHJ [59]. The development of postoperative bile leak has a high association with late stricture formation and warrants lifelong surveillance.

6.6.6 Following Surgery for Hydatid Disease of the Liver

Hydatid disease of the liver is associated with a cystobiliary communication (CBC) in about 10% of patients [64]. Surgery for hydatid disease of the liver, such as a cysto-partial pericystectomy or hepatic resection, may lead to development of an EBF. After cysto-partial pericystectomy, the development of an EBF is a particularly difficult management problem, as most EBFs do not heal and remain persistent. A fibrous wall at the fistula site prohibiting spontaneous closure is usually the cause for such persistence. The authors have experienced a 40% incidence of CBC in 188 hepatic hydatid cysts managed surgically by them over 15 years [65].

An EBF may develop due to a missed CBC intraoperatively or a failed CBC repair due to distal biliary obstruction caused by cyst membranes. Management is aimed at early control of fistula and biliary decompression with endoscopic intervention (sphincterotomy and/or stenting after clearing the CBD of hydatid membranes, if present). Another option is to definitively decompress the CBD in all cases with CBCs using a T-tube intraoperatively. The same may be used to do a 'pneumo-cholangiogram' test, which avoids missed CBCs during surgery [65].

With this management strategy, most of the fistulas will heal, although it may take a long time (6 months to 1 year). If the fistula becomes chronic and persistent, a fistulojejunostomy or hepatectomy may be warranted at a later date.

6.7 The Impact of the BPR Approach

The BPR approach to management of EBF is an algorithmic approach based on scientific principles with the use of acronyms for an easy recall—a handy aid for young postgraduates and practising surgeons. The authors instituted the approach as a standard practice at their centre since the year 2000 to minimise errors and resultant poor outcomes. Between 1989 and 2000, they managed 210 cases of BDIs, 70%

of which presented as EBF, with an overall mortality rate of 1.9%. Following institution of the BPR approach, between 2000 and 2012, another 395 patients of BDIs with a similar proportion of EBFs were managed, with an overall mortality of 0.5%—an altogether 75% reduction.

Conclusion

EBF represents an unwelcome, complex and devastating problem. It results not only in tremendous physical, but also mental, stress to the patient. It is important to understand the intricacies of the problem and the ravages caused by it and follow an algorithmic approach such as the bare, prepare and repair (BPR) strategy when managing these patients to achieve the best outcomes. While outstanding results of surgery may be achieved at dedicated high-volume centres, the BPR approach aims at creating a uniform protocol for the assessment and management of EBF across centres irrespective of the volume of patients treated by promoting an interdisciplinary culture where surgeons, interventional radiologists and endoscopists work in harmony to achieve the best outcomes for the patient. Inability to manage or lack of facilities to adequately manage such patients warrants an appropriate referral as early as possible to centres equipped to handle such patients.

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Benign Biliary Strictures

7

Rachel Loh, Glenn Kunnath Bonney,
and Krishnakumar Madhavan

7.1 Epidemiology and Aetiology

The aetiology of benign biliary strictures is diverse [1]. In the recent past, the most common cause of benign biliary strictures in Western countries appears to be postoperative causes, while in Asia it is due to infection such as *Clonorchis sinensis* in parts of Southern China [1]. This may no longer hold with the growing affluence in Asia and the influx of Asian immigrants into the West. The aetiology of benign biliary strictures can be broadly classified into postoperative, inflammatory and infective.

7.1.1 Postoperative

7.1.1.1 Cholecystectomy

Strictures can occur secondary to operative injury (most commonly following laparoscopic cholecystectomy), following bile duct reconstruction, or orthotopic liver transplant [1]. In a previous analysis of 42,474 patients who underwent open cholecystectomy, it was found that the risk of strictures resulting from open cholecystectomy ranges from 0.1 to 0.2% [2]. With the advent of laparoscopic cholecystectomy in 1985, this has increased to 2.8% [3, 4]. It is estimated that 1400–7700 patients will suffer a major bile duct injury during laparoscopic cholecystectomy annually. Initially attributed to the steep learning curve that surgeons had to adapt to when first getting used to laparoscopic surgery, recent studies showing national databases of bile duct injury rates ranging from 0.2 to 1.1% [5–8] suggest that bile duct injuries could not be solely attributed to the learning curve.

R. Loh · G. K. Bonney · K. Madhavan (✉)
Division of Hepatobiliary and Liver Transplantation Surgery, National University Hospital, Singapore, Singapore
e-mail: krishnakumar_madhavan@nuhs.edu.sg

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Majority of bile duct injuries from laparoscopic cholecystectomy are related to errors in appreciating or defining the anatomy, complicated by acute or chronic inflammation of the gallbladder or the Calot's area. Termed the "classical injury" [9], the common bile duct is most commonly mistaken to be the cystic duct, while less commonly, an aberrant duct is misidentified as the cystic duct [10]. Other factors that are believed to be inherent to the laparoscopic approach include the two-dimensional view, insufficient tactile sensation, different traction forces to the gallbladder, and indiscriminate use of electrocautery inside the Calot's triangle [11]. Interventions to reduce bile duct injuries in laparoscopic cholecystectomy that have been reported include timing of the procedure, patient selection [12], intensive training of surgeons [13], photographic documentation of the "critical view of safety" (first described by Strasberg et al. in 1995) [14], and the use of intraoperative cholangiography [15].

7.1.1.2 Liver Transplantation

Strictures related to liver transplantation are often due to a combination of both surgical technique and ischaemia [16]. The incidence of biliary complications following liver transplantation is higher in living donor liver transplantation and donation after cardiac death (DCD) liver transplantation. Biliary complications are seen in 10–20% of patients after liver transplant, of which the most common being extrahepatic bile duct strictures [17]. Seventy-five percent of these patients had strictures at the anastomotic site or just proximal to the anastomosis [18].

Depending on the time of presentation, strictures can be classified as early (i.e. within 1 month of liver transplantation) or late. Early strictures can be attributed to surgical technique, while strictures that appear later are often the result of arterial insufficiency [19].

Strictures can also occur anywhere in the biliary tract and, depending on the stricture site, can be classified as either anastomotic or non-anastomotic. Anastomotic strictures are the most common type. They are usually the result of surgical technique in combination with local ischaemia and fibrotic healing. Non-anastomotic strictures, on the other hand, are otherwise termed ischaemic type biliary lesions. They often involve the hilum and associated with multiple strictures involving the intrahepatic ducts. Risk factors contributing to the development of this type of stricture include chronic ductopenic rejection, postoperative cytomegalovirus (CMV) infection, ABO incompatibility leading to vasculitis, and the presence of primary sclerosing cholangitis (PSC) [17].

7.1.2 Inflammatory

7.1.2.1 Chronic Pancreatitis

The incidence of biliary strictures in chronic pancreatitis ranges from 3 to 46% [20]. A significant number of patients with bile duct strictures are discovered incidentally [21]. Pancreatic fibrosis in chronic pancreatitis causes partial common bile duct obstruction, resulting in increased portal pressure which stimulates ductular

proliferation and secondary biliary fibrosis [22]. As pancreatic fibrosis tends to develop in advanced pancreatic disease, these strictures show a predilection for patients with more advanced disease and those with chronic calcific pancreatitis [23].

7.1.2.2 IgG4 Cholangiopathy

IgG4 cholangiopathy refers to the manifestation of IgG4-related systemic disease in the biliary tree and can occur in association with autoimmune pancreatitis or as an isolated biliary disease [24, 25]. It can cause intrahepatic, proximal extrahepatic, or intrapancreatic benign biliary strictures [26]. Distinguished by elevation of gamma globulin (IgG) and autoantibody seropositivity, autoimmune mechanism as a cause of biliary stricture was originally proposed by Yoshida et al. in 1995 [27]. Hamano et al. later demonstrated increased serum levels of IgG4 in Japanese patients with sclerosing pancreatitis, but not in patients with chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or Sjögren's syndrome. Despite frequent overlaps between these conditions, Hamano's findings showed that sclerosing pancreatitis is a distinct disease entity, differing immunologically from the other autoimmune diseases [28]. Prevalence of IgG4-sclerosing cholangitis still remains unclear, although a recent national Japanese survey has suggested a higher incidence in males compared to females (3.3 males: 1 female) and the mean age of 69.3 years (47.6–87.4) in IgG4-sclerosing cholangitis [28, 29]. The diagnosis of intrahepatic cholangiopathy relies on histological confirmation and/or treatment response to a trial of corticosteroids [26].

7.1.3 Infective

Commonly found in East Asia, *C. sinensis* (also known as Chinese liver fluke) is a trematode that lives in the biliary tract of humans, who acquire the infection from eating raw freshwater fish. The incidence of infestation was reported to be as high as 70% in Southern China, where lifestyle and hygienic conditions favour the life cycle of the parasite. In endemic areas, it can cause biliary complications such as intrahepatic stones, recurrent bile duct stones, cholangitis, cirrhosis, pancreatitis, and cholangiocarcinoma. The fluke *C. sinensis* requires three different hosts to complete its life cycle, namely, freshwater snails, fish, and mammals. The freshwater snails eat *C. sinensis* eggs in the water and serve as intermediate hosts for the eggs to hatch into miracidia, which grow into sporocyst and then develop into rediae that then produce cercariae. These cercariae are shed by the snails into the water where they swim actively to find their second intermediate host, the cyprinid fish. They invade the skin of the fish and mature there into metacercariae (larvae). These larvae can survive in the fish muscle for up to 1 year. When humans ingest these fishes, excystation of the larvae into the duodenum occurs within minutes, and they rapidly migrate into the biliary tree. Upon reaching the intrahepatic bile duct, these larvae mature into adult flukes and can live in humans for more than 26 years. Each worm can produce up to 3000 eggs a day, and these eggs are excreted with bile into the intestinal system and then with faeces into water, where it continues its life cycle

[30]. Where it used to be a rare disease in the West, the influx of Asian immigrants in the 1980s have also brought attention to these parasites, which can survive in the human body for more than 20 years [31]. A prevalence rate of up to 15.5% has been reported in these Chinese immigrants [32].

Biliary tuberculosis (TB) is a rare cause of biliary strictures. Only a handful of cases have been reported, the majority of which are found within Asia where TB is prevalent. Hepatobiliary TB can be largely classified into (1) hepatic tuberculoma, (2) military hepatic TB, and (3) biliary TB. They most commonly result from the spread of caseous material from the portal tracts into the bile ducts but may also result from either the secondary inflammation-related tuberculous periportal adenitis or the spread of caseous material through the ampulla of Vater and ascending along the CBD [33].

Clinical features and cholangiography often do not distinctly differentiate biliary TB from other causes of biliary strictures such as cholangiocarcinoma or primary sclerosing cholangitis. Proposed characteristic cholangiographic patterns of hepatobiliary TB include a tight hilar stricture with dilated intrahepatic ducts, a long smooth stricture involving the distal bile duct, pruning of the distal intrahepatic ducts, and sclerosing cholangitis-like changes [34]. Presence of associated scattered, "chalky" and confluent hepatic calcifications or nodal-type calcifications along the course of the CBD favours the diagnosis of hepatobiliary TB [35]. Most of the reported cases of tuberculous biliary stricture are diagnosed after surgery, where histopathologic findings of TB include caseating granulomatous inflammation and Langhans giant cells [36]. Although the yield is low, there were some cases diagnosed by detection of acid fast bacilli (AFB) through staining or culture of the biliary fluid aspirate during endoscopic retrograde cholangiopancreatography (ERCP). Polymerase chain reaction (PCR) technique for *Mycobacterium* tuberculosis from biliary fluid may also be helpful.

First described in 1986, the incidence of human immunodeficiency virus (HIV)-related or acquired immunodeficiency syndrome/AIDS cholangiopathy is now higher in developing countries than the Western world, largely contributed by affluence and therefore the access to antiretroviral therapy [37]. The underlying mechanism is thought to be related to opportunistic biliary infections such as *Cryptosporidium*, *Microsporidia*, *Cyclospora*, and *Mycobacterium avium-intracellulare*, leading to a chronic cholestatic state. This leads to the characteristic histological findings of patchy inflammation, fibrosis, and stricturing of the intra- and/or extrahepatic biliary tract. Experiments conducted in vitro has also showed that active viral replication in the presence of *Cryptospodium* infection may increase cholangiocyte apoptosis. HIV cholangitis is considered a secondary form of sclerosing cholangitis and is associated with advanced immunosuppression (CD4 count <100/mm^3) [38]. In recent times, this condition has been diagnosed in people of less advanced HIV, suggesting a growing resistance to antiretroviral medications [39].

Some evidence has also suggested that infections such as histoplasmosis, *Cytomegalovirus*, *Ascaris lumbricoides*, and *Opisthorchis viverrini* can rarely lead to biliary strictures, details of which will not be discussed in this chapter [40, 41].

7.2 Risk Factors

7.2.1 Patient-Related Factors

While in the previous sections we have described the causes for biliary strictures, in this section, we will discuss about the predictors and risk factors of developing these diseases.

Patient-related risk factors associated with an increase in biliary complications include:

1. Active inflammation
2. Severe chronic inflammation
3. Active peritonitis
4. Aberrant anatomy
5. Delay in referral
6. Increased bleeding diathesis leading to difficult haemostasis
7. Severe liver disease

7.2.1.1 Genetics

IgG4 cholangiopathy is part of a systemic fibroinflammatory condition termed IgG4-related disease. Risk factors including chronic exposure to chemicals and toxins among "blue-collar workers" (e.g. building contractors, plumbers), clinical history of allergy and/or atopy, and coexistent history of other autoimmune disease may contribute to disease development. Independent studies among the Dutch and the United Kingdom (UK) cohorts have found that 61–88% of patients with IgG4 sclerosing cholangitis had "blue-collar" occupational exposure, compared to 14% in patients with PSC and 22% in those with PSC and raised serum IgG4 levels [42]. Chronic exposure to solvents, pigments, oil, and industrial and metal dusts in the automotive industry were one of the most frequent potential occupational hazards [42]. A high proportion of patients with IgG4 cholangiopathy were reported to have longstanding allergies, peripheral blood eosinophilia, and serum IgE elevation. Whether it is the processes inherent to IgG4 cholangiopathy itself or atopy contributing to eosinophilia and IgE elevation is still controversial [43].

7.2.1.2 Pre-operative Clinical Predictors

The incidence of biliary injury is reported to be higher when laparoscopic cholecystectomy is performed during acute cholecystitis than in an elective setting. Active inflammation increases vascularity and friability of tissues and promotes adhesion formation. Severe chronic inflammation, on the other hand, often leads to a shrunken and contracted gallbladder, which binds closely to its surrounding tissue. These can obscure the anatomy, obliterate the dissection planes, and increase the complexity of the surgery [44].

A retrospective analysis of 241 consecutive orthotopic liver transplants demonstrated that preoperative serum bilirubin level was an independent predictor of

biliary complications after liver transplant. It was hypothesized that patients with high preoperative serum bilirubin level have poor liver function, and complete haemostasis is difficult to achieve after implantation. As a result, frequent mobilization and rotation of the liver graft, for exposure of retroperitoneum and hepatoduodenal ligament to achieve haemostasis, may result in minor or unrecognized disruption of the biliary anastomosis. Drugs such as steroids, commonly used in liver transplant recipients, may impair wound healing and enhance minor leakage. Subsequent inflammatory reaction and fibrosis around the anastomosis may therefore predispose to anastomotic strictures [44].

7.2.2 Procedure-Related Factors

In one retrospective study of bile duct injury, post-cholecystectomy, open cholecystectomy, and intraoperative complete bile duct injury were found to be most predictive of benign biliary stricture development. The authors speculated that the reason for increased risk during open cholecystectomy could be related to the fact that difficult cases were more likely to be scheduled for open surgery instead of the laparoscopic approach [45].

Biliary stricture is a major complication of liver transplantation. Although patient survivals are rarely affected, retransplantation and graft loss rates were significantly greater in recipients who developed biliary stricture. Hepatic artery thrombosis and prolonged warm and cold ischaemia times independently increase the risk of stricture formation [46]. Although the use of a T-tube across an anastomosis permits monitoring of bile flow and allows easy performance of cholangiography, they have also been associated with a higher cholangitis and biliary leak rate. The occurrence of recurrent cholangitis may induce more fibrosis of the ductal wall and lead to late stenosis [44].

In two studies which looked at the risk of biliary stricture post Whipple's procedure, small common bile duct (CBD) diameter < 5.0 mm and the use of 6-0 sutures for repair were also implicated in the future development of biliary strictures, demonstrating the technical challenges with anastomosis in a small CBD [47].

Procedure-related risk factors associated with an increase in biliary complications

1. *Cholecystectomy*
   (a) Injuries at or above the biliary bifurcation
   (b) Complete bile duct injury
   (c) Open cholecystectomy
2. *Liver transplant/Whipple's procedure*
   (a) Hepatic artery thrombosis
   (b) Prolonged ischaemia time
   (c) Use of a stent or T-tube for splinting the anastomosis
   (d) CBD diameter < 5 mm

7.2.3 Surgeon-Related Factors

The "learning curve" effect as a risk factor for bile duct injury was suggested by several reports in the 1990s. One of which is a case series of 1518 laparoscopic cholecystectomies, which showed that most injuries occurred within the first 13 procedures performed by a surgeon. They reported an incidence rate of 2.2% bile duct injuries in the first 13 patients compared to 0.1% in subsequent patients [48]. In the era beyond the laparoscopic learning curve, a study of more than 150,000 laparoscopic cholecystectomy cases between 2005 and 2010 demonstrated that the rate of bile duct injury has decreased to 0.08%. This rate is almost equivalent to that of open cholecystectomy and reflects increased experience, advanced instrumentation, and movement beyond the "learning curve" [49].

7.3 Pathophysiology

Pathophysiology of biliary strictures is related to their aetiology.

7.3.1 Iatrogenic

In a study on animals with iatrogenic CBD injury, it was shown that the bile duct mucosa was often poorly healed with chronic inflammation [50]. Over deposition of collagen in the submucosa and poor reconstruction led to overgrowth of the scar and subsequent stricture. The presence of myofibroblasts was singled out as the main cause of scar contracture and stricture. High numbers of macrophages found in the injury site and high expression of transforming growth factor (TGF)-beta 1 were closely related to the proliferation of the biliary scar.

7.3.2 Inflammatory

Distal CBD strictures occur as a consequence of inflammation-induced periductal fibrosis in chronic pancreatitis [23]. In up to 85% of people, the CBD traverses the pancreatic head while lying posteriorly in the remainder [51]. Recurrent acute inflammatory episodes lead to periductal fibrotic stricture of the intrapancreatic portion of the CBD and occur more commonly in advanced chronic pancreatitis especially with the calcific component [52]. As the CBD length traversing the pancreas varies from 1.5 to 6 cm, the stricture length seen in clinical practice also varies accordingly [53].

Biliary strictures as a result of IgG4 cholangiopathy develop differently. Although the precise pathogenic mechanism remains unclear, susceptible genetic factors, abnormal innate and acquired immunity, decreased naïve regulatory T cells, and

specific B cell responses may be involved in its development. Okazaki et al. devised the concept of a biphasic mechanism of "induction" and "progression" to explain a possible pathogenic mechanism [29].

They postulated that decreased naïve regulatory T cells (Tregs) induce a Th1 immune response, leading to the release of pro-inflammatory cytokines (IFN-c, IL-1beta, IL-2, and TNF-a) to unknown antigens, e.g. self-antigens (LF, CA-II, CA-IV, PSTI, and alpha-amylase) or microorganisms (Helicobacter pylori, commensal bacteria, and viruses). Subsequently, Th2 immune responses with the production of IgG, IgG4, and autoantibodies may assist in the disease progression. Both B cell activating factor from monocytes and basophils and IL-10 from inducible memory Tregs may upregulate IgG4 production. Tumour growth factor-beta (TGF-β) secreted from inducible memory Tregs infiltrating into the involved organ may induce fibrosis. This massive infiltration of IgG4-positive plasma cells, storiform fibrosis, and/or obliterative phlebitis in the bile duct wall are characteristic and termed lymphoplasmacytic sclerosing cholangitis (LPSC). The fibroinflammatory mechanism mainly takes place in the submucosa of the bile duct, leaving the epithelium intact.

7.3.3 Infective

In hepatic clonorchiasis, the immature worms attach to the CBD lining, migrate along the epithelial lining of the duct, and mature into adult worms within the intrahepatic ducts. This migration of the immature worm traumatizes the bile duct epithelium, resulting in ulceration and desquamation. The epithelial injury leads to adenomatous hyperplasia and goblet cell metaplasia, which forms fibrous tissue and extensive bile duct thickening (i.e. encapsulating duct fibrosis). Repeated exposures may provoke a diffuse involvement of the biliary tree, leading to cirrhosis.

Hepatobiliary TB is usually caused by invasion of the *Mycobacterium tuberculosis* organism via the haematogenous route, from either an active or inactive tuberculous infection of the lungs through the hepatic artery [54], or less commonly through the portal vein (especially with concurrent gastrointestinal TB infection) [55]. Other rarer routes of invasion include spread through the lymphatics or rupture of the tuberculous lymph node in the portal tract leading into the portal vein [35]. Biliary tuberculosis can manifest in four ways, namely, (1) rupture of caseating granulomas into the bile duct resulting in biliary tract tuberculous strictures or cholangitis, (2) rupture of periportal lymphatics into the adjacent walls of biliary ductules, (3) when periportal/peripancreatic tuberculous adenitis or pancreatic tuberculous mass leads to secondary inflammation or compression, (4) postinflammatory stricture after TB treatment, and (5) compression from tuberculous pseudotumour [56].

7.4 Classification

There are several classifications associated with biliary strictures; these can be divided into biliary strictures associated with bile duct injuries, IgG4 cholangiopathy, biliary strictures after liver transplantation, and biliary strictures from chronic pancreatitis.

7.4.1 Biliary Strictures Associated with Bile Duct Injuries

Several classifications for bile duct injury have been proposed, but none have been universally accepted as each has its own limitations. The most commonly used by clinicians are the Bismuth's classification and Strasberg's classification.

Bismuth's classification is used for patients with established biliary stricture and is based on the location of the biliary stricture in 1978 (Table 7.1) [57]. Bismuth type I strictures are located >2 cm distal to the confluence of the left and right hepatic ducts (hepatic bifurcation) (Fig. 7.1). Type II strictures are located <2 cm from the hepatic bifurcation (Fig. 7.2). Type III lesions are present at the bifurcation. Type IV lesions involve the right or left hepatic ducts, while type V lesions extend into the right or left hepatic branch ducts.

Strasberg's classification is used for acute injuries with bile leak, lateral injuries, and transection. Strasberg type A injury refers to bile leak from a minor duct still in continuity with the CBD. These leaks may occur at the cystic duct or from the liver bed, for which their presentation and management are almost identical. Type B injury results from the occlusion of part of the biliary tree, largely from an injury to an aberrant right hepatic duct. The aberrant duct may be a segmental duct, a sectoral duct, or even the main right duct. When this is transected without occlusion, it is considered type C injury. Type C injuries are usually diagnosed in the early postoperative period. Strasberg's type D injury involves lateral injury to the extrahepatic bile ducts, which may be the CBD, common hepatic duct, or the right or left bile duct. It often requires a laparotomy for repair, which may later lead to CBD stenosis. Circumferential

Table 7.1 Bismuth's classification of biliary strictures

Bismuth classification	Location
I	>2 cm distal to the hepatic bifurcation
II	<2 cm distal to the hepatic bifurcation
III	At the level of the hepatic bifurcation
IV	Involves the right or left hepatic duct
V	Extends into the right or left hepatic branch ducts

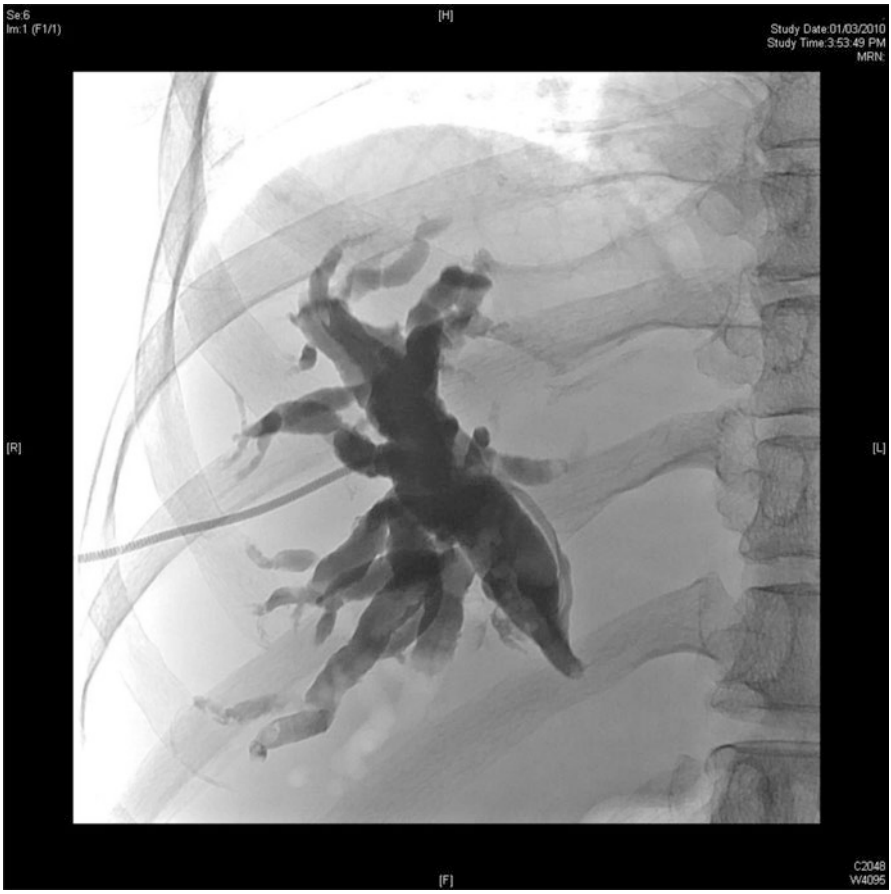

Fig. 7.1 Bismuth type 1 biliary stricture following laparoscopic cholecystectomy. Anatomy was delineated via percutaneous transhepatic cholangiogram puncture through the right anterior duct

injury of major bile ducts is classified as type E injury (correlating to Bismuth class I to V). Type E injuries cause the hepatic parenchyma to be separated from the lower ducts and duodenum via ductal stenosis, resection, or ablation [10] (Table 7.2).

7.4.2 IgG4 Cholangiopathy

Ohara et al. devised a classification for IgG4 cholangiopathy based on the location of stricture and differential diagnosis [58].

- Type 1: stenosis only in the distal common bile duct, which often occurs in pancreatic cancers.

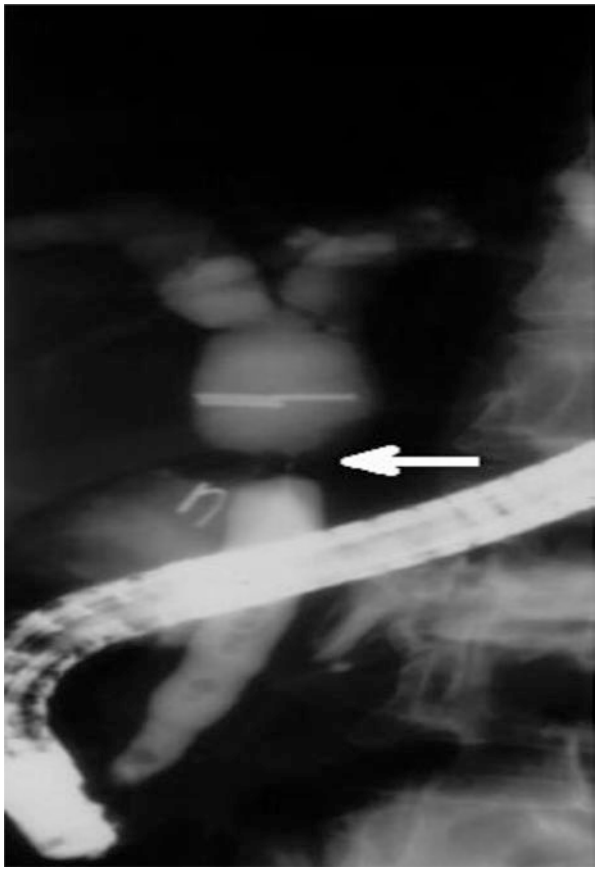

Fig. 7.2 Bismuth type 2 biliary stricture following laparoscopic cholecystectomy with clips seen on the common hepatic duct

Table 7.2 Strasberg's classification of bile duct injuries

Strasberg classification	Injury
A	Bile leak from a minor duct still in continuity with the CBD
B	Partial biliary tree occlusion
C	Bile leak from duct not in communication with the CBD
D	Lateral injury to extrahepatic bile ducts
E	Circumferential injury of major bile ducts

- Type 2: stenosis is diffusely distributed throughout the intrahepatic/proximal bile ducts, a differential of which is primary sclerosing cholangitis.
- Type 3: stenosis in both the hilar and the distal common bile duct.
- Type 4: stenosis only at the hilar.

Type 3 and 4 stenoses have to be distinguished from cholangiocarcinoma.

7.4.3 Biliary Stricture After Liver Transplantation

Lee et al. proposed a classification for intrahepatic biliary strictures (IHBS) post-liver transplant based on cholangiographic appearance of the biliary tree.

The authors classified patients with IHBS into four groups:

Unilateral focus (UF)—stricture only in the segmental branch of the unilateral hemi-liver
Confluence (CO)—several strictures at the confluence level
Bilateral multifocal (BM)—multiple strictures bilaterally
Diffuse necrosis (DN)—long segment diffuse obliteration of peripheral ducts or destruction of the central architectural integrity

This classification was used to assess prognosis after interventions. The study reported that patients classified as IHBS with UF or CO had better prognosis as their complications were more easily controlled with fewer interventional therapies. Only half of the patients classified as IHBS with BM, on the other hand, experienced symptomatic improvement with more aggressive repeated interventions. The DN type classification was associated with the worst prognosis without timely retransplantation, as the condition was not controlled by interventional therapies and is therefore associated with a high rate of graft failure [59].

7.4.4 Biliary Stricture Resulting from Chronic Pancreatitis

In order to differentiate and characterize common bile duct stricture due to chronic pancreatitis from other causes, Caroli devised a classification system comprising of five types of bile duct strictures, based on their cholangiographic appearances [20].

- Type I: long retropancreatic stenosis
- Type II: main bile duct dilatation with sphincter of Oddi stricture
- Type III: hourglass stricture
- Type IV: symptomatic due to
  - Type IVa—cyst
  - Type IVb and IVc—cancer
- Type V: pancreatic cancer

7.5 Clinical Presentation

Symptoms of biliary strictures are often non-specific, and the diagnosis is often made after laboratory testing. Patients may present with features suggestive of bile leak or obstruction including abdominal pain, fever, anorexia, pruritus, and jaundice. Charcot's triad is classically used to describe three common symptoms and signs related to ascending cholangitis, namely, right upper quadrant pain, jaundice,

and fever. This triad is named after Jean-Martin Charcot, a French neurologist who first described the combination of signs and symptoms related to this disease in the eighteenth century. Reynold and Everett later combined Charcot's triad with the features of shock and altered mental status, describing a pentad of signs and symptoms suggestive of the diagnosis of obstructive ascending cholangitis. This pentad is now termed Reynold's pentad [60].

It has been reported that the incidence of jaundice at presentation in patients with bile duct injury ranges from 15 to 49% [45]. In another study, of the 2% of 352 patients who developed biliary strictures post-Whipple's procedure, 86% presented by postoperative day 5 with new onset jaundice [61].

Abdominal pain is often the result of peritoneal and visceral structures exposure to bile content. However in liver transplant, the classical right upper quadrant pain may be absent due to immunosuppression and hepatic denervation [17]. Mode of presentation of bile leak (i.e. external biliary fistula, biloma, biliary ascites, and biliary peritonitis) has also been shown to be a poor predictor of stricture development [45].

7.6 Investigations

7.6.1 Laboratory Investigations

Symptoms are usually also accompanied by an increase in serum transaminase or bilirubin levels in liver function tests. Alkaline phosphatase (ALP) levels are usually increased to more than three times normal. This is often accompanied by increases in gamma-glutamyl transpeptidase (GGT) and 5′ nucleotidase. Prothrombin time (PT) and international normalized ratio (INR) may also be prolonged [40].

An important aspect of investigation is to rule out an underlying malignancy in the stricture, especially in those patients who present without any prior biliary intervention. When there is a more significant rise in ALP and AST levels, together with a bilirubin level of more than 84 micromol/L, malignancy should be suspected [62]. Tumour markers such as carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) may also increase diagnostic yield. CA 19-9 has proved to have a sensitivity of up to 53% in diagnosing cholangiocarcinoma, with a true negative rate of 92% in benign bile duct stricture groups [62].

7.6.2 Ultrasound

An abdominal ultrasound is generally the first step in imaging a patient with an obstructive picture on liver function tests, largely to assess for presence of biliary dilatation and fluid collection. It must be borne in mind that biliary dilatation may be absent in up to 71% of patients when the system has been decompressed by a bile leak in iatrogenic bile duct injuries [63]. Should a collection be found on ultrasound, it can be used to guide percutaneous aspiration which is useful to differentiate between an abscess and a biloma [64].

7.6.3 HIDA Scan

In addition to routine transabdominal ultrasound, hepatic scintigraphy (HIDA) is an option for detecting biliary obstruction. Scans post cholecystectomy have demonstrated a high sensitivity of 93% in predicting obstruction, with an overall accuracy rate of 80%, but with a low specificity of 64%. It, however, does not provide much information regarding the nature of these obstructions [65].

7.6.4 CT Cholangiography

A cholangiography is a study used to assess areas of leak or strictures by producing axial and three-dimensional images, providing a functional dimension that conventional MRCP does not. It also allows concurrent percutaneous treatment of benign biliary strictures with balloon dilatation and stenting [66].

7.6.5 MRCP

Magnetic resonance cholangiopancreatography (MRCP) is excellent for diagnosis of possible biliary disease, specifically strictures, dilatation, and filling defects larger than 3 mm. For stricture detection, it has a high sensitivity rate of up to 87% and specificity of 94% in locating the level of stricture formation. Many studies have also demonstrated that it is equally sensitive for both extrahepatic and intrahepatic strictures.

Compared to ERCP, MRCP also has the ability to detect the presence of subhepatic collections and show the site of bile leakage. However, unlike ERCP, MRCP lacks therapeutic function. MRCP also continues to be limited for small stones ($\leq$3 mm) and periampullary disease (due to the complex surrounding anatomy). If clinical suspicion for choledocholithiasis remains high despite negative MRCP findings, a patient should undergo ERCP or endoscopic ultrasonography (EUS) [67].

At present, the use of diffusion weighted imaging (DWI) to complement MRI is still controversial. A study performed in 2014 compared the results of purely using MRCP alone versus the use of MRCP with DWI. The sensitivity increased from 61 to 100% in the former ($P < 0.001$) and 44 to 90% in the latter ($P = 0.002$) [68]. These results were disputed by a later study, which showed no statistical significance in diagnostic improvement [69].

7.6.6 ERCP

ERCP is highly effective in detecting bile leaks, with sensitivities of up to 95%. It also offers the clinician therapeutic options. The use of ERCP is particularly helpful in determining whether a stricture is of a malignant origin, where presence of the

Table 7.3 Atypical Biliary Brushing score (ABBS)

Age > 60	+1
Endoscopic impression malignant	+2
Procedure indication pancreatic mass	+1
Stricture in common hepatic duct	+2
Stricture in distal common bile duct	+1
Presence of PSC	+2
CA19-9 > 300 U/mL	+1

"double duct sign" (dilation of both the pancreatic duct and CBD) in patients with obstructive jaundice was 85% sensitive in diagnosing malignant lesions [70].

The use of biliary brushings during ERCP to diagnose malignancy is debatable. Biliary brushings tend to be highly specific for malignancy with values approaching 90% but are only 56% sensitive [71]. In 2013, Burnett et al. published a 10-year review of the literature of 1556 patients who underwent ERCP with biliary brushings. It showed only a sensitivity rate of 41.6% with a negative predictive value of 58% for detection of malignancy [72].

Dilatation of bile duct strictures to improve yield of brushings has been suggested. Mohandas et al. in a study of 64 patients believed that dilating biliary strictures to 10F gauge during ERCP disrupts the tumour and enhances the sensitivity of bile cytology. This can be used as an adjunct to other techniques for tissue diagnosis of malignant biliary strictures [73].

Results of biliary cytology are mainly benign, malignant, or atypical. Several scoring systems have been developed for those with "atypical" biliary brushing results, including the Atypical Biliary Brushing score (ABBS), seen here in Sect. 7.2.2. Patients with a score of four or more are considered to be at high risk of harbouring malignancy [72] (Table 7.3).

7.7 Treatment

Endoscopic treatment has emerged as the optimal initial management for biliary strictures from benign causes. Due to its non-invasive nature, safe utilization in high-risk patients, and easy accessibility in tertiary centres, the endoscopic approach is now preferred as first-line treatment. Surgery, which is traditionally the mainstay treatment for benign biliary stricture but associated with significant morbidity rates, has a recurrent stricture rate of 10–30% [74–76]. As such, management of benign biliary stricture is shifting from surgical to endoscopic therapy (Fig. 7.3), except for those who require repeated stenting or has a complete transection or ligation of the bile duct [77]. A third option through the percutaneous route has also been shown to be favourable in situations where patients have a history of biliodigestive anastomosis or tight low biliary strictures [78]. Ultimately, the aims of treatment should be to improve and maintain bile duct patency and also to prevent stricture recurrence through the most ideal procedure possible.

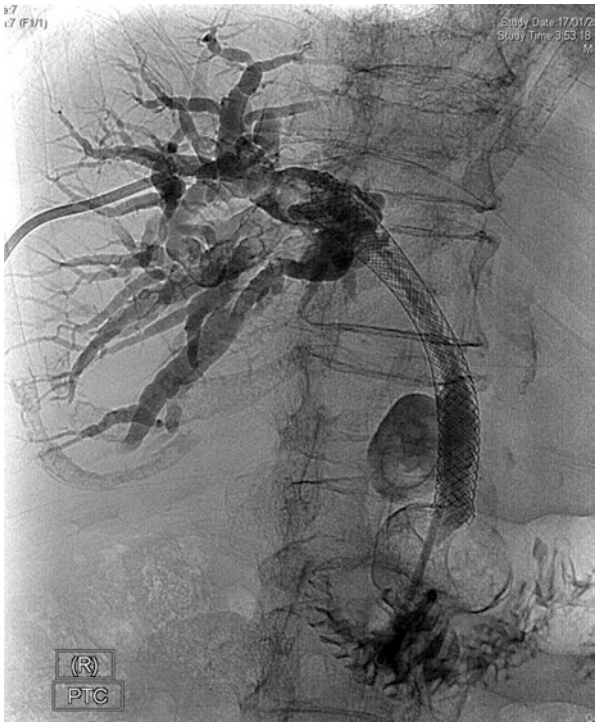

Fig. 7.3 Metal stenting of a common bile duct stricture via ERCP in a patient with advanced comorbidity

7.7.1 Percutaneous

First described in 1978 by Molnar and Stockum, percutaneous management of benign biliary stricture is largely through balloon dilatation and stent insertion. Main indications for treatment are (1) when the patient's premorbid condition is poor and deemed not a suitable surgical candidate, (2) in the presence of altered anatomy that does not favour the endoscopic approach, and (3) a septic status that requires early or immediate biliary tree decompression. Main contraindication is the presence of any non-correctable bleeding disorder [66].

Percutaneous approach can either be performed with ultrasound or fluoroscopic (i.e. percutaneous transhepatic cholangiography) guidance. Stenosis especially if malignant often causes the biliary system to be dilated, allowing easier percutaneous access with ultrasound-guided puncture. However, biliary dilatation from benign causes is often less remarkable; and ultrasound-guided puncture will be more difficult for biliary tree access. In such circumstances, a cholangiographic picture should be obtained and fluoroscopically guided puncture can be used instead. Upon entering the biliary tree, a guidewire is usually introduced and advanced across the stenotic tract. Internal-external drainage catheters can either be inserted and changed every 3 weeks with a larger diameter one to gradually dilate the tract, or balloon dilation can be performed every 2–3 weeks with a five French access catheter left in situ between sessions. The former method may require a period of up

to 4–6 months, predisposing the patient to infections with an external line [66]. Stricture patency rates have been reported to be at 84, 78, 74, and 67% at 1, 2, 5, and 10 years, respectively, after treatment [79].

7.7.2 Endoscopic

Endoscopic treatment for benign biliary strictures has been used increasingly in the past decade. The success rates range from 74 to 90%, where distal strictures have a higher success rate than proximal hilar strictures [80]. After stent removal, the chance of restenosis within 2 years has been quoted to be approximately 20–30%.

For endoscopic treatment to be successful, an aggressive approach is required. Multiple plastic biliary stents are generally exchanged periodically every 3–4 months for at least a year, with or without balloon dilatation of the stricture. This has been shown to give better long-term results than leaving a plastic stent in situ for the same period of time [81–83]. The late 1980s also saw the introduction of self-expandable metallic stents (SEMS), which has been reported to have higher patency rates compared to plastic stents [84–86]. Metallic stents are often made with stainless steel (cobalt-chromium) or an alloy, e.g. nitinol (nickel-titanium), and can expand fully to a diameter of 6–10 mm, with a typical stent length of 4–12 cm [87]. These stents can be classified into closed-cell or open-cell types, according to the lattice structure, and further classified into crosswire, hookwire, or hook- and crosswire structures according to the weave of the metallic fibres [88]. Covered SEMS using covering materials of polyurethane, silicone, and polytetrafluoroethylene have also been developed to overcome limitations and prolong patency duration in malignant strictures [88].

Balloon dilatation is performed with balloons of 4–12 mm diameter, advanced over a guidewire and across the stricture under fluoroscopic guidance. The size of the balloon chosen depends on the size of the bile duct above and below the stricture. The balloon is fully inflated for 30–60 sec until the balloon waist disappears. Within the first 4 weeks after surgery, balloon dilatation should be performed with smaller diameter balloons as it carries an increased risk of anastomotic dehiscence [17, 89].

Endoscopic treatment is generally not suitable for patients with benign biliary strictures that completely occlude the bile duct. Most benign strictures can be traversed with the standard 0.035 inch guidewires. Several strategies recommended for traversing very tight strictures include using fully coated hydrophilic guidewires with an angled tip or smaller diameter guidewires (i.e. 0.021 inch and 0.018 inch) and inflating a stone extraction balloon below the stricture while exerting downward tension to straighten the bile duct and modify the axis of the guidewire. Once the stricture is traversed, the hydrophilic guidewire should be exchanged for a stiffer 0.89 mm guidewire or non-hydrophilic guidewire, as they are less likely to be lost during catheter exchange and allow subsequent dilation and stent placement [90]. Other options available for assisting guidewire insertion in complex benign biliary strictures are the use of a

steerable catheter with tapered tip sizes ranging from 3.9 to 4.9 Fr or the use of a 7–8.5 Fr screw-type device [91, 92] Angioplasty balloons mounted on 3 Fr catheters may also be useful [93].

Endoscopic management of benign biliary strictures may also vary according to their aetiology.

7.7.2.1 Postoperative Causes

In cholecystectomy and liver transplantation, early or late presentations of these biliary strictures can affect the efficacy of endoscopic management. Early strictures are usually located at the anastomosis and as a result of surgical technique (i.e. excessive periductal tissue dissection, excessive use of electrocautery, and tension of the duct anastomosis). Delayed presentation, on the other hand, is commonly associated with ischaemic injury and fibrosis and thus often less responsive to endoscopic therapy [26].

A study of post-cholecystectomy benign biliary strictures showed that distal strictures (i.e. Bismuth I and II) have a better success rate after endoscopic treatment than proximal hilar strictures (Bismuth III) with an 80% versus a 20% success rate [82]. The 1-year patency rate was reported to be 74–90%, while the stricture recurrence rate within 2 years of stent removal is 20–30% [82, 94].

Patients who developed anastomotic stricture within the first 1–2 months after liver transplantation have the best response to endoscopic balloon dilatation and stent placement [95]. In the majority of cases, stricture resolution is usually achievable. Patients with late presentations commonly require multiple endoscopic dilatation and stent exchanges up to 2 years. Using both balloon dilatation and stenting is associated with long-term success rates of 70–100%, with a reported stricture recurrence rate of approximately 18% [89, 96–100]. Non-anastomotic strictures, as a consequence of hepatic artery thrombosis, increased cold ischaemia time, or ABO blood type incompatibility accounts for only 10–25% of all stricture complications after transplantation [101, 102]. These strictures are usually multiple and longer than anastomotic strictures and located at the hilar and intrahepatic biliary ducts [17, 103, 104]. They tend to be less responsive to endoscopic therapy with a long-term treatment response rate of 50–75%, often require more repeat interventions, and have a higher likelihood for recurrences. In these circumstances, endoscopic therapy can be considered as a bridge to retransplantation.

7.7.2.2 Chronic Pancreatitis

Surgical biliary decompression is generally recommended for patients with clinical features of biliary obstruction [105]. Endoscopic management is an alternative to surgery but is more appropriate for patients who are poor surgical candidates, or as a short-term treatment prior to surgical bypass. The surrounding fibrotic pancreatic tissue (instead of only fibrous deposition in anastomotic strictures) causes biliary strictures secondary to pancreatitis to be more resistant to aggressive endoscopic treatment [106]. Long-term success of endoscopic therapy is determined by stricture resolution and the absence of obstructive symptoms. Stent migration and occlusion are frequent complications [105]. Similar to endoscopic management for

postoperative strictures, multiple stent exchanges have better outcomes in chronic pancreatitis, with an overall success rate of 65.2% [82, 107, 108]. Patients with calcifying pancreatitis and those who have poor compliance to follow-up have worse outcomes following endoscopic treatment [26].

7.7.2.3 Primary Sclerosing Cholangitis

Long extra-hepatic dominant biliary strictures develop in 35–50% of patients with PSC [25, 109–111]. Patients with these dominant strictures may benefit from endoscopic therapy in situations where clinical or biochemical deterioration of PSC develops. The goal of endoscopic management in these instances is to dilate the bile duct stricture up to 6–8 mm with a balloon dilator, with or without stent placement. Short-term stent placement for approximately 10 days may be as effective as balloon dilation, without the complications of long-term stent placement such as stent occlusion or migration [112]. As the incidence of cholangitis is higher in those with PSC compared those who do not, antibiotic prophylaxis is recommended for all patients with PSC undergoing endoscopic treatment [113].

7.7.2.4 IgG4 Cholangiopathy

IgG4-associated cholangitis (IAC) can cause intrahepatic, proximal extrahepatic, or intrapancreatic benign biliary strictures. Intrahepatic IAC biliary strictures are similar to those seen in primary sclerosing cholangitis but tend to be more segmental and longer and frequently affect the distal common bile duct [26]. Endoscopic stent placement can temporarily relieve the biliary obstruction. However, the primary treatment will still be with corticosteroids [114].

7.7.3 Surgery

When endoscopic techniques are not effective, surgical management should be considered [74, 115, 116]. Roux-en-Y hepaticojejunostomy (HJ) is the most commonly used type of biliary reconstruction [116–119] (Fig. 7.4), although hepaticoduodenostomy can be selectively used for Bismuth-Strasberg classification E1 or E2 strictures [120]. A few technical considerations are worth mentioning at this stage. Firstly, where possible, a transactional end-to-side hepaticojejunostomy is preferable, though a side-to-side (non-transactional) hepaticojejunostomy can also be used. Transactional hepaticojejunostomies can be technically challenging in scenarios with dense inflammation around the portal structures. Here care should be taken in encircling the bile duct as inadvertent damage to the artery (laterally) or the portal vein/accessory arteries posteriorly may occur. In biliary reconstructions following liver transplantation, the anatomy here can be greatly varied. In scenarios where uncertainty exists in identifying the bile duct, a blue (23G) needle may be employed to puncture and aspirate the structure to confirm prior to dissection. Secondly, smaller ducts can result in size discrepancy (in duct-to-duct anastomosis) or anastomosis of undilated/first/second-order ducts can make an anastomosis technically challenging. In transactional end-to-side hepaticojejunostomy, the duct

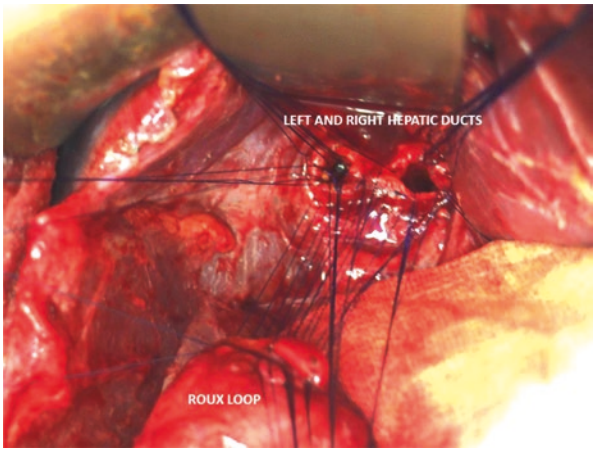

Fig. 7.4 A Roux-en-Y hepaticojejunostomy being created. An end-to-side anastomosis between the left and right hepatic ducts with an enteric limb is performed with interrupted 5/0 PDS sutures. Here the posterior line of sutures has been secured to the enteric limb prior to "parachuting" this limb and securing the posterior layer. Anterior wall sutures that are already placed (pictured) at the hepatic ducts are then completed on the enteric side before securing

may be widened by spatulating the duct. Here a small slit is made in the duct to provide a larger diameter for anastomosis. A note of caution should be made to the blood supply of the biliary tree. For example, where the arterial supply to the common hepatic duct is located in the 3 and 9 o'clock positions, an anterior slit would mean the blood supply to the anastomosis would not be compromised, thereby reducing the risk of stricture formation. Similarly, for side-to-side anastomosis of the left hepatic duct, the duct can be opened anteriorly in parallel to the curve of segment IV to provide a wider anastomosis. The authors routinely perform interrupted anterior wall and "parachuting" continuous posterior anastomosis for hepaticojejunostomy.

Factors that can affect the outcome of bilio-enteric anastomosis include the surgical technique used, timing of repair [119, 121], any vascular injury [122], level of anastomosis [123], and any associated concurrent sepsis [124]. For high-level strictures, a tension-free repair using a Hepp-Couinaud approach with good exposure of healthy bile ducts is crucial in achieving optimal long-term results [125]. A high injury is often accompanied by hepatic artery injury [122, 126]. Thus, a right hemihepatectomy is sometimes required [119, 123].

The Hepp-Couinaud approach is described as follows:

- Expose the origin of the main hepatic duct and the left main hepatic duct by incising the Glissonian capsule at the base of the vasculobiliary sheath overlying the proximal extrahepatic biliary system.
- The Roux-en-Y loops is brought through the right transverse mesocolon for a 2–3 cm, side-to-side, biliary enteric anastomosis [77].

7.7.3.1 Postoperative

As discussed in the previous section, anastomotic strictures after liver transplantation are best managed endoscopically. When endoscopic access to the stricture is difficult to be obtained, the percutaneous approach is recommended, with reported success rates of 40–80%. This however, is still considered a second-line therapy, as the invasiveness of the procedure and associated complications, e.g. bile leak and haemobilia, can cause significant morbidity [127]. Uncomplicated anastomotic strictures have a long-term success rate of more than 60% with either the endoscopic or percutaneous approach [77].

In contrast, non-anastomotic strictures usually respond less well to endoscopic dilation and stent placement than anastomotic strictures. Only 10–70% of patients with non-anastomotic strictures have a long-term response to endoscopic therapy, compared to 60–100% of patients with anastomotic stricture [77]. In patients with non-anastomotic strictures located primarily in the extrahepatic bile duct and the duct bifurcation, resection of the bifurcation and Roux-en-Y hepaticojejunostomy can be a successful treatment [128]. However, intrahepatic ischaemic-type biliary strictures tend to be more diffuse and difficult to manage, requiring repeat transplantation or permanent indwelling percutaneous drainage in up to 50% of patients [129–132].

7.7.3.2 Primary Sclerosing Cholangitis

Disease progression in PSC is not amenable to any medical therapy, and the only definitive treatment in advanced PSC is liver transplantation. Patients with PSC usually require repeat interventions, which make endoscopic intervention the preferred option [133, 134]. When endoscopic therapy fails, extrahepatic bile duct resection with cholangiojejunostomy and transhepatic stenting can be considered in patients without liver cirrhosis [135]. This is associated with a better 5-year survival of 85% compared to 59% in those patients treated with nonsurgical biliary dilatation with or without stent placement [136]. Liver transplantation is the procedure of choice for patients with deteriorating liver function and cirrhosis in the setting of diffuse ductal involvement. Recurrent PSC has also been reported to affect graft survival after liver transplantation [137].

7.7.3.3 Chronic Pancreatitis

Biliary strictures from chronic pancreatitis tend to occur in patient with advanced disease. These patients often have accompanying comorbidities such as diabetes, exocrine pancreatic insufficiency, and portal hypertension. Endoscopic therapy is difficult in these patients due to the dense fibrotic tissue and associated calcification surrounding these strictures [138]. Approximately 10% of patients experience endoscopically inserted stent failure and require surgical drainage [139].

7.7.3.4 IgG4 Cholangiopathy

Autoimmune biliary strictures from IAC can usually be reversed with steroid therapy in the acute phase [140]. At a later stage, however, the strictures undergo irreversible fibrosis and are no longer treatable with steroids alone [141]. Surgical intervention may be required in these circumstances.

7.8 Future Direction

As previously mentioned, the diagnostic yield in differentiating a malignant from a benign biliary stricture remains frustratingly low. This is made difficult in two ways: firstly, getting proximity to strictures within the biliary tree, and, secondly, the molecular-based tests in differentiating these two clinical entities.

A recent diagnostic tool in approaching intrabiliary lesions is peroral cholangioscopy (POCS). The main instrument that has been developed in this area is the SpyGlass system (Boston Scientific, Natick, MA) [142], with an advancement on the initial prototype called SpyGlass DS Direct Visualization System. This tool allows for the insertion of a fibreoptic camera within the biliary tree with the later model having an advancement of easier insertion due to its tapered tip, favourable visualization due to a 120° digital field of view, and injection and suction functions. The SpyGlass DS system has shown great potential in small series to help in diagnostic and therapeutic yields in patients with cholangiocarcinoma, PSC, IgG4 biliopathy, bile leaks postoperatively, and iatrogenic strictures [143–145]. This tool coupled with continued advances in stent technology has great promise in the diagnostic and therapeutic options for biliary strictures.

In parallel to advancements in therapeutic and diagnostic tools, there have been recent advances in molecular studies in biliary strictures in differentiating benign from malignant disease. Proteomics is the large-scale identification of the proteome, the functional end product of the genome. A large number of studies have interrogated the biliary and urinary proteome for diagnostic purposes in this area and recently reviewed [146–148]. Recent studies have successfully identified peptide signatures that when placed into diagnostic models were able to accurately distinguish choledocholithiasis and PSC from cholangiocarcinoma [149]. However, proteomic-based approaches like these have come under criticism as, while the diagnostic yield is impressive, peptide signatures have limited biological utility as they lack information of parent proteins and (often) reproducible results. Similarly such advances have been made in metabolomics [150] and lipomic [151] studies in increasing diagnostic yield.

In summary, biliary strictures remain a common clinical problem. The mainstay in management of this disease is preventing them surgically, accurately diagnosing the underlying cause, and appropriately treating it, leading many authors to conclude the biliary tree as the “Achilles heel” of hepatobiliary surgery.

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Portal Biliopathy

8

Moinak Sen Sarma, Surender Kumar Yachha, and Adarsh Chaudhary

8.1 Introduction

The term "portal biliopathy" (PB) refers to abnormalities of the entire biliary tract, including intrahepatic and extrahepatic bile ducts, cystic duct, and gallbladder in patients with portal hypertension [1].These changes are believed to be caused by the pressure of the venous collaterals on both the intrahepatic and extrahepatic bile ducts and the gallbladder. More recently, PB due to extrahepatic portal venous obstruction (EHPVO) has been renamed "portal cavernoma cholangiopathy (PCC)," by the Indian National Association for Study of the Liver (INASL) task force [2]. PCC in adults is asymptomatic in 81–100%. Despite EHPVO being a non-cirrhotic disease with a favorable outcome, the cholangiopathy is identified only when the patient becomes symptomatic with jaundice or cholangitis (biliary strictures or calculi) as seen in 5–38% of adults [1]. However, once symptoms ensue, the course of illness becomes tenacious, with the progressive worsening necessitating biliary decompression, shunt surgery, or even liver transplantation in terminal stages. PB is also known to occur in cirrhosis (0–33%) and idiopathic portal hypertension (9–40%).

8.2 Venous Drainage of the Biliary System

Venous drainage of the bile duct is an amalgamation of the tributaries of portal vein with superior mesenteric vein (Fig. 8.1a). There are two plexuses around the bile duct: the epicholedochal venous plexus of Saint which forms a fine reticular meshwork on

M. S. Sarma · S. K. Yachha
Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

A. Chaudhary (✉)
Department of Gastrointestinal Surgery, Medanta Medicity Hospital, Gurgaon, India

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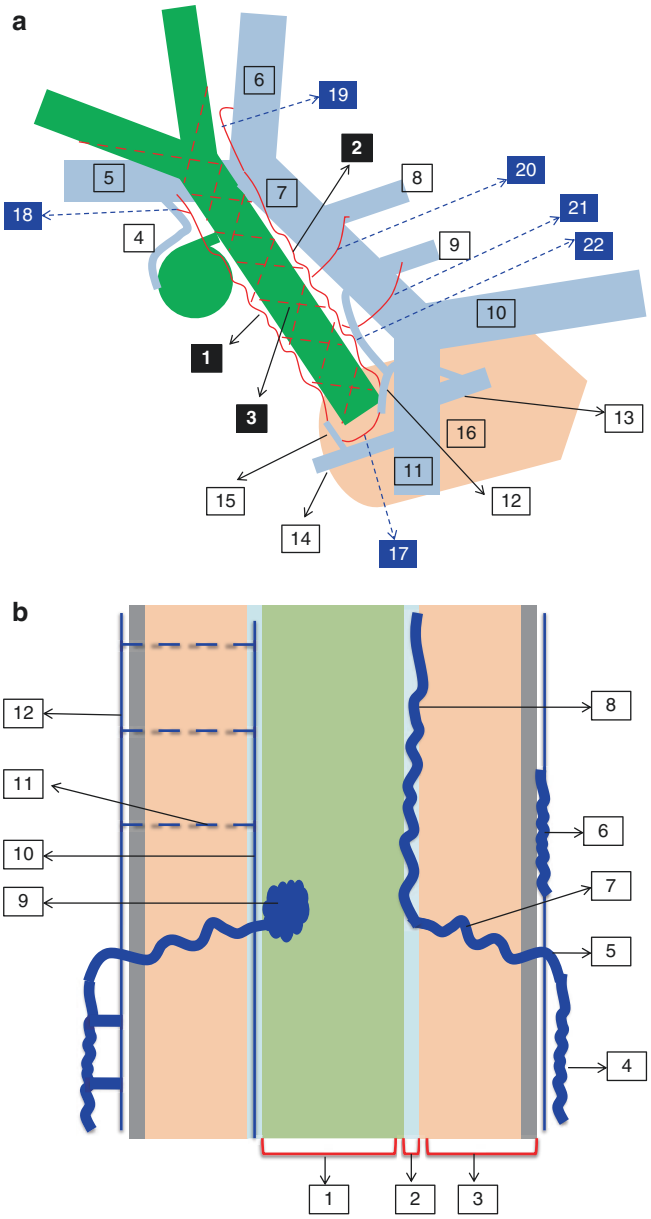

Fig. 8.1 Venous drainage of the biliary system. (**a**) 1, 3 o'clock marginal vein (right paracholedochal plexus); 2, 9 o'clock marginal vein (left paracholechal plexus); 3, epicholedochal plexus of Saint; 4, cystic vein; 5, right branch of portal vein; 6, left branch of portal vein; 7, main portal vein; 8, right gastric vein; 9, left gastric vein; 10, splenic vein; 11, superior mesenteric vein; 12, posteroinferior pancreaticoduodenal vein; 13, first jejunal vein; 14, gastrocolic trunk; 15, anterosuperior pancreaticoduodenal vein; 16, head of pancreas; 17–22, tributaries. (**b**) 1, lumen of bile duct; 2, subepithelial layer; 3, fibromuscular layer; 4, paracholedochal varices; 5, pericholedochal varices; 6, epicholedochal varices; 7, choledochal perforator; 8, subepithelial varices; 9, intracholedochal varices; 10, subepithelial venous plexus; 11, intramural venous plexus; 12, epicholedochal plexus

the surface of the bile duct and the paracholedochal plexus of Petren which probably represents obliterated right umbilical vein. The paracholedochal plexus in turn comprises two veins, namely, the 3 o'clock and 9 o'clock marginal veins on the right and left sides, respectively. The right half of paracholedochal plexus communicates with the right branch of portal vein, cystic vein gastrocolic trunk, and anterosuperior pancreaticoduodenal veins. The paracholedochal plexus on the left side communicates with the first jejunal vein, left and right gastric veins, left branch of portal vein, and posterosuperior pancreaticoduodenal vein. The pancreaticoduodenal veins are important in the formation of the portal cavernoma. The anterosuperior pancreaticoduodenal vein drains into the gastrocolic trunk, which communicates across the pancreatic head to the posterosuperior pancreaticoduodenal vein, which joins the portal vein near the hepatic hilum. The inferior pancreatic veins drain into the first jejunal vein or less commonly directly into the superior mesenteric vein.

The common bile duct (CBD) wall has three layers, namely, the fibromuscular layer, subepithelial layer, and epithelium (Fig. 8.1b). Paracholedochal varices lie away from the fibromuscular layer. Pericholedochal varices, on the other hand, lie adjacent to the fibromuscular layer. Perforators enter through the muscular layer of the CBD and are connected to subepithelial varices beneath the epithelium or intracholedochal varices within the CBD. The epicholedochal varices are present mainly on the surface of the CBD [3].

8.3 Clinical Features

The vast majority of patients remain asymptomatic in the presence of radiological evidence of PB. Symptomatic patients usually present with features of bile duct obstruction.

In an elegant study, Llop and colleagues prospectively followed up two groups of adults (acute portal vein thrombosis and chronic portal cavernoma) with PCC. The cohort demonstrated 22.2% prevalence of symptomatic PCC. The 5-year and 10-year actuarial probability of symptomatic PCC after diagnosis of chronic portal vein thrombosis was 9% and 13%, respectively. The 5-year probability of developing symptoms of PC after acute portal vein thrombosis was 19% [4].

The diagnosis is established by the typical cholangiographic signs (as mentioned below) and demonstration of pericholedochal collaterals. In the evaluation of PB, magnetic resonance cholangiography (MRC) confirms hepatobiliary structural changes, whereas vascular imaging (MR portovenography/MRPV and endoscopic ultrasonography/EUS) delineates venous anatomy and collaterals. The typical signs of PB on MRC are as follows:

- *Wavy changes*: Fine irregularities on the duct walls due to contiguous shallow indentations less than one quarter of ductal diameter (Fig. 8.2a).
- *Smooth indentations*: Smooth noncontiguous thumb-like impressions giving a nodular contour less than one quarter of ductal diameter (Fig. 8.2b).
- *Angulations*: Ductal kinking of <145° at the intersection of imaginary lines drawn along the long axis of the bile duct above and below the angle (Fig. 8.2c).

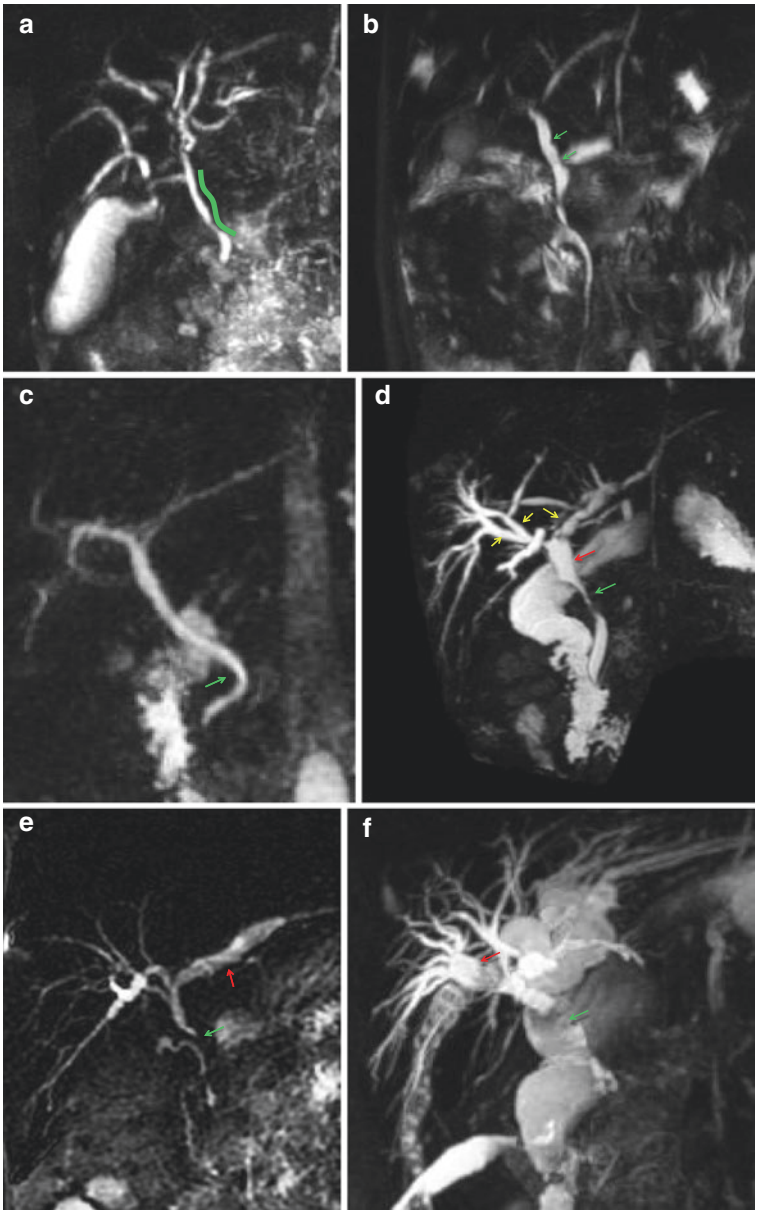

Fig. 8.2 Typical signs of portal biliopathy on magnetic resonance cholangiography (MRC) (abbreviations: *CBD*, common bile duct). (**a**) Green outline shows wavy compressions on common bile duct (CBD). *Wavy compressions: fine irregularities on the duct walls due to contiguous shallow indentations less than one quarter of ductal diameter*. (**b**) Green arrows show smooth indentations on CBD. *Smooth indentations: smooth noncontiguous thumb-like impressions giving a nodular contour less than one quarter of ductal diameter.* (**c**) Green arrow shows angulation on CBD. *Angulation: ductal kinking of* $< 145^{\circ}$ *at the intersection of imaginary lines drawn along the long axis of the bile duct above and below the angle.* (**d**) Green, red, and yellow arrows show long CBD stricture, dilated common hepatic duct, and dilated intrahepatic biliary radicles, respectively. (**e**) Green arrow shows abrupt termination of mid-CBD. Red arrow shows irregularly dilated left hepatic duct. (**f**) Green arrow and red arrow show dilated CBD and right hepatic duct with large calculi

- *Strictures (extrahepatic or intrahepatic)*: Variable length narrowing of the ductal lumen, in reference to well-opacified downstream duct segment. Narrowed segment is usually > ½ of the ductal diameter (Fig. 8.2d).
- Other changes (Fig. 8.2e, f) are *upstream dilatation* and *intraluminal filling defects* (calculi, sludge, prolapsing intracholedochal varices) [5].

Nowadays, endoscopic retrograde cholangiopancreatography (ERCP) is reserved solely for therapeutic interventions [1].

8.4 Pathophysiology

The postulated mechanisms of biliary changes in EHPVO are extrinsic compression by portal collaterals and the development of an ischemic stricture of the bile duct due to injury at the time of portal venous thrombosis or a combination of both. There is evidence to support both theories of compression and ischemia. In a study of five cases, Dhiman et al. showed that repeat ERCP done after 4–8 weeks of shunt surgery demonstrated total disappearance of cholangiographic changes in one, partial disappearance in two, and no change in the remaining two cases [5, 6]. This indicates that while in some patients compression plays an important role, in others ischemia alone, or in combination with compression, causes biliary changes. Similarly, Chaudhary et al. supported the compression theory by documenting relief of jaundice in five of seven patients within 3–7 weeks of shunt surgery with the remaining two patients requiring a second-stage hepaticojejunostomy [7].

8.5 Management of PB

The existing guidelines of management in PB in adults are focused mainly on the symptomatic group where the disease has advanced considerably. Management of asymptomatic PB has not been addressed as there is lack of prospective literature on the same. So far, only symptomatic PB is a definite indication for intervention [2]. Primary biliary tract surgery has significant morbidity and mortality due to extensive collaterals around the bile ducts. Some clinicians believe that shunt surgery should be done first in all cases with symptomatic biliopathy to decompress the portal hypertension followed by a second-stage biliary surgery if it fails to resolve the biliary obstruction [7]. Others advocate that endoscopic management should be performed upfront. Patients with choledocholithiasis without associated biliary stricture can successfully undergo endoscopic sphincterotomy and stone extraction. Patients with choledocholithiasis and stricture will require multiple sessions of endoscopic therapy with balloon dilatation and stent placement. Endoscopic failure should be managed by a two-staged surgery (portosystemic shunt followed by biliary surgery) [1, 2, 8, 9]. There are no clear guidelines for timing of biliary surgery following shunt. It is suggested that a longer interval (up to 1 year) and documentation of a patent shunt with decompressed collaterals on color Doppler or magnetic resonance angiography may help in determining the optimum time for surgery [10–12].

8.6 Issues Exclusive to Children

Existing literature and consensus statements are centered around adults with this disease. There is paucity of data in children on the natural history of PB in children. EHPVO is the main cause of portal hypertension (68–75%) in children [13]. It is a disorder that occurs predominantly in children with its manifestation and persistence throughout childhood, adolescence, and into adulthood. In contrast to adults, the onset of portal vein thrombosis and its natural evolution is difficult to assess in children with EHPVO as most are silent and innocuous. Gauthier-Villars et al. reported an incidence of 6% symptomatic PB in 121 children with EHPVO [14]. Khuroo and colleagues noted that none of the 13 children in their series of 21 patients were symptomatic [9].

Current grading systems have limitations as they are neither applicable nor do they address the appropriate intervention in children. The Chandra grading of PCC is limited to biliary anatomical involvement and does not classify the severity [15], while the Llop grading system, though based on cholangiographic severity, does not take into account intrahepatic involvement or presence of biliary calculi [4]. Moreover, the latter system defines adult diameters of biliary ductal dilatation which are not suitable for the pediatric age group. There is a need for a better grading system exclusive for children using pediatric cut-off diameters.

In an unpublished prospective study of 72 EHPVO children from Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, PCC was comprehensively studied using MRC-MRPV and EUS. The authors showed that PCC exists in 92% of chronic EHPVO children (asymptomatic 85%; symptomatic 7%) which is comparable to adult data. Eighty-five percent of children with PCC were asymptomatic and could not be identified clinically or biochemically. Advanced cholangiopathy was seen in 87% of asymptomatic (74% of the total group), and hence this was a high-risk group identified for early surgical intervention. Progressive severity of cholangiopathy was associated with increasing age and duration of disease indicating the long-standing variceal and structural changes on the biliary system that evolve and progress over the years. The absence of patency of the superior mesenteric vein (SMV) as noted in 64% of individuals was noted to be important for the development, as well as the severity, of PCC (67% asymptomatic; 100% symptomatic). It is well known that the portal cavernoma contributes to PCC. With an additionally blocked SMV, the venous plexuses are unable to drain adequately and hence enlarge significantly and further compress the CBD. Blocked SMV was significantly associated with development of intracholedochal varices (ICV), choledochal perforators (CPF), intramural gallbladder collaterals, and EUS-biliary stones (Fig. 8.3a, b).

The Baveno VI Pediatric Satellite Meeting strongly recommended the use of the meso-Rex shunt for all children with EHPVO as pre-primary, primary, and

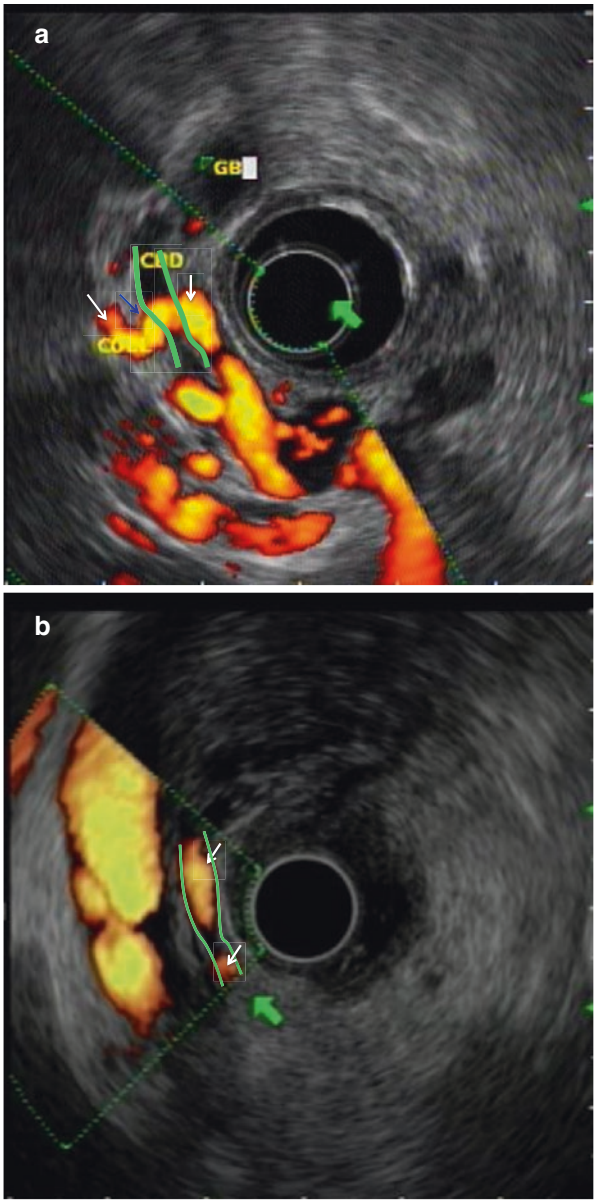

Fig. 8.3 Radial endosonography images in portal biliopathy. (**a**) Green outline showing CBD with surrounding pericholedochal varices (white arrows) and choledochal perforator (blue arrow). (**b**) Green outline and arrow showing CBD with intracholedochal varices (white arrows)

secondary prophylaxis [16]. In contrast, the authors' data has indicated that despite SMV occlusion being a definite risk factor for advanced cholangiopathy, the widely popular meso-Rex or mesocaval shunts would be rendered unsuitable. These findings also suggest that those with an occluded or blocked SMV but a

patent splenic vein only have the option of undergoing a non-meso-Rex surgical shunt irrespective of the grade of cholangiopathy to arrest further progression of the disease. Splenectomy with a splenorenal shunt has been our preferred surgical procedure and has proven to be an effective and durable procedure in decompressing the pericholedochal varices. The role of EUS assumes significance in identification of ICV (58%) and CPF (51%). This would imply caution with regard to the choice of endoscopic procedures (stricture dilatation, stone extraction, and stent placement) performed in children owing to the risk of intrabiliary bleeding [17]. EUS can also identify smaller (<5 mm) biliary calculi at the lower end of the CBD (5% A-PCC) that may be missed on MRC [18]. Hence the authors advocate the use of noninvasive, radiation-free MRC-MRPV in routine evaluation of PCC >10 years of age as 85% are asymptomatic with advanced cholangiopathy and recommend earliest of the early portosystemic shunt surgery in those with additional SMV occlusion.

The only pediatric study by Gauthier-Villars et al. that included eight children with symptomatic biliopathy in EHPVO demonstrated regression of cholestasis in all patients after shunt surgery (mesocaval shunt in six and meso-Rex in two). Following surgery, serum aminotransferases and gamma-glutamyl transpeptidase normalized within 1–6 weeks in five children and remained normal on follow-up from 5 to 15 years. Liver function tests took 2–2.5 years to normalize in the remaining three cases. After a follow-up of 4.5–15 years, all children were alive and displayed no dilatation of bile ducts on abdominal ultrasonography except one who had partial regression [14].

A management algorithm approach for portal cavenorma cholangiopathy (Fig. 8.4) has been suggested which would be pertinent in both children and adults.

8.7 Future Directions for Research

There is a paucity of prospective well-controlled studies to highlight the natural history and therapy of PB or PCC. The following questions remain unanswered in literature and certainly warrant further research: (a) At what age does the pathophysiologic process of PB commence in a child? (b) Are there specific risk factors for the development of PB? (c) Does variceal eradication preferentially force the blood away from esophagogastric bed to the hepatobiliary area thereby worsening PB? (d) What is the ideal shunt surgery for PB? (e) How early should we intervene in early cholangiopathy? (f) Can we identify a subgroup of patients who are at a higher risk for persistence of the biliary obstruction despite a successful portosystemic shunt surgery? (g) Is PB medically preventable by beta-blockers or anti-angiogenesis drugs in a setting of portal hypertension?

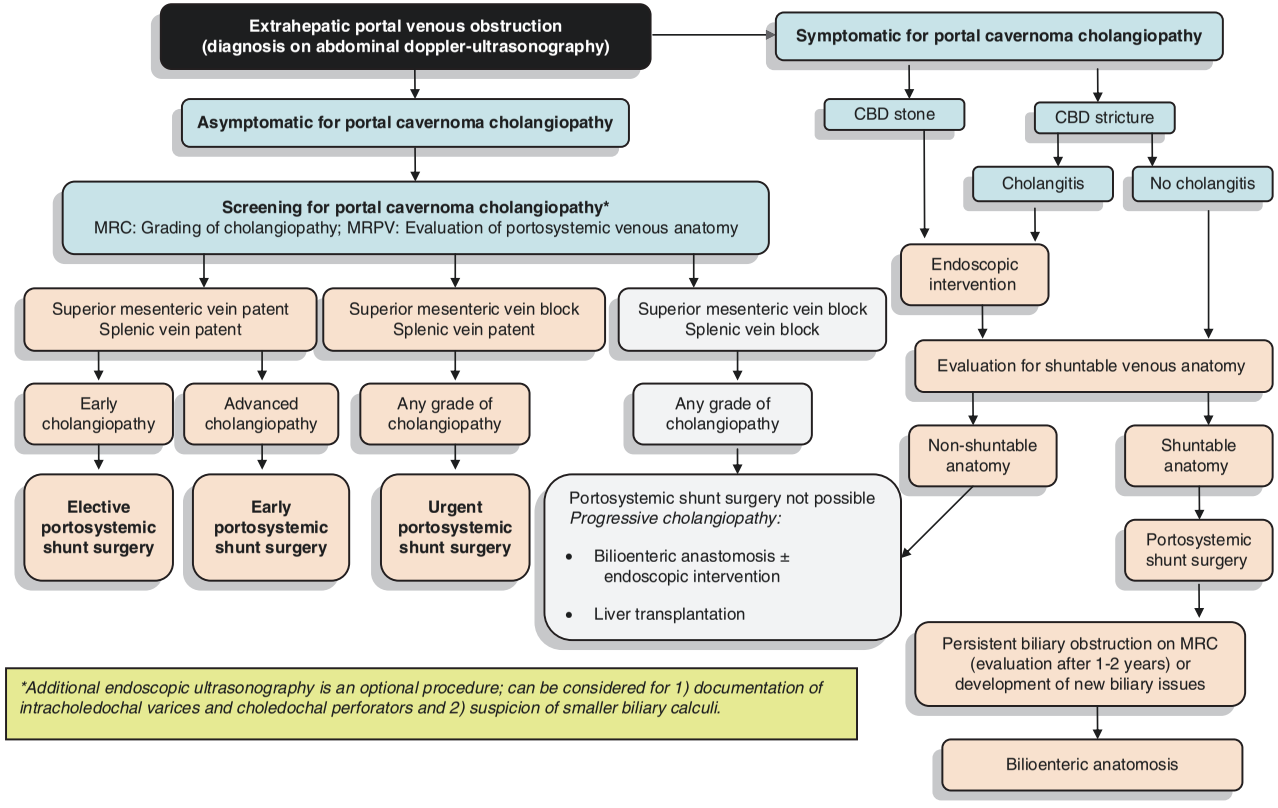

Fig. 8.4 Practical algorithm for the management of asymptomatic and symptomatic PCC. *MRC*, magnetic resonance cholangiogram; *MRPV*, magnetic resonance portovenogram; *CBD*, common bile duct

Conclusion

Portal biliopathy is a unique complication of portal hypertension that has propensity to progress toward secondary biliary cirrhosis. In EHPVO, asymptomatic PCC needs to be treated by a timely portosystemic shunt surgery.

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Acute Pancreatitis

9

John A. Windsor

9.1 Introduction

Acute pancreatitis is a common disease and patients usually present with severe upper abdominal pain. The mild form of the disease is self-limiting, but severe and critical disease is characterized by infected pancreatic necrosis, multiple organ failure and a high mortality [1].

It is no longer believed that acute pancreatitis completely resolves with no symptomatic or morphological sequelae. Necrotizing pancreatitis can leave significant scarring and strictures as well as impairment of exocrine and endocrine pancreatic function. Recurrent acute pancreatitis can lead to chronic pancreatitis [2].

Many advances in the management of acute pancreatitis have resulted in an overall improvement in the clinical outcome for patients with acute pancreatitis. Many specific treatments have been tested in experimental and clinical studies, but none have entered clinical practice. Further improvement in outcome will need to come from successful trials of specific treatments that target outcome-determining pathophysiology.

The aim of this chapter is to provide an update on acute pancreatitis and its management, highlighting areas for further research.

J. A. Windsor
Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

HBP/Upper GI Unit, Auckland City Hospital, Auckland District Health Board, Auckland, New Zealand
e-mail: j.windsor@auckland.ac.nz

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9.2 Epidemiology

Acute pancreatitis is the most common acute gastrointestinal disease admitted to hospitals in the United States [3]. Worldwide the incidence of acute pancreatitis ranges from 5 to 80/100,000 of the population, with the highest incidence recorded in Finland and the United States [4]. The incidence is increasing in many countries around the world, including the United States where there has been a 30% increase since 2000 [5]. The incidence of acute pancreatitis varies with the prevalence of aetiological factors and ethnicity. The annual incidence of acute pancreatitis in Native Americans is 4 per 100,000, while in Caucasian it is 5.7 and in Afro-Americans it is 20.7 [5]. The incidence of acute pancreatitis also varies with gender with males having a higher incidence of alcohol-related acute pancreatitis and females a higher incidence of gallstone-related acute pancreatitis [6]. The median age of patients at the time of index acute pancreatitis varies by aetiology. For alcohol-related acute pancreatitis, it is usually during the third or fourth decade, while for gallstone-related acute pancreatitis, it is during the sixth decade. Smoking and obesity are both independent risk factors for acute pancreatitis [6, 7].

The crude mortality rate of 1.0/100,000 ranks it as the 14th most common disease overall and the 9th most common cause of non-cancer gastrointestinal deaths [3]. The risk of mortality is related to the severity of acute pancreatitis. The risk is less than 1% for those with mild disease, increasing to around 10% for those with moderate disease, but for severe (20–40%) and critical (>50%) disease, the mortality risk is much higher.

9.3 Aetiology

The most common factors causally associated with the development of acute pancreatitis are gallstones and alcohol (Table 9.1), which account for up to 80% of cases. Other aetiologies are less common, and sometimes a cause is never found, as in ‘idiopathic’ acute pancreatitis.

9.3.1 Gallstones

The presence of gallstones does not confirm causality. But the timing of the onset of acute pancreatitis symptoms, the presence of gallstones, the absence of other aetiological factors and the presence of new liver dysfunction (in particular the elevation of ALT) suggest gallstone-related acute pancreatitis. It remains unclear how a small gallstone causes acute pancreatitis [8]. The ‘common channel’ hypothesis suggests that an impacted stone allows bile to reflux into the pancreatic duct. Another hypothesis is that the transient incompetence of the sphincter after the passage of a stone allows duodenal fluid and bile to reflux into the pancreatic duct. A further possibility is that the gallstone obstructs the pancreatic duct leading to pancreatic duct hypertension which might cause minor ductal disruption and premature enzyme activation. Sometimes ultrasound of the gallbladder does not reveal gallstones, with

Table 9.1 Aetiology factors for acute pancreatitis

Obstructive
Gallstones
Peripancreatic tumour
Pancreas divisum
Sphincter of Oddi dysfunction
Trauma
ERCP
Operative trauma
Blunt or penetrating trauma
Toxins
Alcohol
Scorpion bite
Metabolic
Hypercalcaemia/hyperparathyroidism
Hypertriglyceridaemia
Renal failure
Idiopathic
Drugs
Genetic
Hereditary pancreatitis cationic trypsinogen
SPINKI mutations
CFTR mutations, cystic fibrosis
Vascular
Ischaemia
Embolism
Vasculitis
Infections
Viral—EBV, mumps, varicella, Coxsackie, HIV, CMV
Bacterial—mycoplasma, legionella, TB
Parasitic—ascariasis, clonorchiasis

posterior shadowing, but there may be the layering of thick bile, sometimes called 'sludge' in the dependent region of the gallbladder. Ultrasonography might also reveal bright spots along the mucosa of the gallbladder, sometimes as small polyps that are typical of cholesterolosis. These can enter the bile and cause gallstone-related acute pancreatitis. Gallstones are too small for detection on ultrasound or MR scanning, but they can sometimes be seen as birefringent crystals under microscopy in bile aspirated by ERCP [9]. This so-called occult microlithiasis may account for up to 50% of those with idiopathic acute pancreatitis. Rarely, a stone will impact in the ampulla and promote concomitant cholangitis.

9.3.2 Alcohol

Alcohol ingestion is associated with acute pancreatitis, and sustained alcohol ingestion is associated with recurrent acute pancreatitis and development of chronic

pancreatitis in susceptible individuals. More important than the type of alcohol is the amount of ethanol consumed (e.g. >150 g) and the pattern of drinking (i.e. binge). There are several mechanisms by which ethanol causes acute pancreatitis, acting on both acinar and stellate cells [2]. The acinar cell metabolizes ethanol by oxidative and non-oxidative pathways and exhibits changes that predispose the cells to autodigestive injury and necrosis, inflammation and cell death. Ethanol causes a brief increase of exocrine secretion followed by a decrease. The secretory burst coupled with ethanol-induced spasm of the sphincter of Oddi is probably an important mechanism in causing acute pancreatitis. Ethanol also induces ductal permeability, which allows prematurely activated enzymes to cause damage to the pancreatic parenchyma. The pancreatic stellate cells are activated by exposure to ethanol, and there is increased synthesis of pro-inflammatory mediators and stimulation of a myofibroblast phenotype. Ethanol also increases the protein content of pancreatic juice and decreases bicarbonate levels and trypsin inhibitor concentration. The formation of protein plugs may also contribute by causing an obstructive element to pancreatic exocrine outflow although this is a feature more common in chronic pancreatitis.

9.3.3 Hyperlipidaemia

Patients with types I and V hyperlipoproteinemia can experience episodes of abdominal pain, and this is often associated with marked hypertriglyceridaemia [2]. Lipase liberates toxic fatty acid moieties into the pancreatic microcirculation, leading to microcirculatory impairment and ischaemia. As with gallstones and alcohol, hyperlipidaemia is a modifiable risk factor for acute pancreatitis. To prevent recurrence, there is the need for dietary modification and usually lipid-lowering drugs.

9.3.4 Hypercalcaemia

Elevated intracellular levels of calcium are an important, although rare, cause of acute pancreatitis. This happens most frequently with hyperparathyroidism and lytic bone disease. A sustained increase of cytosolic calcium concentrations, as observed in various models of acute pancreatitis, sabotages crucial cellular defence mechanisms and initiates premature trypsinogen activation [10].

9.3.5 Genetic Factors

Hereditary pancreatitis is an autosomal dominant disorder that is most often related to mutations of the cationic trypsinogen gene (*PRSS1*). This causes premature activation of trypsin and abnormalities of ductal secretion, both of which promote acute pancreatitis. Another important mutation is that of the SPINK1 protein, which blocks the active binding site of trypsin. Variations in penetration and phenotype are

common, and there are many other mutations that are now being implicated. Mutant enzymes activated within acinar cells can overwhelm the first line of defence (pancreatic secretory trypsin inhibitor) and resist backup defences (e.g. proteolytic degradation, enzyme Y and trypsin itself), allowing activated mutant cationic trypsin to trigger the enzyme cascade [11].

9.3.6 Iatrogenic

Acute pancreatitis can result from a number of interventions, including core biopsy (with damage to the pancreatic duct) and bile duct exploration (with trauma to the sphincter of Oddi). There are a number of situations in which acute pancreatitis is secondary to ischaemia, to which the pancreas is particularly susceptible. Pancreatic hypoperfusion can occur as a result of reflex splanchnic vasoconstriction secondary to haemorrhagic shock, cardiopulmonary bypass, cardiac transplantation and major trauma. The most common iatrogenic cause of acute pancreatitis however is ERCP, which can occur in up to 10% of cases. It appears that the risk factor is the repeated and high-pressure infusion of the contrast when performing pancreatography. It is even more likely to happen in patients with sphincter of Oddi dysfunction. The risk of ERCP-related acute pancreatitis can be reduced through the use of prophylactic rectal non-steroidal drugs [12] that is a more effective strategy than prophylactic pancreatic duct stenting [13].

9.3.7 Tumours

A pancreatic or periampullary tumour should be considered as a possible cause of acute pancreatitis in patients with idiopathic acute pancreatitis, especially in those over 50 years old. Approximately 1–2% of patients with acute pancreatitis have a pancreatic tumour, and the episode of acute pancreatitis can be the first clinical manifestation. The development of prediabetes or diabetes in the preceding 2 years might also be a clue to the diagnosis of a pancreatic adenocarcinoma. Patients over the age of 50 who have no attributable cause should have a CT scan done after the resolution of the acute pancreatitis.

9.4 Pathology

Despite the diverse aetiology, the pathological changes of acute pancreatitis are remarkably similar. There is a spectrum of histological severity that mirrors the spectrum of clinical severity. Acute pancreatitis starts within the acinar cell but quickly leads to pancreatic inflammation, which when severe is associated with pancreatic necrosis. The recruitment and activation of inflammatory cells within the pancreas contributes to both the local and systemic inflammatory response and to distant organ dysfunction and/or failure [14] (Fig. 9.1).

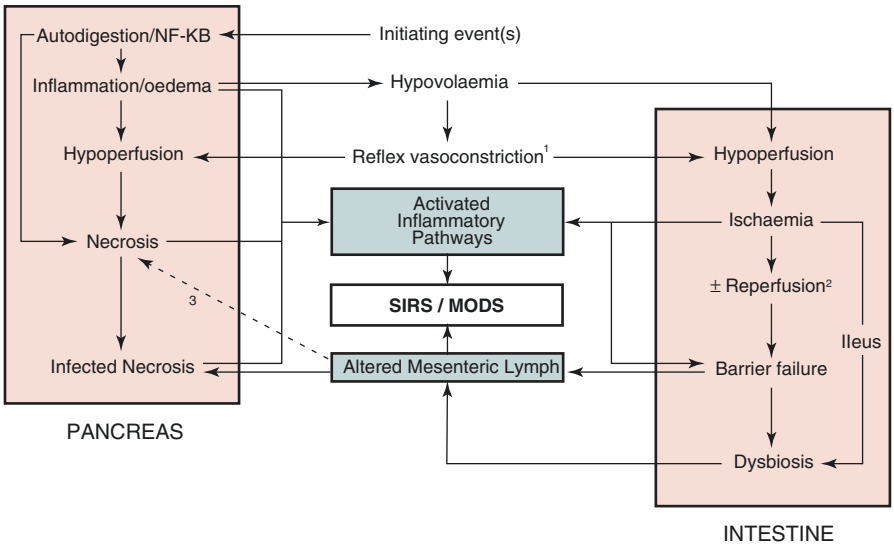

Fig. 9.1 Representation of the key pathophysiological events in the pancreas and intestine that are responsible for driving the severity and outcome of acute pancreatitis (Used with permission)

9.4.1 Acinar Events

For more than a century, acute pancreatitis has been considered to result from 'autodigestion' where activated pancreatic enzymes injure the pancreas. Since then the intra-acinar activation of zymogens has been demonstrated in experimental acute pancreatitis models and is accepted as a key-precipitating event [15, 16]. There is now considerable evidence to support the role of premature activation in trypsin in the pathogenesis of acute pancreatitis. Mice without an important isoform of trypsinogen sustain less severe acute pancreatitis [17]. Mice with acute pancreatitis have been shown to have significant intra-acinar expression of active trypsin [18]. An understanding of the genetics of hereditary acute pancreatitis (above) has also advanced our understanding since elevated intracellular trypsin activation [19] and activation of trypsinogen cause acute pancreatitis [20].

The intra-acinar activation of trypsin must overwhelm the local defences before pancreatic 'autodigestion' can occur. The mechanisms that reduce the risk of this occurring include the production of enzymes as inactive precursors (i.e. zymogens) that are transported, secreted and activated remote from the pancreas, in the duodenum where enterokinase normally activates trypsin to initiate the cascade reaction. Another important protective mechanism is the presence of trypsin inhibitors that are transported and stored along with zymogens to inhibit any prematurely activated trypsinogen within the acinar cells. This mechanism can be overwhelmed as well.

Trypsinogen activation has been elegantly demonstrated to occur when the zymogen granules co-localize with lysosomes that contain lysosomal enzymes (e.g. cathepsin B) [21]. This co-localization is probably due to increased calcium levels

as it is prevented when calcium is blocked [22]. Activated trypsin permeabilizes the vacuoles to release cathepsin B into the cytosol where it results in the opening of a mitochondrial pore in the membrane. The resulting release of cytochrome C from mitochondria initiates apoptotic death of the acinar cells [23].

Intra-acinar inflammatory pathways are also activated in acute pancreatitis, and these are associated with the switching from apoptosis to necrosis and the further recruitment of inflammatory cells, including macrophages. Important transcription factors initiate these inflammatory pathways, including nuclear factor kappa-B (NFκB) and activator protein-1 (AP-1). Activation of NFκB parallels trypsin activation in acute pancreatitis but appears to be independent of it, as it occurs in trypsin knockout mice [17]. These transcription factors are regulated by calcium, calcineurin and protein kinases C and D. Sustained calcium increase, which leads to trypsinogen activation, is critical for NFκB activation since attenuation of cytosolic calcium abrogates NFκB activation [24]. Once activated, NFκB regulates synthesis of multiple cytokines and chemokines, leading to the recruitment of various inflammatory cells that then magnify and propagate systemic inflammation.

9.4.2 Pancreatic Events

Although intra-acinar events initiate acute pancreatitis, events occurring after this stage appear to be most important in determining the ultimate severity of pancreatitis (Fig. 9.1). Inflammatory cells are recruited and activated in the pancreas and release superoxide (the respiratory burst) and proteolytic enzymes (cathepsins, elastase and collagenase) that cause further pancreatic injury. Macrophages also release cytokines (including tumour necrosis factor-alpha (TNF-α) and interleukin (IL-1, IL-2, IL-6 and IL-8)) that mediate the local and the systemic inflammatory response [14]. These inflammatory mediators cause an increased pancreatic vascular permeability, leading to oedema and peripancreatic fluid collections. Microthrombi, vascular injury and hypoperfusion contribute to microcirculatory failure and the development of necrosis. Two forms of acute pancreatitis are distinguished in clinical practice although there is considerable overlap: interstitial oedematous pancreatitis and necrotizing pancreatitis [25]. The latter is diagnosed by contrast-enhanced CT scanning when there are regions of hypoperfusion (patchy or confluent). The diagnosis of the local complications of acute pancreatitis is now done on the basis of morphological criteria from the Revised Atlanta Classification (Table 9.2) [25, 26].

Table 9.2 The local complications of acute pancreatitis, modified from the Revised Atlanta Classification [26]

	Acute (<4 weeks, no defined wall)		Chronic (>4 weeks, defined wall)	
Content	No infection	Infection	No infection	Infection
Fluid	Acute pancreatic fluid collection	Infected APFC	Pseudocyst	Infected pseudocyst
Solid ± fluid	Acute necrotic collection	Infected ANC	Walled-off necrosis	Infected WON

9.4.3 Intestinal Events

In parallel with these, pancreatic events are important events within the intestine events, and together they contribute to the systemic inflammatory response and end-organ dysfunction (Fig. 9.1). The intestine and the pancreas are both vulnerable to ischaemia from reflex splanchnic vasoconstriction that occurs to maintain the perfusion of vital organs. Intestinal ischaemia and any reperfusion injury that results from fluid resuscitation contribute to intestinal injury and the breakdown of the barrier between the gut lumen and the portal circulation. The way in which the intestine influences systemic events has been conceptualized in various ways including the 'translocation' of intestinal bacteria and toxins and the 'second hit' from activated inflammatory cells in the intestinal wall [27]. More recently, the influence of 'toxic lymph' draining the intestine (and the pancreas) has been shown to result in systemic inflammation and end-organ dysfunction (Fig. 9.1) [28].

9.4.4 Systemic Events

Inflammation is triggered from events within the acinar cell, the pancreas and the intestine, as outlined above. And although there appears to be an orderly sequence from initiation to escalation of systemic inflammation, the underlying mechanisms are complex and not fully understood. The inflammatory cascades include considerable redundancy and interaction, which represents a considerable challenge to the development of cytokine-targeted treatments. The contribution of systemic inflammation to the development of organ failure is also not well understood. But what is striking is that the patterns of systemic inflammation and organ failure are very similar for a wide range of acute and critical diseases.

In acute pancreatitis, organ failure can develop at any stage, and it is helpful to distinguish early and late variants, as the underlying mechanisms appear to be different [25]. Early organ failure (within the first 4–7 days) is associated with an overwhelming pro-inflammatory response. Later organ failure is usually associated with infection of pancreatic necrosis. The development of pancreatic necrosis, the breakdown of the intestinal barrier and the suppression of the immune response through the compensatory inflammatory response contribute to the development of infected pancreatic necrosis, the incidence of which peaks in the third to fourth week. And this is usually associated with a secondary systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome/failure (MODS/F).

Organ failure is scored using the Marshall or Sequential Organ Failure Assessment (SOFA) systems [25]. The three organ systems most frequently affected are the cardiovascular, respiratory and renal. Multiple organ failure is defined as two or more organs registering two or more points on these scoring systems [25]. Monitoring organ failure over time and in response to treatment is an important part of management. The responsiveness of the organ failure not only predicts severity and mortality [29]; it is also important in determining the optimal timing of intervention.

9.5 Management

9.5.1 General Considerations

Patients with acute pancreatitis present with a wide spectrum of severity, from a self-limiting mild acute pancreatitis that requires no more than a few days in hospital to critical acute pancreatitis that requires months of intensive hospital care. All patients with suspected acute pancreatitis should be admitted to hospital because the ultimate severity of acute pancreatitis is not readily determined by clinical assessment.

An important management priority is the early identification of high-risk patients and prompt transfer [30]. It is acknowledged that in many places around the world, there is no possibility of transferring a patient to a regional centre that has the expertise and facilities to manage these complex patients. The principles of management that are discussed here are still relevant no matter where the patient is managed. These patients can be admitted under different specialties, from general surgeons and general physicians to specialist gastroenterologists and specialist HBP surgeons. No matter which specialty takes the lead, it is important that there is a coordinated multidisciplinary management plan [31]. The essential requirements for the management of acute pancreatitis are accurate diagnosis, appropriate triage and high-quality supportive care, and monitoring for and treatment of complications [32]. The following important aspects of management are discussed in the order that they tend to arise after a patient with acute pancreatitis has been admitted (Fig. 9.2).

9.5.2 Diagnosis

The diagnosis of acute pancreatitis requires the patient to have abdominal pain consistent with acute pancreatitis (i.e. acute-onset severe constant epigastric pain which often radiates through to the mid back) and the significant elevation of serum amylase or lipase (i.e. >3 times upper limit of normal). The degree of elevation is not related to the severity of acute pancreatitis. Imaging (usually by contrast-enhanced CT scanning) is only required for the diagnosis of acute pancreatitis when these diagnostic criteria are not met [25]. Because there are many causes of hyperamylasaemia, it is important to use either the pancreatic isoenzyme of amylase or lipase [31]. The diagnostic accuracy was recently evaluated in a Cochrane Review, highlighting that 10% of those diagnosed with acute pancreatitis did not have the disease and 25% of those with the diagnosis were not diagnosed [33]. More accurate diagnostic biomarkers are required.

The clinical signs of acute pancreatitis in support of the diagnosis include abdominal tenderness and often peritonism in the upper abdomen. Usually later in the clinical course, retroperitoneal fluid and blood from the pancreas may cause bruise-like discolouration around the umbilicus (Cullen's sign) or in the flanks (Grey Turner's sign). Other rare clinical signs include tetany (from hypocalcaemia) and a cutaneous panniculitis (from lipase).

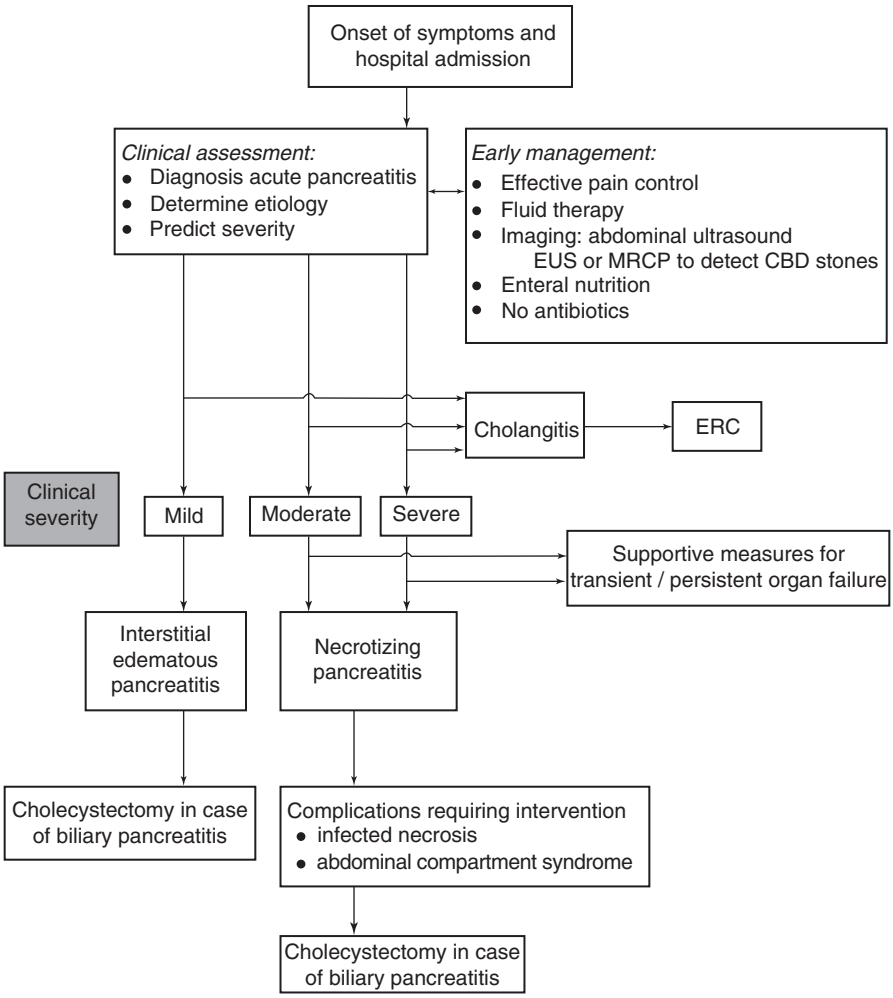

Fig. 9.2 Flow chart of the management of acute pancreatitis (Used with permission)

The diagnosis of acute pancreatitis is also supported by typical changes in routine blood tests, which are related to the severity of acute pancreatitis; these include haemoconcentration (elevated haematocrit), leucocytosis, azotaemia (elevated blood urea nitrogen and creatinine), hyperglycaemia, hypocalcaemia, hypoxaemia and hypoalbuminaemia.

9.5.3 Pain Management

Pain is the cardinal symptom of acute pancreatitis and its relief is a clinical priority [31]. Prompt alleviation of pain will also attenuate the physiological response to

pain and may moderate the immune response. The choice of analgesic is problematic because of a lack of high-quality evidence. It is reasonable to take a similar approach to that taken with post-operative patients. The route of administration should be intravenous because of unpredictable absorption and should continue until oral intake is established. Those with less severe pain can often be managed with a non-steroidal anti-inflammatory drug, while those with more severe pain are best managed with narcotic analgesics. There is no evidence to support on opiate over another [34]. Because of the potential for respiratory depression, it is important to monitor oxygen saturation when intravenous morphine is required. There remains some debate about whether morphine should be avoided because it can induce sphincter of Oddi spasm and risk exacerbation of the severity of acute pancreatitis. In China, acupuncture is often used to avoid the need for narcotic analgesia.

9.5.4 Fluid Resuscitation

Fluid resuscitation to restore and maintain circulating blood volume and vital organ perfusion is the most important intervention in the early management of acute pancreatitis [35]. Despite that, there are critical unanswered questions including which fluid to give, how aggressively to administer it, what resuscitation goal to use and how to best monitor the response [36]. Most recommendations are based on expert opinion [32]. While there are proponents for vigorous fluid therapy (5–10 mL per kilogram per hour), especially in the first 24 h [32, 35] and for specific resuscitation goals [37], it is probably best to resuscitate with a balanced crystalloid and aim to restore normal blood volume, blood pressure and urine output. In one study, lactated Ringer's solution was superior to normal saline in reducing the systemic inflammatory response [38]. Caution needs to be exercised in patients with cardiac and renal disease and in the elderly, where the risks of over-resuscitation are greater. While the focus of fluid resuscitation is on optimizing the delivery of oxygen, glucose and other metabolites to cells in vital organs, it is also important to consider how best to optimize their utilization [39]. This is an area for further research.

9.5.5 Determining Aetiology

The two most important aetiologies are gallstones and alcohol. Gallstones should be investigated for by ultrasonography soon after admission. Gallstones are more likely in patients that are females and over the age of 50 with an elevation of alkaline phosphatase (>300 iu/L), alanine transferase (>100 iu/L) and amylase (>4000 iu/L). The history of alcohol ingestion must be ascertained as reliably as possible, and an elevated admission blood ethanol may help. In the absence of gallstones and alcohol, a systematic approach to the identification of other possible aetiologies should include taking a history of drugs, trauma, ERCP and infection and measuring serum triglycerides and calcium/parathyroid hormone.

9.5.6 Predicting Severity

Prediction and classification are sometimes used interchangeably, and yet they are used for quite different purposes. Where classification relates to the present or past severity of acute pancreatitis, prediction is about the future and ultimate severity. Accurately predicting the severity of acute pancreatitis is important in making triage decisions about whether a patient should be transferred to a regional centre or be admitted to an intensive care unit. It is also important for making decisions about intervention, including fluid resuscitation, endoscopic biliary clearance and the drainage of pancreatic collections [40]. The accuracy of severity prediction should be well over 90% when making important clinical decisions in the care of individual patients. Unfortunately most approaches in clinical use today have an accuracy of around 70–80% [41]. This means that there is misclassification error of 20–30%, and this has significant clinical implications in regard to under- and overtreatment. It also has a major confounding effect on the results of any clinical studies.

There is a large published literature on attempts to find predictive markers that accurately predict severity. The most widely used are the modified Glasgow criteria or Ranson's criteria. Both use clinical and biochemical parameters scored over the first 48 h of admission. When there are three or more positive criteria, it is considered that the disease is 'predicted severe'. There are many other approaches to predicting severity. At 24 h after admission, an APACHE II score of 8 or more or a serum C-reactive protein level of >150 mg/dl has a similar accuracy in predicting severity as Ranson's criteria [41]. The more recently proposed Bedside Index for Severity of Acute Pancreatitis (BISAP) is calculated from blood urea nitrogen (>25 mg/dl), impaired mental status (GCS <15), presence of systemic inflammatory response syndrome, age > 60 years and pleural effusion. Although it has the advantage of relative simplicity and can be performed within the first 24 h of admission, it performed no better than other predictors [42]. The presence of SIRS also has prognostic significance [43] and has been recommended in the IAP/APA international guidelines for severity prediction [31], and yet the evidence for this is not strong. Another approach to severity prediction is to identify those who will have an uncomplicated clinical course and for whom de-escalation of care and early discharge might be appropriate. A 'harmless acute pancreatitis score' [44] has been developed which comprises three criteria that can be determined on admission: absence of rebound tenderness or guarding, normal haematocrit and normal serum creatinine. This is accurate in 94% [45] or 98% [44] of patients with acute pancreatitis.

There is the need for new biomarkers that can provide the accurate prediction of severity for the management of individual patients. In the meantime there are a number of ways to better use existing predictors. These can be combined or sequenced [46], or they can contribute to machine learning algorithms (e.g. artificial neural networks), an approach which has shown considerable promise [47].

The prediction of severity should enhance clinical decision-making and not replace it [32]. It is important to regularly review patients at the bedside, as the response of the patient to initial treatment and trajectory of their clinical course will

also reveal important information about the severity of the patient. The IAP/APA international guidelines recommend a three-dimensional approach to predicting outcome combining host risk factors (e.g. age, co-morbidity, body mass index) and risk stratification (e.g. Glasgow criteria, APACHE II score, SIRS, CRP) and monitoring the response to initial therapy (e.g. blood urea nitrogen, haematocrit, organ failure scores) [2, 31, 32]. While currently untidy, this approach will be refined with further research.

9.5.7 Classification of Severity

Accurately classifying or staging acute pancreatitis severity is important for clinical decision-making, communication and allocation into groups for clinical trials. The original Atlanta Classification included two grades of severity (i.e. mild and severe). This binary approach proved inadequate as those with severe acute pancreatitis encompassed subgroups of patients across a wide spectrum of severity. The key determinants of severity on which a classification should be based are local complications (absent, sterile or infected) and systemic complications (absent, transient organ failure, persistent organ failure) [1, 48]. Three classification systems have been proposed in the last few years: the three grades (mild, moderately severe and severe) of the Revised Atlanta Classification (RAC) [25], four categories (mild, moderate, severity, critical) of the Determinant-Based Classification (DBC) [49] and the four (+1) groups of the Modified Determinant-Based Classification (MDBC) [50] (Table 9.3). The RAC is the most widely cited classification. Multiple retrospective validation studies demonstrate reasonably equivalent performance between the RAC and DBC. The prospective multicentre study from which the MDBC was proposed has demonstrated that the severe category of DBC is made up of two distinct groups (i.e. those with persistent organ failure and not infected pancreatic necrosis and the reverse) in regard to morbidity, mortality and intervention profiles [50]. The value of classifying severity is more apparent in regional centres. The classification of severity is also helpful in tracking the clinical trajectory

Table 9.3 The three classification systems for the severity of acute pancreatitis: Revised Atlanta Classification (RAC), Determinant-Based Classification (DBC) and Modified Determinant-Based Classification (MDBC)

RAC	Mild (*No OF, No LC*)	Moderately severe (*TOF and/or LC*)		Severe (*POF*)	
DBC	Mild (*No OF, No LC*)	Moderate (*TOF and/or SN*)	Severe (*POF or IN*)		Critical (*POF and IN*)
MDBC	Excluded	Group 1 (*TOF and/or SN*)	Group 2 (*IN without POF*)	Group 3 (*POF without IN*)	Group 4 (*POF and IN*)

Note that the DBC has a narrower definition for local complications than RAC, leading to a slightly broader range of mild acute pancreatitis in this Table

OF organ failure, *LC* local complication, *TOF* transient organ failure, *POF* persistent organ failure, *SN* sterile necrosis, *IN* infected necrosis

(monitoring) of an individual patient's course and can be applied on a daily basis. It can also be very useful when reporting cohort and audit studies.

9.5.8 Nutritional Support

In contrast to analgesia and fluid therapy, there is a sound evidence base for nutritional support in acute pancreatitis. It is no longer acceptable to 'rest the pancreas' by avoiding oral or enteral intake. The mainstay of nutritional support [51] in acute pancreatitis is enteral nutrition, and it has been shown to decrease hospital stay and decrease infection rates and mortality [52]. It appears that the early initiation of enteral nutrition (within the first 24 h of admission) is not superior to allowing an oral diet for up to 72 h [53]. If oral diet is not tolerated over 48–72 h, then nasogastric tube feeding can be started and increased in stepwise fashion over 2–3 days [54]. The tube can be advanced to the jejunum, by endoscopy or fluoroscopy, if there is evidence of feeding intolerance. While delayed initiation of enteral nutrition may contribute to the development of intestinal ileus and feeding intolerance, early enteral feeding, particularly before adequate resuscitation, may put the patient at risk of non-occlusive mesenteric ischaemia. There is no evidence to support the use of immune-enhancing or elemental formulas over standard polymeric formulas [55]. In predicted mild acute pancreatitis, the recommencement of oral intake is commonly delayed until the resolution of pain and normalization of enzyme levels, but it now appears safe to allow patients to resume intake ad libitum (i.e. patient-controlled nutrition). Parenteral nutrition is more expensive, is associated with more complications and is not more effective than enteral nutrition. It should only be offered as supplementary nutritional support when the enteral route cannot achieve the patient's calculated nutritional requirements.

9.5.9 Therapeutic Endoscopic Retrograde Cholangiopancreatography

There has been a tendency to perform therapeutic ERCP too frequently. Four randomized trials have demonstrated that early ERCP (within 24 or 48 h of admission) does not decrease mortality in patients with predicted severe gallstone-associated acute pancreatitis. Therapeutic ERCP is not indicated for patients with mild acute pancreatitis and is not indicated in those with severe acute pancreatitis in the absence of cholangitis [56]. There are clear benefits for therapeutic ERCP for the treatment of cholangitis. Abnormal liver function tests or cholestasis should not be an indication for early ERCP as this usually resolves over the first 2–3 days with the passage of the stone. If there is persistent cholestasis, a less invasive MRCP or endoscopic ultrasonography should be done to determine whether there is a common duct stone and can be used as a prerequisite for a therapeutic ERCP [57]. EUS is superior for excluding small stones in the common duct, while MRCP is less invasive, is

operator dependent and is more widely available [31]. Persisting cholestasis without cholangitis may require an ERCP but not usually in the acute setting.

9.5.10 Cross-Sectional Imaging

It may be necessary to perform an early CT scan to diagnose acute pancreatitis in patients who are severely ill (and other diagnoses are entertained), when the admission is delayed (and the enzymes do not reach diagnostic levels) or in those presenting with undifferentiated abdominal pain. There is no advantage over other methods in using the CT scan to predict the severity of acute pancreatitis, with a CT severity index (CTSI) [25, 31]. The primary purpose of cross-sectional imaging is the diagnosis of local complications, in particular the development and extent of pancreatic necrosis and the different types of collections (Table 9.2) [25]. And CT scanning is important to guide the insertion of percutaneous drains in the treatment of local complications (see below). A limitation of CT scanning is that it is poor at determining the presence and extent of solid necrosum within a collection, and for this purpose MR scanning and ultrasonography are superior. A further indication for CT scanning is when a pseudoaneurysm is considered to be a possible cause of bleeding. An arterial phase CT scan (CTa) is performed in this setting, with selective angiography reserved for embolization once the pseudoaneurysm or bleeding has been confirmed.

9.5.11 Antibiotics

Although the use of broad-spectrum antibiotics to treat established infection in acute pancreatitis is a well-established practice, there has been considerable controversy surrounding the use of prophylactic antibiotics [31]. The over-use of antibiotics has been associated with a documented rise in fungal infections and resistant organisms. The most recent trials and meta-analyses do not support the use of prophylactic antibiotics to reduce the frequency of pancreatic infectious complications, surgical intervention and death [58]. Selective gut decontamination, probiotics and continuous regional arterial infusion of antibiotics are also not recommended [31]. It may be appropriate to commence therapeutic antibiotics when there is a high suspicion of infection.

9.5.12 Managing Local Complications

The decision to treat a local complication is one of the most difficult decisions in the management of acute pancreatitis. The timely and accurate diagnosis of local complications requires repeated review of the patient's clinical status and the tracking of their response to intensive care treatment. Clinical monitoring is aided by measuring daily C-reactive protein and, when a local complication is suspected, a

pancreatic protocol CT scan. In practice intervention is delayed to allow the local complication to be walled off in order to reduce the risk of bleeding, disseminated infection and collateral damage to adjacent organs with intervention (Fig. 9.2). It is now recommended that intervention should be delayed for 3–4 weeks from the onset of symptoms.

It is the development of infection, a fluid collection or walled-off necrosis, that necessitates intervention. A deteriorating patient with 'pus under pressure' requires drainage. Fine needle aspiration is now rarely used to confirm infection because the insertion of a needle at the time of planned drainage allows confirmation of the suspected infection. Drainage should be offered by either the endoscopist (transmural gastric drainage) or the interventional radiologist (guided percutaneous drainage). A hybrid approach might also be required, depending on the complexity, site and morphology of the collection(s). Drainage with one or more catheters often produces improvement or stabilization of the patient's overall clinical status [59], and in this way drainage 'buys time'. Recent data suggests that primary percutaneous catheter drainage may be the only intervention required in a third to a half of patients and that this proportion might increase further if there were a policy of regular catheter exchange, upsizing and irrigation [59].

Drainage is often not sufficient for the treatment of the solid component of collections, and subsequent debridement is required in a proportion of patients. There is a wide array of minimally invasive interventions to choose from [58]. These interventions can be classified on the basis of the method of visualization, route taken to the lesion and the purpose of the intervention [60]. In practice the approach taken will depend on local expertise and equipment as well as the location and type of the specific local complication.

A Dutch randomized trial has shown that open surgical debridement should only be considered in those who fail to respond to the step-up approach, which is prior to drainage and minimally invasive intervention [61]. Another randomized trial has compared endoscopic transgastric debridement and the videoscope-assisted retroperitoneal debridement through a flank incision (Fig. 9.3). The data shows that the endoscopic approach is superior, although the latter has a role when the walled-off necrosis is remote from the stomach or duodenum, as in the left flank [62].

The management of an acute noninfected pseudocyst is usually conservative, as more than half of these will resolve spontaneously. Intervention is on the basis of symptoms and/or infection and not on size and/or duration. When pseudocysts do not resolve, it is often because of a communication with the main pancreatic duct and/or distal ductal stenosis. Percutaneous drainage should be avoided in this situation because of the risk of external pancreatic fistula [63]. EUS-guided internal drainage into the stomach or duodenum or transpapillary stenting is the preferred approach.

9.5.13 Managing Organ Failure

The primary cause of death in severe and critical acute pancreatitis is persisting organ failure despite maximal intensive care support. The details of intensive care

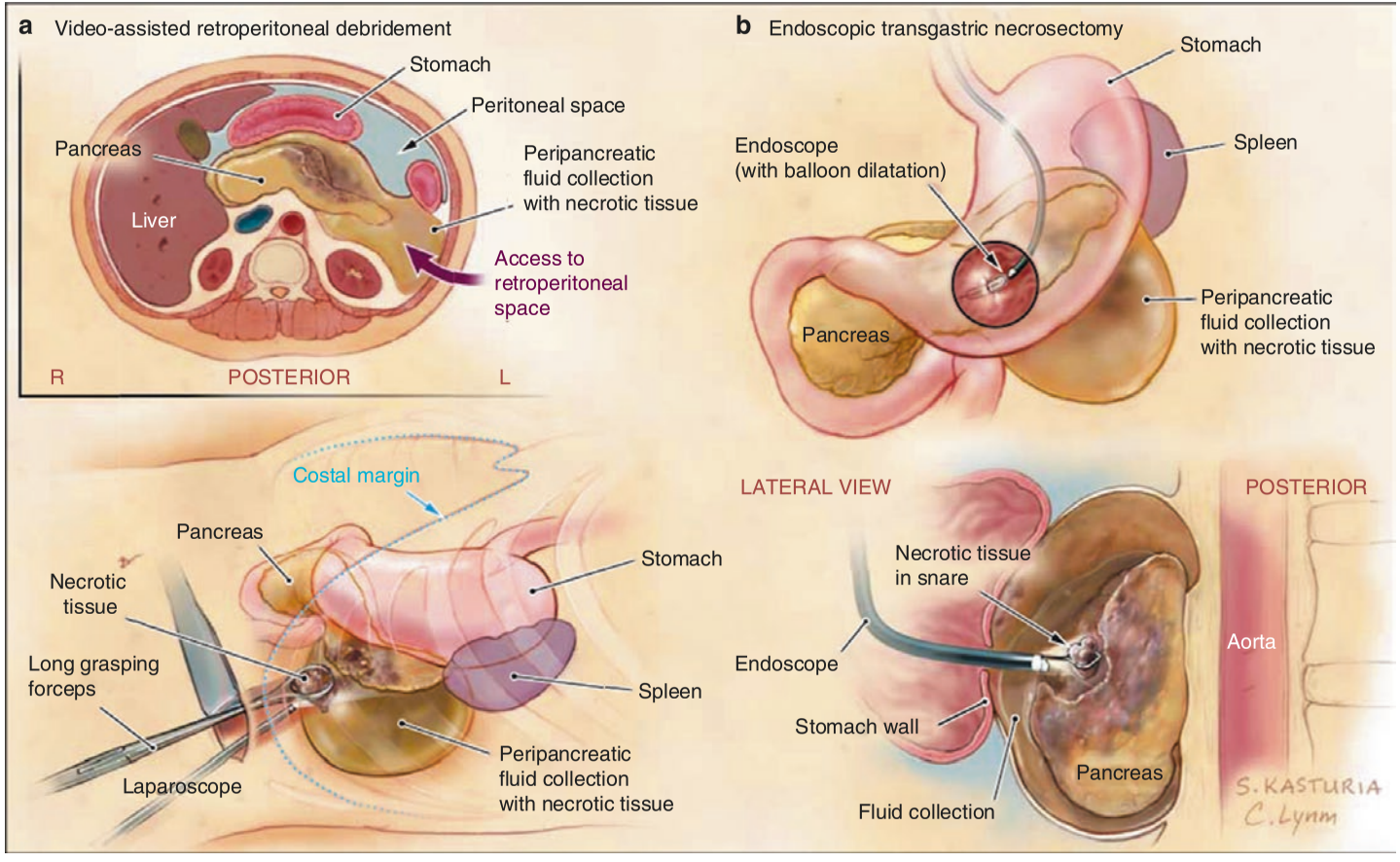

Fig. 9.3 Two minimally invasive approaches to pancreatic necrosectomy: (**a**) video-assisted retroperitoneal debridement and (**b**) endoscopic transgastric necrosectomy [62] (Used with permission)

management are beyond the scope of this chapter. The early identification of organ dysfunction and failure is important because it allows the timely transfer of patients to an intensive care unit to optimize management, provide organ support and allow more intensive monitoring. The severity of organ failure can be scored (Table 9.4). The classifications of severity (above) do not specifically take into account organ failure that occurs early, including at the time of admission. These patients have the highest mortality risk. Response to fluid resuscitation over the first 48 hours is an important prognostic clue. Those that respond have 'transient' organ failure and have a better outlook than those who do not respond and have 'persistent' organ failure [64]. Organ failure that develops later in the disease course is usually secondary to infection of a local complication and should be managed accordingly.

Table 9.4 Sequential Organ Failure Assessment (SOFA) score in acute pancreatitis [66]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3$/L	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (mol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine[a]	Dopamine 5.5–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (mol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/d				<500	<200

Fio_2 fraction of inspired oxygen, *MAP* mean arterial pressure, *Pao_2* partial pressure of oxygen

[a]Adapted from Vincent et al. [27]

[b]Catecholamine doses are given as g/kg/min for at least 1 h

[c]Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function

9.5.14 Cholecystectomy

While it is widely accepted that cholecystectomy is essential to prevent recurrent gallstone-related acute pancreatitis, the debate has been around the timing of it. Index cholecystectomy, done in the same admission and prior to discharge, appears safe and can almost always be accomplished laparoscopically [65]. It has also been shown to be the safest (with a reduction in recurrent pancreatitis, biliary colic and cholangitis) and the cheapest approach (without the need for further hospital admissions). But index cholecystectomy is not suitable for all patients, particularly some who have had local pancreatic complications, which includes a large inflammatory mass that extends into the porta hepatis. These patients may require an interval cholecystectomy after resolution of the inflammatory process. If surgery is required for the management of local complications, then a cholecystectomy is often performed at that time. An endoscopic sphincterotomy has been shown to reduce the risk of recurrent gallstone-related acute pancreatitis in those who are not fit for surgery or when there is an inevitable delay.

Conclusion

In conclusion, the management of acute pancreatitis remains a formidable challenge due to the variety and severity of the many associated complications. There have been many advances in the understanding of the pathophysiology of acute pancreatitis, and improved management strategies have resulted in better outcomes. These include the treatment of pain, fluid resuscitation, antibiotic prophylaxis, enteral nutrition, therapeutic ERCP and cholecystectomy. There have also been significant improvements in the treatment of local complications (e.g. delayed drainage before considering less invasive debridement) and support of systemic complications in the intensive care unit. Further improvements in outcome will result from a better understanding of the mechanisms that drive severity and which provide targets for treatment.

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Chronic Pancreatitis

10

Hariharan Ramesh

10.1 Introduction and Definition

The term "chronic pancreatitis" (CP) implies an irreversible change in the acinar and ductal elements of the pancreas. This is based on the initial descriptions of the disease in the 1990s [1]. More recently an international mechanistic definition has emerged—"a persistent and often progressive fibro-inflammatory disease of the pancreas, most often seen in alcoholics, smokers and genetically predisposed individuals, which presents clinically with recurrent bouts of pancreatitis in its early stages and manifests with pain, ductal calcification, diabetes and steatorrhea in its later stages [2]". However, this definition overlooks the fact that the condition in its preclinical early stages may neither be persistent nor progressive and not necessarily be irreversible. The pathophysiology of the disease is far from clear; many causes exist and each may affect the pancreas in its unique way. Thus chronic pancreatitis may represent a watershed pathomorphologic condition caused by various aetiologies.

10.2 Epidemiology, Aetiology and Pathogenesis

The epidemiology of CP is not completely unravelled. This is due to the fact that early disease is not easy to diagnose, and further the development of CP from acute pancreatitis does not follow a predictable course. In general, the incidence and prevalence of CP have increased [3]. The disease produces a wide range of manifestations from abdominal pain, diabetes mellitus (type 3c insulin dependent [4], but with low alpha cells, with a consequent risk of hypoglycaemia [5]), increased risk for pancreatic cancer [6] and a high mortality of up to 50% within 25 years of

H. Ramesh
Department of Surgical Gastroenterology and Liver Transplantation, VPS Lakeshore Hospital, Cochin, India

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diagnosis [7, 8]. Risk factors for the development of CP include alcohol intake, cigarette smoking, genetic causes and some ductal anomalies. In some cases, a cause is never found.

Alcohol is the leading cause of CP in the Western world. It appears that heavy alcohol use (greater than five drinks per day) for several years is needed to produce CP [7–9] and that less than two drinks per day may even be protective [10]. Also, less than 5% of alcoholics develop CP indicating that a combination of factors may be responsible, such as genetic susceptibility or smoking [11].

Smoking is not only an independent risk factor for CP but can also accelerate its development due to alcohol use. The effect is dose dependent [12], and further smoking also increases the risk of pancreatic cancer [13].

Hereditary pancreatitis must be suspected whenever there is recurrent acute pancreatitis in childhood or when there is recurrent acute pancreatitis or CP in two first-degree relatives or three second-degree relatives [14]. In this condition, a gain-of-function mutation is found in the PRSS1 gene which codes for trypsin [15]. The disease is transmitted as an autosomal dominant trait with variable expression [16].

Ductal obstructions due to strictures and recurrent acute pancreatitis due to pancreas divisum, can also lead to subsequent CP [17].

10.3 Pathogenesis

When acute pancreatitis occurs, pro-inflammatory cytokines are released from the acinar cell; this potentiates an inflammatory cycle which may eventually cause cellular and tissue necrosis. In many cases, resolution occurs, and the pathology does not progress to chronic pancreatitis [18]. Activation of the pancreatic stellate cell (PaSC) is believed to play a part in progression to chronic pancreatitis [19]; in its activated, myofibroblastic state, it not only produces collagen and other proteins to lead to fibrosis but also secretes cytokines such as a tumour growth factor-beta (TGF-β) which in its turn produces cytokines [20, 21], and such activation can be promoted by external factors such as smoking [22]. A diagrammatic representation of the possible pathogenesis is shown in Fig. 10.1.

The pathophysiology of Tropical calcific pancreatitis (TCP) is even more unclear. Most previously held theories such as nutritional and dietary causes (use of the tuber cassava—*Manihot esculenta*) have not been substantiated [23], and the genetic mutations, not dominant. A two-hit hypothesis was suggested by Mahurkar and colleagues where genetically susceptible individuals would produce a super trypsin with recurrent attacks of acute pancreatitis, and these would cause necrosis and fibrosis [24]. The pathophysiology of TCP assumes great importance in the light of epidemiologic data which have shown that CP, regardless of age, sex or aetiology, has a higher risk of developing pancreatic cancer as compared to normal individuals [25]. In patients with TCP, the risk has been reported as fivefold [26].

The two commonest causes of chronic pancreatitis in the Indian subcontinent are alcoholic and tropical. There is considerable controversy about the nomenclature

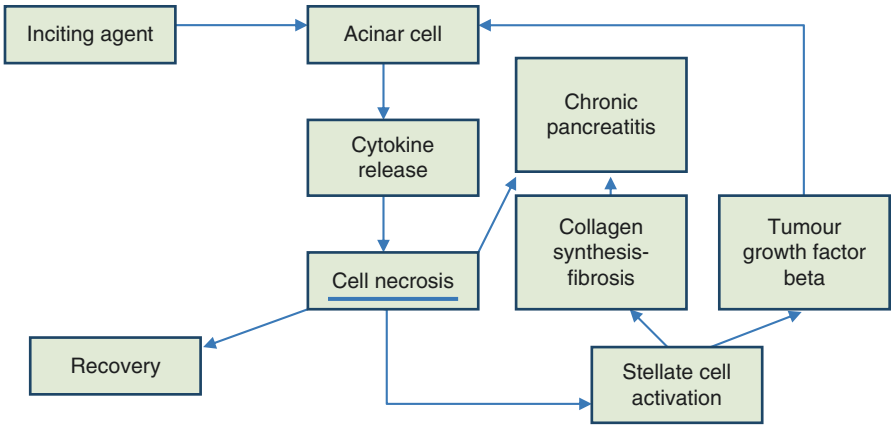

Fig. 10.1 Possible pathophysiology of chronic pancreatitis

with several Indian workers trying to emphasize that "tropical pancreatitis" is a misnomer and that this form of non-alcoholic pancreatitis is better off described as "idiopathic" [27]. However for the present, the syndrome of chronic pancreatitis affecting young, non-alcoholic individuals in India is still referred to as tropical chronic pancreatitis (TCP) [28].

Classic descriptions of TCP came from Geevarghese in Kottayam, Kerala, in the southwest of India as "pain in childhood, diabetes in adolescence, and death in the prime of life". Improved nutrition and better management of diabetes mellitus have however resulted in patients presenting later on in their lives with TCP, even in their sixth or seventh decades but with new sequelae such as pancreatic adenocarcinoma [29, 30].

10.4 Autoimmune Pancreatitis (AIP)

This rare condition, first described over 40 years ago, is being recognized increasingly. Although there may be increase in serum levels of immunoglobulin (IgG4) and infiltration of the pancreas with IgG4-positive plasma cells and involvement of other organs such as the kidneys, bile ducts, salivary glands and retroperitoneum suggesting an autoimmune disease, the aetiopathogenesis is not clearly understood [31]. Despite various criteria (HISORt, Japanese, International Association of Pancreatology), there remain two problems: first, mistaking AIP for cancer and performing an unnecessary resection and, second, mistaking cancer for AIP and not resecting it in time. In order that this error may be minimised, two groups of patients have been described: (a) highly suggestive of AIP (diffusely enlarged pancreas, delayed enhancement and a low attenuation rim) and (b) highly suggestive of cancer (low-density focal mass, pancreatic duct dilatation >4 mm, pancreatic duct cut-off and atrophy of the pancreas upstream from the mass). In addition, high serum IgG4

levels and involvement of other organs would also point towards a diagnosis of AIP. Core biopsy may be needed in around 30% of cases [32]. A 3-week steroid course followed by tapered doses is recommended, but long-term therapy is not standardised, and relapses are common. There are reports of sequelae of AIP which present similar to advanced chronic pancreatitis with ductal dilatation, calculi, pancreatic functional deficiency and even cancer being described [33].

The main causes of chronic pancreatitis are outlined in the list below:

- Alcohol abuse
- Tropical
  - Tropical calcific pancreatitis
- Fibrocalculous pancreatic diabetes
- Idiopathic
  - Early-onset
  - Late-onset
- Metabolic
  - Hypercalcaemia
  - Hypertriglyceridaemia
- Post-necrotic
- Autoimmune
- Genetic
  - Autosomal dominant
    Hereditary pancreatitis
  - Autosomal recessive
    Cystic fibrosis transmembrane regulator (CFTR) gene
    Serine protease inhibitor Kazal type-1 (SPINK1) gene
- Obstructive
  - Benign
    Trauma
    Main duct strictures due to acute pancreatitis
    Pancreatic pseudocyst
    Pancreas divisum
    Sphincter of Oddi dysfunction
  - Malignant
    Periampullary and pancreatic adenocarcinoma
    Intraductal papillary mucinous neoplasm

Does acute pancreatitis progress to CP, or is the aetiopathogenesis of the two conditions separate from each other?

It is clear that not all patients with acute pancreatitis progress to CP. While the Comfort hypothesis suggested that it was the case with alcohol abuse [34], it is well accepted that gallstone disease ordinarily does not lead to CP. This needs further research to determine if CP is the result of prolonged alcohol abuse or whether severe acute pancreatitis is naturally likely to proceed to the chronic state [35]. Current

literature reports that recurrent acute pancreatitis may progress to CP in 4–24% [8, 36, 37]. Factors such as continuing alcohol use and smoking may play a role as well as genetic susceptibility.

10.5 Genetic Mutations in the Causation of CP

Various genetic mutations are associated with the pathogenesis of CP. All of them contribute to increasing the amount of active trypsin within the pancreas. Major mutations include the cationic trypsinogen gene (PRSS1), the serine protease inhibitor Kazal type 1 (SPINK1) gene and the cystic fibrosis transmembrane conductance regulator (CFTR) gene with the commonest being the gain-of-function missense R122H mutation in the PRSS1 gene. In the case of the SPINK1 gene, the mutation deregulates the inhibitory effect that SPINK1 has normally on zymogen activation in the pancreas [38].

Many other genes coding for alpha-1-antitrypsin (AAT), angiotensin-converting enzyme (ACE), aldehyde dehydrogenase 2 (ALDH2), cathepsin B (CTSB), chymotrypsin C, carboxypeptidase A, HSP70-2, monocyte chemoattractant protein-1 (MCP-1) and glutathione transferase have been studied [27, 38–41]. However, genetic testing in CP is still a research tool and does not find routine application in clinical practice.

10.6 Pathophysiology of Pain in CP

Several mechanisms have been suggested, and they have implications for management: (a) the ductal obstruction hypothesis, which leads to ductal [42] and intraparenchymal [43] hypertension: (b) the toxic-metabolic hypothesis, where the acinar cell damage and stellate cell activation initiate inflammation and then fibrosis; and (c) the necrosis-fibrosis hypothesis characterised by necrosis with healing by fibrosis. It is not clear as to why prolonged alcohol use is required to produce CP and why it only occurs in a few drinkers. It is believed that a genetic susceptibility to alcohol-related damage may be present and may result in the sentinel acute pancreatitis event (SAPE) [44]. It has also been hypothesized, but not proven, that neuroimmune alterations may play a contributory role [43, 45, 46]. Thus, it is unclear if the plumbing or the wiring was responsible, or if pancreatic pain resulted from a combination of factors [45, 47, 48].

10.7 Pathology

The pathologic changes vary according to the stage of the disease. In the early stages, there in an inflammatory cell infiltrate comprising lymphocytes, macrophages and plasma cells. Ducts may have eosinophilic plugs, and islets are preserved. Later on, fibrosis sets in, and the protein plugs calcify.

Both these lead to ductal obstruction, and a vicious cycle of stones and strictures sets in. Stellate cells have been identified by the special stains and may be at the centre of the fibrotic process. Cuboidal and squamous metaplasia of the ductal epithelium may follow. Distinguishing chronic pancreatitis from ductal adenocarcinoma on a needle biopsy specimen may also be difficult [49]. In obstructive pancreatitis, the fibrosis is less and confined to upstream ducts and is therefore reversible. In autoimmune pancreatitis, a lymphoplasmacytic infiltrate is present which stains for immunoglobulin G subtype 4 (IgG4) [50]. In some cases a duct-centric pancreatitis is seen with neutrophilic infiltration [51]. Over a period of time, a uniform pathologic picture of fibrosis and calcification is seen.

10.8 Clinical Presentation and Diagnosis

Patients with CP may present to the clinician in one of the following ways:

(a) Incidental findings picked up on imaging or health check
(b) Abdominal pain
(c) Diabetes mellitus or complications
(d) Loss of general health—decrease in body weight and easy fatiguability
(e) Fat intolerance—maldigestion of fat with or without symptoms of steatorrhoea
(f) Symptoms arising from complications (complications of CP and their manifestations are shown in the below list)
    (a) Obstruction to adjacent structures
        1. Bile duct—biliary obstruction
        2. Duodenum—duodenal obstruction
        3. Pancreatic duct—obstructive pancreatitis
        4. Splenic/portal vein—extrahepatic portal vein obstruction—gastrointestinal bleeding
    (b) Disruption of the pancreatic ductal system
        1. Pancreatic pleural effusion
        2. Pancreatic ascites
        3. Pancreatic pseudocysts
    (c) Infection
        1. Abscess
        2. Peripancreatic fluid collections
    (d) Inflammation
        1. Mass-forming chronic pancreatitis
    (e) Malignant change
        1. Pancreatic cancer
        2. Intraductal papillary mucinous neoplasm
    (f) Erosion into adjacent vessels
        1. Pseudoaneurysm

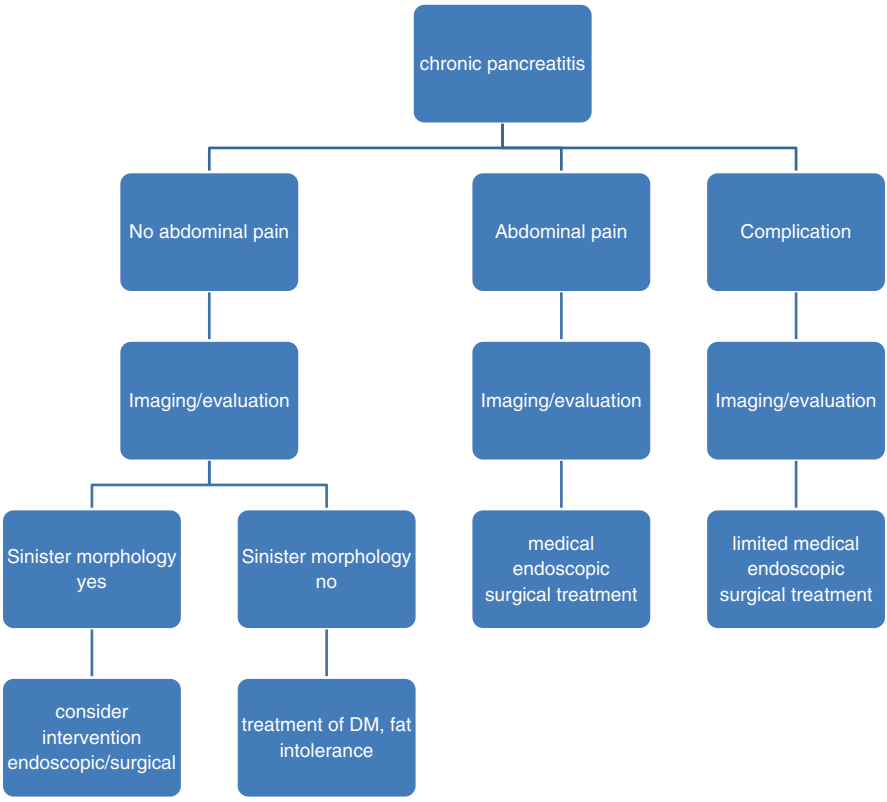

Fig. 10.2 An algorithmic approach to chronic pancreatitis based on symptoms

Weight loss may be multifactorial—uncontrolled diabetes, fat maldigestion, poor oral intake either due to anorexia or fear of abdominal pain or sepsis.

Patients with CP may be asymptomatic, have abdominal pain or suffer complications, and they may or may not have functional deficiency. According to these, they may present primarily to a physician, gastroenterologist, surgeon or endocrinologist (Fig. 10.2).

10.9 Classification of Chronic Pancreatitis and Its Relevance to Management Approach

In 1963, the Marseilles classification was introduced, based on morphology and histology, and was modified in 1984 and 1988; it did differentiate acute from chronic pancreatitis, but further resolution required histopathology which was not available in most cases [52]. The Cambridge system classified the

disease on the basis of severity of changes on endoscopic retrograde cholangiopancreatography (ERCP); however, pancreatic function and symptomatology may have no correlation with the ductal appearance [53]. The TIGAR-O system ((1) toxic-metabolic, (2) idiopathic, (3) genetic, (4) autoimmune, (5) recurrent and severe acute pancreatitis or (6) obstructive) provided an insight into the aetiology of the disease; however, it did not indicate disease severity [54]. The ABC classification [55] is useful in providing critical clinical information about the state of the disease. Thus, patients who have no pain are classified as grade A, those with pain but no complication as grade B and those with complications (pain usually present) as grade C. Each of these grades is subdivided into 0 (no diabetes mellitus or steatorrhoea), 1 (diabetes only), 2 (steatorrhoea only) or 3 (both diabetes and steatorrhoea). It can be gleaned that patients in A1 group are pain-free but diabetic, whereas those in C3 group have both diabetes and steatorrhoea and also a complication. It is simple, clinical-based and also allows the natural history of the disease to be unravelled. A criticism of this staging system is that neither this nor the Manchester system (2006) [56] allowed a clear distinction of grades. The severity of pain was not indicated by this staging. Two staging systems have been recently introduced by the Mannheim [57] and the Heidelberg groups [58]. European researchers have regarded chronic pancreatitis as a progressive disease with pancreatic insufficiency as the final stage of the disease. While Ammann postulated on the basis of his patient data that "burnout" is the inevitable consequence in all patients with chronic pancreatitis [7], there is no consensus on this [59]. In non-alcoholic pancreatitis, there is evidence to suggest that patients may actually develop serious life-threatening complications after a long asymptomatic period [30]. There also appears to be a disconnect between patient symptomatology and complications on the one hand and functional deficiency on the other. Often clinicians encounter two consecutive patients with complications, where one of them has no functional deficiency whatsoever, while the other has severe functional deficiency [60, 61]. This phenomenon underlines the value of the ABC system which takes into account patient symptomatology and functional deficiency. As the natural history is as yet unclear, this also offers a good opportunity to determine the course of symptoms and functional status and also the impact of therapy on modifying the natural history. A summary of the published staging systems is shown in Table 10.1.

Table 10.1 Classification systems for chronic pancreatitis and their strengths and weaknesses

Name	Year	Salient features	Limitations
Comfort	1946	Initial descriptions of the disease	Not comprehensive
Marseilles	1963	Acute, relapsing acute, chronic, relapsing chronic	Required histology to confirm
Marseilles	1984	Chronic calcifying pancreatitis, chronic obstructive pancreatitis	Histology required
Cambridge	1984	ERCP-based severity classification	Not relevant as clinical features do not mirror morphological changes
Marseilles-Rome	1988	Added chronic inflammatory pancreatitis	Histology required
Mannheim	1994	A detailed aetiological and functional classification	Difficult to apply clinically
Zurich	1994	Differentiation between definite and probable CP	Only confined to alcoholic pancreatitis
Japan Pancreas Society	1994	A detailed system based on clinical, imaging and histological findings	Histology required
TIGAR-O	2001	A detailed aetiological system, toxic–infective–genetic	Clinical relevance questionable
ABC	2002	A simple clinical classification which is easy to adopt: grade A, no pain; grade B, pain but no complication; grade C, complication. Allows study of natural history of the disease	Does not cover all groups of patients; limited separation of clinical entities
Manchester	2006	A simple clinical system: grade A, mild; grade B, moderate; grade C, severe	Does not cover all groups of patients; limited separation of clinical entities
Mannheim	2007	A complex staging system: M, multiple; A, alcohol; N, nicotine; N, nutritional; H, hereditary; E, efferent duct; I, immunological; M, miscellaneous	Complex and difficult, does not address severity; based on this, further clinical staging needs to be done
Heidelberg ABC	2009	Grade A, pain but no functional loss; grade B, pain with complication, but without functional loss; grade C, functional loss with or without complication	Attempt to use the Child–Pugh staging for liver disease as an analogy; however, functional loss does not necessarily mean more severe disease

ERCP endoscopic retrograde cholangiopancreatography, *CP* chronic pancreatitis

10.10 Investigations

These may be grouped into three types, (1) those which image the gland morphology to help guide treatment, (2) those which assess exocrine pancreatic function and (3) those for research purposes only.

10.10.1 Morphological Imaging

Imaging is best performed by computed tomography (CT) scan or magnetic resonance imaging (MRI). Ultrasound examination can be used as a preliminary screening test. Endoscopic ultrasound (EUS) is used in patients with obscure masses, where cross-sectional imaging does not resolve the diagnosis. However, EUS is highly sensitive and runs the risk of revealing minor abnormalities which may have no therapeutic implications. Use of EUS for diagnosis of chronic pancreatitis may be unreliable despite a restrictive Rosemont classification [62]. Features suggestive of chronic pancreatitis may be present in other diseases, and the clinical implications are as yet unclear [63]. In mass lesions, specificity of EUS is poor unless biopsy is added. EUS elastography may have a more definitive role, but its efficacy needs further data [64]. Diagnostic ERCP is no longer done. An abdominal flat plate is a useful radiograph which can be displayed in the operating room/endoscopy suite to guide the therapeutic procedure.

10.10.2 Pancreatic Function Testing

Exocrine pancreatic function is best evaluated by the coefficient of fat absorption (CFA), based on an estimation of faecal fat excretion which is a laborious process and is seldom done. Faecal elastase is a reasonable surrogate marker which may be superior to acid steatocrit [65]. C-peptide levels and glucose tolerance tests are used to assess beta cell function.

10.10.3 Research Investigations

This group includes pancreatic function tests such as the bentiromide test, N-benzoyl-tyrosyl para-aminobenzoic acid (NBT-PABA) test and tests for genetic mutations.

10.11 Investigating a Mass Lesion Associated with CP

A major area of diagnostic difficulty is the presence of mass lesions in CP. Cross-sectional imaging including EUS may help as well as the duct penetrating sign on MRCP [66] in distinguishing a benign inflammatory mass from superimposed/

associated cancer. Fine needle cytology is often required but may be inconclusive due to the low cellular yield from within a fibrotic gland. More than one biopsy may be required in suspicious cases, for a preoperative diagnosis of malignancy allows a direct radical surgical approach, rather than an operating table dilemma with multiple frozen section histopathology, which may also be inconclusive. In such cases, the final approach may rely entirely on clinical judgement.

10.12 Clinical and Laboratory Assessments at the Time of Presentation

(a) Assessment of pain: An objective assessment of pain severity is desirable as patients may exhibit wide subjective variations. The visual analogue scale (VAS) and the Izbicki pain score are two well-known mechanisms for assessment. The author's group uses a modified pain score where the severity of pain is graded according to whether there is interference with normal life and whether the pain is relieved by medications (categories of pain in chronic pancreatitis [80] are shown in the below list) [67].
   1. No pain
   2. Pain present, but relieved by medication and not interfering with normal lifestyle
   3. Pain present, relieved by medication, but interfering with normal lifestyle
   4. Unrelieved pain

(b) Exocrine deficiency: The faecal elastase test is preferred. Values below 200 indicate pancreatic exocrine insufficiency (PEI) and below 100, severe PEI.

(c) Blood glucose monitoring, glycosylated haemoglobin and oral glucose tolerance tests are performed routinely, as well as a baseline and periodic surveillance for complications of diabetes mellitus. C-peptide levels (fasting and stimulated) help to establish the degree of beta cell function in these patients.

10.13 Treatment Approach to CP Based on the ABC System

10.13.1 Management of Type A Patients

Patients with CP who do not have abdominal pain should be evaluated by cross-sectional imaging and for the presence or absence of exocrine or endocrine deficiency. If such deficiency is present, then appropriate medical measures are required. If there are morphologic changes that suggest cyst/mass/obstruction to adjacent structures, then a careful assessment should be made of the risks and benefits of intervention versus medical treatment.

Is intervention among patients with type A disease appropriate?

Currently the indications for intervention by endoscopy or surgery are intractable pain, complications or suspected or proven malignancy. However, there is a trend

towards early intervention in CP during the pain-free phase. This is based on the following findings:

(a) The potential for preservation of pancreatic function with earlier intervention. Bali quantified pancreatic exocrine function in normal subjects and in patients with chronic pancreatitis (CP) before and after pancreatic duct drainage procedures (PDDP) with dynamic secretin-enhanced magnetic resonance cholangiopancreatography (S-MRCP). There was a significant increase in pancreatic flow output and total excreted volume of pancreatic juice [68]. Sidhu demonstrated improvement in diabetes mellitus following surgical drainage [69]. Nealon published in 1988 and in 1994 regarding the preservation of pancreatic function in patients who had undergone surgical drainage as compared with those managed medically [70, 71]. In another series, 18% of patients who underwent pancreatic duct drainage had improvement in pancreatic endocrine function [67]. Earlier intervention may have a better prospect of good long-term outcomes with more sustained pain relief, lower rates of functional deficiency and lower intervention rates [72, 73]. A large multicentre randomized trial (the ESCAPE trial (Early Surgery Versus Optimal Current Step-Up Practice for Chronic Pancreatitis trial; ISRCTN45877994)) may provide the ultimate answer [74].
(b) Can drainage procedures diminish the risk of pancreatic cancer? Our data (unpublished) showed that while 1 out of 8 patients presenting with intractable pain had histological evidence of carcinoma, only 6 out of the first 900 patients followed up for a median of 15 years developed cancer (when in fact over 100 patients should have developed cancer). All these six patients had extensive residual calculi. In 2013, the Japanese Pancreatic Society published the results of a nationwide survey involving 22 centres, which showed that the development of cancer was lower among operated patients as compared with those who were treated medically. Among the medically treated, patients who continued to smoke had a higher incidence of developing cancer [75].

10.13.2 Management of Type B Patients

A thorough clinical assessment of the symptoms and their characteristics and severity is mandatory. It is imperative to determine if the symptoms impact on the quality of life (QOL). A systematic assessment of QOL should be made at the index presentation so that further changes can be documented. An SF-36 or the EORTC-QLQ30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) with a PAN-26/28 supplementary form is preferable [76]. Imaging and functional assessment would be necessary as in type A patients, as patients with morphologic abnormalities may require intervention.

10.13.3 Management of Type C Patients

Because of the presence of complications, a more expedient approach may be required. Therefore intervention should be planned and executed according to the complication.

10.13.3.1 Medical Treatment

Goals of medical treatment for CP include pain relief, pancreatic enzyme replacement, nutritional support and control of diabetes. As the disease is progressive and incurable, and treatment primarily directed to symptom control and managing complication, counselling is essential at every step of management. A relatively newer concept of minimising functional loss has resulted in a more proactive approach to intervention in some cases.

10.14 Pain Relief

Approximately 85% of patients with CP suffer from abdominal pain, which is the most compelling reason to seek medical attention. Pain in CP results from several independent and concurrently occurring mechanisms (mechanisms of pain in chronic pancreatitis are shown in the list given below). It is difficult to know the contribution of individual factors in the causation of pain. Therefore a holistic approach with periodic patient counselling is desirable. It is also necessary to concurrently evaluate the morphology of the gland, as it would be inappropriate to treat patients with obvious inflammatory masses, pseudocysts or ductal obstructions with medications alone. Many patients with chronic pancreatitis may ingest alcohol regularly or smoke or exhibit narcotic dependence. Although this may represent a poor risk group, care must be taken to also address the cause of pancreatic pain if identifiable, and abstinence must not be made a prerequisite for intervention.

A. Intraductal hypertension
   - Calculi
   - Strictures

B. Parenchymal/interstitial causes
   a. Tissue hypertension and ischaemia
   b. Oxidative stress
   c. Chronic inflammation

C. Neuropathic mechanisms
   a. Nociception
   b. Pancreatic neuropathy and neuroplasticity

i. Temporal summation
ii. Inflammatory hyperalgesia
iii. Mechanical allodynia
c. Central neuropathy and neuroplasticity
D. Local (peri)pancreatic complications
a. Inflammatory pancreatic head mass
b. Pseudocysts
c. Pancreatic cancer
E. Extrapancreatic complications (significant pain may often not be present)
a. Duodenal obstruction
b. Biliary obstruction
F. Treatment-related
a. Opiate-induced gastroparesis
b. Constipation

Analgesics may be used as a monotherapy or combinations. It is desirable not to include narcotic drugs at the outset if feasible. Many physicians decry the use of narcotics altogether. Tramadol, despite its low potency, is preferred, although fentanyl patch may be required to relieve severe pain [77]. Addition of pregabalin may help reduce the intensity of pain, as also tricyclic antidepressants and selective serotonin reuptake inhibitors [78–80]. A step-up approach as advised by the WHO is recommended, although a rapid assessment of gross morphologic abnormalities is desirable. Prolonged medical therapy in the presence of a large pseudocyst is unlikely to be rewarding.

10.15 Antioxidants/Micronutrients

Oxidative stress has been proposed as an important mechanism of CP. Over the past decade, nine trials have evaluated the role of antioxidants/micronutrients in the management of pain in CP. Of these, a recent trial from India that used a daily cocktail of organic selenium (600 μg), ascorbic acid (0.54 g), β-carotene (6000 IU), α-tocopherol (270 IU) and methionine (2 g) for 6 months led to significant reduction in the number of painful days and use of analgesics. It was also found that markers of oxidative/electrophilic stress such as Thiobarbituric acid reactive substances (TBARS)—a test of products of oxidative stress—decreased, thereby linking oxidative stress with pain. There was significant pain relief in 46% of patients even at the end of 1 year [81]. However, these results were negated by another recent randomized trial from Manchester which concluded that even though micronutrients increased the antioxidant levels in blood, they did not produce adequate pain relief. Two reviews including a Cochrane review suggested that there may be some benefit of antioxidants in reducing pain in CP, although the evidence is not conclusive [82, 83].

When we consider that the development of pain in CP may be multifactorial and may be due to an underlying pathomorphologic abnormality such as mass, pseudocyst, etc., it is probably inappropriate to treat patients on medical therapy alone.

10.16 Pancreatic Enzymes

A recent systematic review of ten randomized controlled trials between 1986 and 2006 with over 350 patients showed that pain reduction in patients taking pancreatic enzymes showed no benefit of pancreatic enzymes in relieving pain [84]. Patients who have fat maldigestion and steatorrhoea experience abdominal discomfort and even pain. These symptoms can be controlled by the use of pancreatic enzymes.

When pain is not relieved by medical measures, some form of intervention—endoscopic or surgical—is warranted. Further management is tailored to the morphology of the ductal system and the gland, and patients may be categorized into three groups:

- Large duct disease where the main pancreatic duct (MPD) is >5 mm in diameter
- Small duct disease where the main pancreatic duct is ≤5 mm in diameter
- Mass lesions

Patients with large duct disease are amenable to endotherapy, whereas those with small duct disease are not. Mass lesions require special attention—distinguishing an inflammatory mass from a malignant one may be difficult.

10.17 Nutritional Support

Malnutrition in CP is often a consequence of exocrine and endocrine insufficiency, changes in gut motility and function, pain and anorexia. Other factors may also operate such as acidic pH of duodenal luminal contents, gut dysmotility and bacterial overgrowth. Dietary counselling is mandatory, and vitamin supplements must be provided. A recent, randomized controlled trial from India showed that good dietary counselling on home-made food was as good as commercially available dietary supplements [85].

A small proportion of patients with CP who have severe acute exacerbation might require nasojejunal (NJ) or nasogastric feeding. Presence of complications such as pancreatic fistulas or duct disruptions along with pancreatic ascites and pleural effusion might also necessitate distal (NJ) tube feeding, occasionally substituted or supplemented by parenteral nutrition [86]. Long-term alternatives of NJ feeding such as percutaneous endoscopic gastrostomy with jejunal extension or direct percutaneous endoscopic jejunostomy are seldom required.

10.18 Treatment of Pancreatic Exocrine Insufficiency (PEI)

The pancreas has a robust secretory capacity for digestive enzymes and pancreatic exocrine insufficiency (PEI) manifests only when the postprandial exocrine secretory output falls to <10% of normal in the duodenum [87]. The usual manifestations

are fat malabsorption. Frank steatorrhoea may not occur if the fat intake is low. Faecal fat excretion >15 g/day may be present. The coefficient of fat excretion (diet fat minus stool fat/diet fat expressed as a percentage) remains the gold standard although faecal elastase or the C13 hydrogen breath test is a valuable substitute [88].

Although pancreatic enzyme supplements contain lipase, protease and amylase, lipase is the most important as it is vulnerable to acid destruction. It has been estimated that about 20,000 units of lipase may be required along with each meal to prevent steatorrhoea. Pancreatic exocrine replacement therapy (PERT) not only helps restore fat absorption and prevent steatorrhoea but also absorption of fat-soluble vitamins. Two recent trials highlighted the therapeutic benefits of PERT in patients with PEI [85, 89, 90]. In general, a patient-controlled dosing, which is somewhat empirical and has the advantages of taking into account the patient's symptoms such as bloating and steatorrhoea [91], is preferred over standard dosing. On the other hand, it has the disadvantage in that it runs the risks of exposing the patient to subtler forms of malnutrition. In countries where pancreatic enzyme replacement therapy (PERT) is not supported by medical insurance, this is a significant problem.

10.19 Endoscopic Treatment

Endoscopic treatment is indicated in the following situations:

1. Dilated ductal system with:
   (a) One or few strictures confined to the head
   (b) Predominantly head calculi
   (c) Ampullary stricture with dilated duct
   (d) Ductal disruptions producing pancreatic pseudocysts, pleural effusions or ascites
   (e) As a temporizing measure in patients with biliary obstruction especially in the setting of cholangitis

However, enthusiastic endoscopic approaches and patient reluctance for surgical therapy have combined to extend the boundaries of endotherapy with the result that many patients undergo endotherapy as a preliminary therapy regardless of the morphology of the ductal system. The European Society of Gastrointestinal Endoscopy has recommended endotherapy with extracorporeal shock wave lithotripsy as the first choice treatment for patients with uncomplicated chronic pancreatitis with surgery to be considered if pain persists at 6 weeks [92].

10.19.1 Endotherapy Techniques

Pancreatic Calculi Initial approaches included sphincterotomy with stone extraction using balloons or baskets, followed by placement of plastic stents. Extracorporeal

shock wave lithotripsy was used to fragment stones greater than 5 mm which cannot be removed by conventional ERCP [93]. Bi-dimensional fluoroscopy and ultrasound are used for stone localisation, and the procedure can be performed under general or epidural anaesthesia. ERCP and stent placement is not mandatory in all cases, and it is generally preferred in radiolucent stones. Success rates vary between 40 and 95%, and pain relief rates between 50 and 95% [93–104]. Contraindications include (a) stones all along the main pancreatic duct, (b) isolated tail stones, (c) multiple strictures of the main pancreatic duct, (d) presence of moderate to severe ascites, (e) pseudocysts and (f) presence of a pancreatic mass lesion [105]. ESWL is generally safe (complication rate of 12.5%, which is usually minor such as skin petechiae) [105]. Occasionally acute pancreatitis or organ damage can occur. If expertise is available, pancreatoscopy with direct lithotripsy can also be done. If stones or strictures are extensive, it is preferable to advise surgical treatment. A recent study also showed that if the main duct diameter was greater than 8 mm and the stone size greater than 12 mm, then the results were generally likely to be unfavourable, and hence surgery may be preferable [106].

10.20 Strictures

ERCP stenting is eminently suitable for a solitary stricture in the head. With more upstream strictures, there are technical issues. Plastic stents are used. In patients with isolated strictures, especially in the absence of calculi, carcinoma has to be ruled out by EUS before stenting is done. Over follow-up periods of up to 6 years, stricture resolution rates of 60% can be expected [107–115]. Endoscopic brush cytology may be helpful to rule out cancer. Stents may get clogged and may require exchange usually on an on-demand basis. In some cases, multiple stents, or the fully expandable covered stents (Bumpy stent), have been used [116–118]. Overall, long-term benefits of standard endotherapy for pancreatic ductal stricture remain unsatisfactory because even after a mean of 4.6 ERCPs per patient for stent exchanges, the stricture relapse rate after 2 years remains at 38% [119]. Ahmed et al. reported better results when fewer than five endoscopic interventions were performed [120].

10.21 Pancreatic Ductal Disruption and Pseudocysts

ERCP stenting is an excellent method of interim management of pancreatic ductal disruption with or without pseudocysts. Trans-papillary stenting may suffice for ductal disruptions, although some cases may also necessitate the use of trans-enteric drainage (usually trans-gastric or trans-duodenal) for larger pseudocysts. Long-term outcomes will depend upon the symptoms of the patient which in turn may depend upon the extent of the main pancreatic duct involvement. In patients with extensive strictures and stones, it may be advisable to offer surgery with endoscopic therapy providing only interim relief. Complications include infection (commonest), bleeding and perforation/leakage, which may require surgical rescue [121].

10.22 Biliary Stricture

A benign biliary stricture is seen in 3–46% of patients with CP and is mostly secondary to pancreatic fibrosis, with a small proportion resulting from pancreatic oedema and compression by a pseudocyst [122]. It is important to rule out malignancy in the former by brush cytology or direct biopsy. Even though the initial clinical success rate of biliary stent placement is impressive, stricture resolution is maintained in a mean of only 32% patients by the end of 1 year, mandating surgery in the remaining for long-term benefit [122]. Use of multiple plastic stents has been associated with stricture resolution in 44–90% of cases at a follow-up of 48 months. Self-expanding metallic stents (SEMS) can be an alternative option for patients with refractory strictures who are not ideal candidates for biliary drainage surgery. Occlusion rates of biliary SEMS have been reported to be 10–62% in patients with CP [123].

10.23 Role of EUS in the Treatment of CP

10.23.1 EUS-Guided Pseudocyst Drainage

EUS is useful in the drainage of non-bulging pseudocysts. In contrast to endoscopic transmural drainage where the maximum thickness between the gut lumen and pseudocyst has to be <1 cm, EUS-guided drainage can be performed using a linear-array echo-endoscope for pseudocysts located further away from the lumen. EUS can help in mapping out an avascular area for puncture in patients with extensive collaterals secondary to portal hypertension [124]. EUS can also identify characteristics of cystic neoplasms and avoid their being mistaken for pseudocysts.

10.23.2 EUS-Guided Rendezvous Technique

This technique is useful when conventional ERCP fails. A guide wire is inserted into the pancreatic duct by EUS-guided transgastric puncture in an antegrade direction and introduced into the duodenum through the papilla. The guide wire is then grasped with the duodenoscope, and ERCP is performed. Though the success rate is good, the procedure requires expertise and is associated with a 5–15% rate of complications such as bleeding, haematoma formation, perforation and severe pancreatitis [125–129].

10.23.3 EUS-Guided Coeliac Plexus Block

Coeliac plexus block with a local anaesthetic (bupivacaine) with or without a combination of steroid (triamcinolone) may be administered in selected cases. Although effective and having a negligible risk of developing paraplegia, which is associated with the percutaneous technique, the overall benefit is poor (55% after 4–8 weeks

and a dismal 26 and 10% after 12 and 24 weeks, respectively). It is preferable in patients with cancer in chronic pancreatitis where life expectancy is poor. Side effects of a coeliac block are seen in 10–33% of patients. The most common side effects include transient self-limiting diarrhoea and orthostatic hypotension, owing to the sympathetic blockade with relatively unopposed visceral parasympathetic activity. Diarrhoea usually settles in 48 hours. The patient may complain of an occasional increase in the pain. Serious complications such as retroperitoneal bleeding and peripancreatic abscess have infrequently been reported. An additional problem with the use of alcohol is the development of dense desmoplasia, which might make future pancreatic surgery difficult [130–133].

Endoscopic therapy may also be required in patients with associated portal hypertension, where obliteration of oesophageal and gastric varices is performed by endoscopic variceal ligation and cyanoacrylate injection, respectively.

10.23.4 Comparative Trials: Endoscopy Versus Surgery

Dite et al. randomized 72 patients to endoscopic stenting versus surgery (36 each). Complete or partial pain relief was present in 85% of surgical patients versus 61% of endoscoped patients although 80% of surgical patients underwent resections and endotherapy did not include ESWL [134]. The second study comprised 19 patients who underwent endotherapy with ESWL and 20 patients who underwent surgical drainage. Pain relief was significantly better in the surgery group (75% vs. 32%) at 24 months [135]. Over a long-term follow-up of 79 months, 80% of patients remained pain free in the surgical group versus 38% in the endoscopy group [136]. Interestingly, this study highlighted the current problem with endotherapy—the lack of standardized technique such as the diameter, length and use of side holes in the stent and the duration of stenting. Future trials which hope to resolve this issue must use standard tools to assess pain, have a control arm and also standardize treatment protocols. These may be difficult to achieve, and for the present, the best approach is to clearly define the clear-cut indications for endotherapy and surgery and examine the remainder through controlled trials [137].

10.24 Surgical Treatment

> Alleviation of pain, nausea and emesis, as well as the prevention of pancreatic atrophy….—Moynihan 1900

10.24.1 History and Evolution

Moynihan removed stones from the pancreatic duct to relieve pain as well as to prevent atrophy in the beginning of the twentieth century. The earliest recorded operation for CP was probably by Sir Alfred Pearce Gould of London who

extracted a stone from the pancreatic duct in 1896, but the patient died. In March 1910, Goethe Link of Indianapolis extracted a pancreatic stone and created a tube pancreaticostomy with a good long-term outcome. He avoided enteric drainage for fear of creating scarring of the duct! Although Cattell performed pancreaticojejunostomy for cancer in the 1940s, it was William Longmire (1951) and later Merlin DuVal (1954) who performed distal pancreatectomy plus caudal pancreaticojejunostomy. In 1958, Charles Puestow and William Gillesby of Chicago added an extended longitudinal opening and dunked the mobilized pancreatic body and tail into a Roux-en-Y loop of the jejunum. In 1960, Philip Partington and Robert Rochelle of Cleveland, Ohio, simplified the procedure by eliminating the caudal pancreatectomy and splenectomy and performed a side-to-side pancreaticojejunostomy. In the 1960s, a concept emerged that if the pancreas were removed, the pain would subside, which led to an introduction of subtotal and total pancreatectomy by Cattell and Warren. Over the next two decades, it became clear that adequate head drainage was necessary, and three procedures were used—the Whipple procedure (a preferred operation in most of North America), the Frey procedure (head coring with lateral drainage) in 1987 from California and the Beger procedure (subtotal resection of the head without lateral drainage) in 1980 from Ulm in Germany. The Whipple procedure was introduced by Longmire, and he referred to the pancreatic head as the "pacemaker" of the gland. Gall from Erlangen in Germany also supported head resection. Nerve interruption procedures had been in vogue since 1945 (Mallet Guy) with mixed success and poor reproducibility. In the last decade of the twentieth century, the operation was performed by thoracoscopy with limited success. Islet cell transplantation for pancreatitis after total pancreatectomy was first introduced in 1977, and the first patient remained insulin-independent for 6 years [138].

An ideal procedure for CP should:

(a) Relieve symptoms
(b) Deal with the entire gland (CP is a progressive disease with the potential to progress after surgical intervention)
(c) Have low morbidity and mortality
(d) Preserve pancreatic function
(e) Improve/preserve quality of life

The indications for surgery are:

1. Intractable pain
2. Complications
   (a) Pancreatic strictures not amenable to endotherapy
   (b) Pseudocysts and abscesses not amenable to endotherapy
   (c) Mass lesions, inflammatory or suspicious for cancer
   (d) Proven superimposed cancer
   (e) Biliary obstruction
   (f) Duodenal obstruction

(g) Ductal disconnection
(h) Pseudoaneurysms not embolised by angiography

10.24.2 Procedures in Current Use

1. Drainage procedures
2. Resection procedures
3. Hybrid procedures
4. Nerve interruption procedures
5. Total pancreatectomy with islet cell transplantation (TP-IAT)

10.24.2.1 Drainage Procedure

The Partington–Rochelle modification of the Puestow–Gillesby procedure is used in patients with dilated ducts without inflammatory mass in the head of the pancreas. Although early results were good in 61–91% of patients [139], pain recurred in over 30% of cases due to various factors such as closure of the anastomosis, pain originating in the undrained segments of the head of the pancreas or the development of other sources of pain (neural inflammation, central nervous system sensitization, duodenal or bile duct obstruction) [140]. This operation can be performed laparoscopically [141], and morbidity and mortality are very low.

10.24.2.2 Resection Procedures

The classical or pylorus-preserving pancreaticoduodenectomy (PD) helps to remove the head of the pancreas which is regarded as the pacemaker of the pancreatic gland. This is indicated where a cancer of the head is proven or suspected and in patients with extensive head disease with multiple pseudocysts of the head and biliary and duodenal obstruction. In the latter instance, only PD could encompass the disease. PD may also be required where a pseudoaneurysm of the pancreatic head is present, and angioembolisation has failed. Early results are excellent (80%), but late results diminish to 50–60% [142–146]. While early functional results may be poor [147], results become comparable with hybrid procedures over a period of time [148]. In another large series, however, overall survival and quality of life were better with the Frey procedure [149]. Total pancreatectomy is not a first-line procedure and is limited to failure of previous resection or severe pain with complete functional deficiency. The indications of total pancreatectomy may include patients who have associated carcinoma or intraductal papillary mucinous tumour. Although this operation was frequently performed in the 1970s, it is rarely performed today except as a part of islet auto transplantation [150–152].

10.24.2.3 Hybrid Procedures

There are four hybrid procedures:

1. Beger procedure: This is a popular operation in parts of Northwestern Europe. It consists of a subtotal resection of the head of the pancreas followed by drainage of the neck of the pancreas and the remnant of the head into a Roux-en-Y loop

of the jejunum. About 50% of patients required decompression of the bile duct and 10–15% required longitudinal drainage of the body and tail ducts. The results over long-term follow-up were excellent (80%), and new diabetes occurred in 8–21% of patients [153].

2. Frey procedure: This procedure is currently widely regarded the surgical procedure of choice for painful CP and is distinct from the Beger procedure in the following steps: (1) the posterior capsule of the pancreas is preserved during head coring, (2) the neck of the pancreas is not divided and (3) lateral drainage of the pancreatic duct in the body and tail of the pancreas is carried out [154]. Many series have shown good results [155–161]. Negi et al. identified preoperative opiate use, continuous pattern of pain and postoperative complications as adverse factors [162]. Amudhan et al. identified narrow ducts and small volume coring as risk factors for poor outcomes [163]. Out of 541 patients in our series with the Frey procedure, 88% had pain relief at 1 year and 93% at 5 years after reintervention. The only factor correlating with poor outcome on multivariate analysis was residual calculi [164]. In general, the data indicate that the thoroughness of head coring during the first operation is critical to good, long-term outcomes.
3. Hamburg procedure: An excavation of the head of the pancreas, along with V-shaped excision of the body of the pancreas [165].
4. Berne procedure: Head coring, without neck transection and without lateral drainage—specifically developed for patients with portal hypertension, where troublesome bleeding may ensue should neck transection be attempted [166–169]. This also highlights that the head drainage can be achieved without neck division (as in the Frey procedure). Further, published data [169] have now identified that the early outcomes after the Berne procedure are superior to the Beger procedure.

When one considers the aims of surgery in chronic pancreatitis and the need to address the whole gland, the Frey procedure is superior in (a) its applicability to large and small ducts, (b) drain the entire gland, (c) deal with inflammatory mass lesions and (d) preservation of pancreatic parenchyma and duodenum.

10.24.2.4 Nerve Interruption Procedures

The concept of nerve interruption as a means to achieve relief of pain is hampered by the fact that multiple spinal levels receive input from the splanchnic nerves and the tremendous variation in the number of splanchnic roots, which make complete neurotomy difficult. Splanchnicectomy is performed thoracoscopically, and unilateral or bilateral division may be carried out. Up to 75% of patients have early but short-lasting pain relief [140, 155].

10.24.2.5 Total Pancreatectomy with Islet Cell Autotransplantation (TP-IAT)

Since its inception in 1977, TP-IAT has gradually grown into the therapeutic options for painful chronic pancreatitis. This procedure is justified in patients (a) who have

a confirmed diagnosis of chronic pancreatitis on CT scan, EUS or histology, (b) those who have hereditary pancreatitis, (c) those with intractable pain with narcotic dependence which has impacted their quality of life, (d) where reversible causes of pancreatitis have been ruled out, (e) who have failed maximum medical/endoscopic or limited surgical treatment and (f) who have adequate islet function (positive C-peptide). This subgroup may represent only 30% of all patients. It is not justified where ductal diameters are wider which permit a satisfactory drainage procedure or where the patient has alcoholic pancreatitis. In 2012, Sutherland et al. published the Minnesota experience; 409 patients were treated including 53 children. Forty-three percent of the patients had idiopathic pancreatitis, and only 7% had alcohol as aetiology. Twenty-one percent had undergone previous pancreatic procedures. About 16% of cases required reoperation (most commonly for bleeding), and while 90% had beta cell function as evidenced by a C-peptide level of greater than 0.6 ng/mL, only 30% were euglycaemic and 33% had partial function. Pain relief occurred in over 85% of cases. Glycaemic outcomes were adversely affected by previous surgery and by a lower yield of islets. Patients with an islet yield of greater than 5000 units/kg had a 72% glycaemic control [170]. It is clear that patients had a good quality of life, and two-thirds had improvement in glycaemic control as compared to preoperative state. In view of the current paucity of islet harvesting centres, remote harvesting has become a reality. Preliminary data suggests that remote harvesting could produce results comparable to those of local harvesting [171].

Suggested strategy for surgical treatment: The following strategy can be recommended for surgical management of intractable pain or complications of CP. It comprises three steps:

(a) *Step 1*: Thorough evaluation of the morphology of the gland by imaging: The author's current preference is a contrast-enhanced triphasic CT scan which provides comprehensive information about the gland, the duct and the complications. MRI is an excellent alternative and may have the advantage in that it avoids radiation exposure and also provides venography in cases where portal hypertension exists. However, the paucity of high-resolution MRI scanners and high-quality interpretation has hampered its widespread application. EUS is indicated in resolving mass lesions of the pancreas, and fine needle aspiration cytology (FNAC)/core biopsy is performed in equivocal cases under EUS guidance. Patients with biliary obstruction and high bilirubin levels, severe weight loss and deterioration of glycaemic control, raised CA 19-9 levels and a positive FNAC for malignancy would mandate head resection with frozen section of neck margins, and total pancreatectomy, if margins were positive. Patients without masses but with ductal strictures and stones undergo head coring with lateral drainage. The operation also allows drainage of pseudocysts either in continuity or separately and relieves biliary obstruction.
(b) *Step 2: Timing of procedure*: Currently, patients with intractable pain or pain interfering with normal lifestyle (Table 10.1) or those with complications not amenable to nonoperative therapy undergo surgery. There are three caveats to this proposal.

1. Nealon and Thompson showed that early drainage of the pancreatic ductal system may help prevent functional loss. The data revealed that (a) none of the patients with severe functional loss improved after operation and (b) 71% of patients treated medically in the mild functional loss group deteriorated over a mean of 47 months as opposed to 16% of those who underwent operative drainage [70]. Yang et al. also showed improved functional results and lower reintervention rates with early surgery [72].
2. Can early surgery decrease or obviate the development of future pancreatic adenocarcinoma? In our unit, 8.3% of patients presenting with pain and complications [30], and 4.1% of patients drawn from a national database in India have revealed pancreatic cancer [29] at the time of presentation. Although data have not emerged to show that surgical clearance of stones and drainage or partial pancreatectomy could reduce the incidence of cancer, it may be worth noting that only 6 out of 900 patients operated for CP developed cancer over a follow-up period of >15 years (unpublished data). Therefore, the case for earlier surgical therapy is gaining strength. In alcoholic pancreatitis, there is at least the prospect of risk modification by abstinence, but such an option does not exist in tropical pancreatitis.
3. Surgery during the acute episode. In general, surgery is to be avoided during an acute episode with the attack being tided over by NJ feeds, antibiotics if there is evidence of infection and supportive measures. Surgery is then performed in the interval. Occasionally, laparoscopy/laparotomy to perform peripancreatic lavage and drainage may be necessary and must be done.

(c) *Step 3: On-table strategy*

1. The choice of procedure is dictated by the morphology of the pancreas and the type of pathology.
   - The Whipple operation is performed when there is a doubt of malignancy in cases with a clear-cut head mass (Fig. 10.3). Frozen section is performed from the neck margin, and, if positive, a total gland resection may become necessary.
   - In cases where malignancy is unlikely, the aim of treatment is to achieve excellent drainage from the entire gland with maximum parenchymal preservation. It is also clear that a pure ductal drainage is unlikely to allow drainage of head ducts adequately [172]. Moreover, the pancreatic duct dips deep into the head such that in a 5 cm head, at a point 3 cm from the medial border of the duodenum, the distance between the duct and the ampulla of Vater is 6 cm. A simple ductotomy can therefore not achieve drainage of head ducts nor can it help drain the side branches including the uncinate process ducts [172].
   - Dissection of peripancreatic tissue can be difficult in CP where considerable peripancreatic inflammation and fibrosis are present. On the other hand, dissection within the limits of a fibrosed gland is safe and technically easier [168].

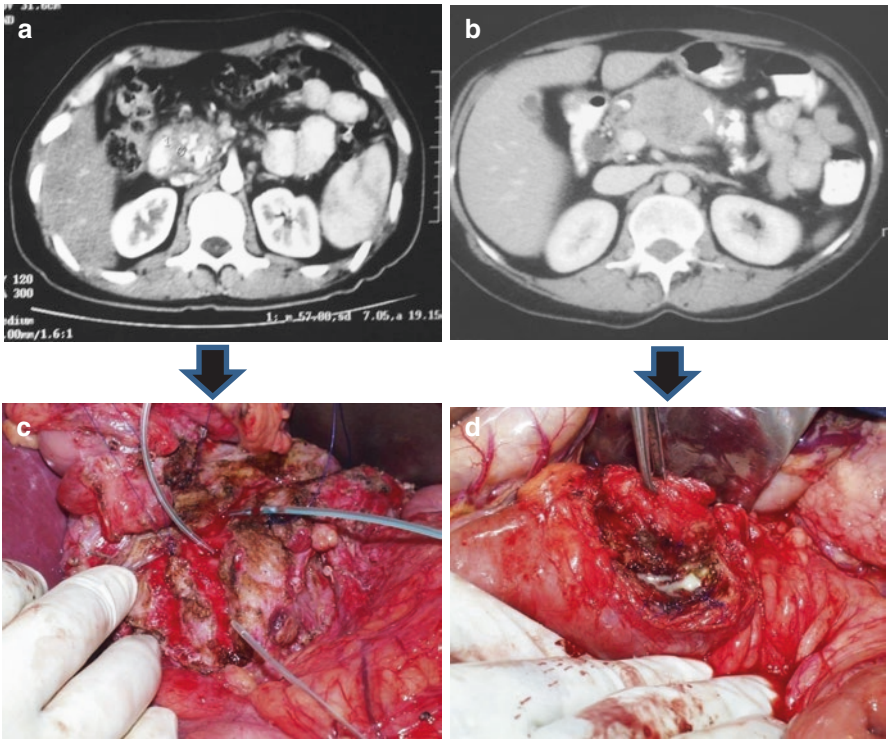

Fig. 10.3 Types of head "mass" in chronic pancreatitis (**a**) with predominant stones and (**b**) with predominant mass in the upper panels and their intraoperative photographs demonstrating their respective management (**c**) and (**d**) in the lower panels. Figures 10.2 and 10.3 reproduced with permission (From The Beger. Frey and Berne Procedure: How to do them safely. In: Chattopadhyay TK, Sahni P, Pal S (eds). *G.I. Surgery Annual. Volume 16.* New Delhi: Indian Association of Surgical Gastroenterology; 2009:13–20)

- Drainage of as much of the gland as possible must be achieved.
- On the basis of the above, the Frey procedure with lateral drainage provides the best opportunity to achieve the stated aims of an ideal procedure (see above). However, the author recommends a considerably greater excavation of the pancreas along the principles mentioned below [164].

2. Complete stone clearance should be achieved as far as possible. This can be done using C-arm fluoroscopy during the surgery to check for residual stones. Stones <5 mm may not be removed. If a portion of the gland has extensive calculi which cannot be cleared adequately, then resection of that part of the gland must be considered.
3. The MPD is identified in the body of the pancreas by palpation, needling or ultrasound. If the duct is not found, then the operation is commenced by head coring.

4. Suspicious tissue is sent for frozen section, and the operation is converted to a Whipple procedure, if histology is positive for cancer [173].
5. If biliary obstruction is present, the operation is commenced by trans-cystic duct cholangiography, the stricture mapped, head coring carried out and repeat cholangiography done. No other procedure is necessary if there is free flow of contrast into the duodenum. If there is a residual stricture, hepatico-jejunostomy, choledochoduodenostomy or internal drainage of the bile duct into the cored out head are carried out.
6. If there is extensive head involvement with biliary and duodenal obstruction and/or multiple head pseudocysts, it may be appropriate to perform a formal head resection in such cases.
7. Two types of pancreatic heads are encountered: (1) a large stone load head, where filleting out of ducts and side branches, clearance of stones is followed by excision of intervening parenchyma (Figs. 10.2a and 10.3a; the duct-dominated head), and (2) an inflammatory head mass, where head coring is done, ducts identified and laid open within the cored segment, and the process is continued until complete clearance has been achieved (Figs. 10.2b and 10.3b, the mass-dominated head) [168].
8. End points of head coring are no stones in the pancreatic area on fluoroscopy, relief of biliary obstruction as checked by cystic duct cholangiography, drainage of all pseudocysts or collections and presence of only a shell of pancreatic tissue posteriorly and around the head of the pancreas.

10.24.3 Comparative Trials

Many randomized trials have compared the efficacy of various surgical procedures (Table 10.2). The following observations emerge from the trials:

(a) Surgery provides lasting pain relief and good quality of life (QOL).
(b) Hybrid procedures fare better than resectional procedures in terms of outcome.
(c) Morbidity is substantially reduced if the posterior capsule of the pancreas is preserved (i.e. the Frey and Bern procedures as opposed to the Beger procedure).
(d) Although early functional results of resection are poorer than those with drainage, they equalize with time. While this may be true in the Western Hemisphere where enzyme replacement therapy is provided, in India, functional replacement (enzymes and insulin) on an outpatient basis is an expensive proposition unsupported by insurance and a major cause of poor QOL.

Table 10.2 Surgical operations and randomized trials

Author (year)	Type	Design	Morbidity	Mortality	Pain relief	New diabetes	QOL score	Follow-up (in years)
Klempa et al. [117]	RCT	PD vs. DPPHR	–	0% vs. 5%	60% vs. 70%	38% vs. 12%	–	5
Buchler et al. [156]	RCT	PPPD vs. DPPHR	–	0% vs. 0%	40% vs. 75%	–	–	0.5
Izbicki et al. [157]	RCT	DPPHR vs. Frey	32% vs. 22%	0% vs. 0%	89% vs. 92%	8% vs. 6%	–	8.5
Izbicki et al. [158]	RCT	PPPD vs. Frey	53% vs. 19%	0% vs. 3%	Similar	Similar	–	2
Aspelund et al. [159]	Single cohort	PD vs. DPPHR/ Frey	40% vs. 25% vs. 16%	6% vs. 0%	–	25% vs. 8%	–	3
Farkas et al. [160]	RCT	PPPD vs. Bern	40% vs. 0%	0% vs. 0%	90% vs. 85%	–	–	3
Strate et al. [161]	RCT	DPPHR vs. Frey	Similar	–	Similar	65% vs. 61%	Similar	7
Koninger et al. [139]	RCT	Berne vs. DPPHR	21% vs. 20%	0% vs. 0%	–	–	71% vs. 66%	2
Diener et al. [162]	Meta-analysis	DPPHR vs. PPPD	Similar	Similar	Similar	Similar	DPPHR better	–

10.24.4 Special Situations

10.24.4.1 Small Duct Disease

Traditionally, small duct disease has been treated by resections. However, data highlight that ductal drainage with head coring can relieve pain over a long period. The duct can be identified by palpation, aspiration, oblique division of the parenchyma, ultrasound, C-arm identification of a stone and cutting down upon it or simply by completing a head coring procedure and identifying the duct within the cored head [174, 175]. Alternatively, an Izbicki 'V' excision can be performed. Yekebas et al. showed that long-term results are good [176, 177].

10.24.4.2 Portal Hypertension

Ramesh et al. treated 57 cases of CP and portal hypertension and emphasized that the varices were preoperatively obliterated by endoscopic ligation or cyanoacrylate injection, and surgical intervention was carried out only for intractable pain or other complications [178]. Surgery could be performed safely, but the technical difficulty prevented the surgeon from performing head coring in every case, and sometimes, only a lateral pancreaticojejunostomy was possible. On the other hand, Bockhorn et al. described surgery as "the last resort" although the eventual outcomes in terms of pain relief and QOL were favourable [179].

10.24.5 Laparoscopy in CP

Numerous reports exist in the literature on cyst drainage, head resection and distal pancreatectomy being performed laparoscopically. Lateral pancreaticojejunostomy has also been reported (about 40 cases with a conversion rate of 13.2%) (Table 10.3). Single incision [180] and robotic pancreaticojejunostomies [181,

Table 10.3 Laparoscopic pancreaticojejunostomy series

Author	Year	Number	Hospital stay (days)	Complications	Result
Kurian [185]	1999	5 (2)	3–7	1	80%
Santoro [186]	1999	1	7	0	NA
Glaser [187]	2000	1	NA	0	Pain free
Tantia [188]	2004	17 (4)	5.2	2	82%
Palanivelu [189]	2006	12	5	0	84% pain free
Khaled [190]	2014	6 (1 reoperated)	5–8	1	4/6 pain free
Deie [191]	2016	2 (children)		0	NA
Kim [192]	2016	11 patients (barbed V-Loc suture)	6–8	0	All well

182] have also been performed successfully, as well as laparoscopic total pancreatectomies for islet cell autotransplantation [183, 184]. Hybrid procedures are currently the gold standard in surgery for CP. The educated sensitive left hand of the surgeon held behind the Kocherized head holds the key to haemostasis and guides the extent of head coring. Therefore, the authors do not perform the Frey procedure laparoscopically [164].

10.24.6 Pre- and Post-Intervention Evaluation

Pain may be assessed by the visual analogue scale, the Izbicki pain score or our own pain score. Exocrine function is assessed by estimating faecal elastase or faecal fat excretion. Endocrine assessment is done by determining the glucose tolerance and the medication requirement on a standard diet. QOL scores are assessed by using the EORTC-QLQ30 form with the PAN 26 form added. QOL scores are calculated on the basis of answers to 56 questions. The recently included pancreatitis quality of life instrument (PANQOLI) [193] represents the first disease-specific instrument to be developed and validated for the evaluation of quality of life in chronic pancreatitis patients. The instrument has four subscales including subemotional function scale, role function scale, physical function scale and "self-worth" scale.

10.24.6.1 Future Directions

The story of chronic pancreatitis has been compared to the tale of the five blind men and the elephant. This is more a pathomorphologic entity with a wide spectrum, which ends up in a watershed of atrophy, and pancreatic insufficiency, and depending upon its presentation, it is treated by different specialists. It is not clear as to what the early stages of the disease represent and whether the disease can be aborted at that time. The aetiology is far from unravelled, and it is not clear yet why some drinkers may develop CP where others do not; in the non-alcoholic forms, the confusion is greater.

It does appear that a multifactorial aetiology is likely. There is lack of clarity as to the approach to the disease with options such as steadfast conservatism at one end to early intervention at the other end. Randomized trials are difficult to perform given that the patient population is heterogenous. Research into aetiopathogenesis, prevention and optimum treatment can improve a lot of these patients who suffer during the prime of their lives.

Conclusion

Regardless of its aetiology, CP is mostly a progressive disease affecting men and women in their prime of life. A clear understanding of the aetiology and pathogenesis of CP will contribute to more effective management in the future. Whereas diabetes mellitus and steatorrhoea are managed effectively, pain relief is a more elusive goal. Medical therapy is largely confined to restoring functional deficiency and providing symptomatic relief during an acute episode (many

patients have long pain-free periods). Intractable pain and complications require intervention. Endoscopic methods are successful in relieving pain in patients with ductal disruptions and pseudocysts, and ESWL helps to clear calculi; but these methods are less effective in strictures. Published data suggest that a hybrid surgical procedure may provide the best opportunity for long-lasting pain relief.

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Non-mucinous Cystic Lesions of the Pancreas

11

Kishore G. S. Bharathy and Sadiq S. Sikora

11.1 Introduction

Non-mucinous cystic lesions of the pancreas are a heterogeneous group comprising both benign lesions and neoplasia with variable malignant potential. These include pseudocyst, serous cystadenoma (SCA), solid pseudopapillary tumour (SPT), cystic pancreatic endocrine neoplasm (CPEN) and other rare lesions.

Few topics in medicine are as controversial as the evaluation and management of patients with cystic neoplasia of the pancreas [1]. In the late 1970s, Compagno and Oertel [2, 3] described serous and mucinous tumours as separate entities. With advances in multi-detector computed tomography (MDCT) and image acquisition protocols using magnetic resonance imaging (MRI), these lesions are being better characterized. Endoscopic ultrasound (EUS) with fine needle aspiration cytology (FNAC) provides further opportunity to characterize these tumours. Molecular markers may further clarify diagnostic dilemmas and help in selecting an appropriate treatment strategy for the individual patient. Specialists encountering these lesions should be able to make a diagnosis as well as be aware of the natural history so as to assign patients to appropriate management strategies such as reassurance, periodic follow-up or surgery. As compared to pancreatic adenocarcinoma, cystic tumours have a favourable prognosis [4].

K. G. S. Bharathy · S. S. Sikora (✉)
Surgical Services, Sakra Institute of Digestive and HPB Sciences, Sakra World Hospital, Bangalore, India

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11.2 Epidemiology

Cystic pancreatic lesions (CPLs) are detected incidentally in many instances, during abdominal CT or MRI performed for other indications [5]. This has led to smaller, asymptomatic tumours being identified, especially in an elderly population. There has been a 20-fold increase in the detection of CPLs over the last 15 years [6]. In imaging performed for unrelated reasons, 2% of the patients were found to have an incidental cystic lesion [7].

A single institution retrospective review of 24,000 CT scans performed over 7 years identified CPLs in 1% of patients [7]. Recently, the prevalence of CPLs has been estimated to increase to 3% using CT [8] and up to 20% using MRI [9]. One study reported prevalence of incidental CPLs on MRI to be around 13.5% and showed that the prevalence and cyst size also increased with age [10]. These findings have been corroborated at autopsy with the prevalence of cystic lesions approaching 25% [11].

11.3 Classification

The WHO classification (2000) describes four major types: SCA, mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN) and SPT [12]. Cystic tumours of the pancreas are defined as a uni- or multilocular cavity-forming neoplasm or non-neoplastic tumours. For the sake of simplicity, CPLs can be classified as either pseudocysts or tumours. Table 11.1 provides a classification system based on the cell of origin.

11.4 Pancreatic Pseudocyst

A pseudocyst is defined as per the revised Atlanta guidelines as an organized acute peripancreatic fluid collection without any internal debris, which has persisted beyond 4 weeks or more from the onset of the attack of acute pancreatitis [13].

Table 11.1 Classification of non-mucinous cystic neoplasms of the pancreas according to the cell of origin

Cell of origin	Example
Epithelial	SCA, cystic degeneration of adenocarcinoma, lymphoepithelial cyst
Exocrine	Acinar cell carcinoma
Unknown/mixed origin	SPT, giant cell tumour, pancreatoblastoma, cystic teratoma
Endocrine	CPEN
Mesenchymal	Sarcoma, lymphoma, lymphangioma
Metastatic	Renal cell carcinoma, lung carcinoma, ovarian carcinoma, melanoma

SCA serous cystadenoma, *SPT* solid pseudopapillary tumour, *CPEN* cystic pancreatic endocrine tumour

Presence of internal debris within a pseudocyst qualifies it to be designated as a walled off pancreatic necrosis (WOPN).

A pseudocyst occurs typically in the setting of acute pancreatitis. The incidence of development of a pseudocyst in acute pancreatitis ranges from 6% to 18.5% [14, 15]. The aetiology of pancreatitis and consequent development of pseudocyst depend upon the age of the patient. In children, the most common cause is trauma, whereas in adults the spectrum of causes is biliary (42%), alcohol induced (23%), post-endoscopic retrograde cholangiopancreatography (9.5%), medications (6.3%) and idiopathic (12%) [16]. About 5–10% of patients with chronic pancreatitis develop pseudocyst [17], which are secondary to episodes of acute pancreatitis or are retention cysts. Sometimes the history of pancreatitis is not forthcoming and in such a setting the possibility of a CPL, cystic lesion from the adrenal, spleen or a retroperitoneal cyst should be considered.

The most accepted classification of pancreatic pseudocyst is that proposed by D'Egidio and Schein [18] which classifies cyst based on underlying pancreatic pathology, pancreatic duct anatomy and communication between the pancreatic duct and cyst. *Type I* cysts are those developing in a setting of acute pancreatitis with a normal pancreatic duct anatomy without any duct communication. These cysts are amenable to either percutaneous or endoscopic drainage with good results. *Type II* cysts are those with abnormal pancreatic duct anatomy in the setting of acute or chronic pancreatitis but without any duct communication. *Type III* cysts are those with underlying chronic pancreatitis with ductal stricture and communication with the pancreatic duct. Patients with Type III cysts most often merit a surgical drainage or a complex endoscopic intervention.

11.4.1 Diagnosis and Imaging

Abdominal CT scanning is the investigation of choice in patients with history of pancreatitis and suspected to have a pseudocyst (Figs. 11.1 and 11.2a). A peripancreatic round or ovoid fluid collection with a thick wall that enhances on contrast administration is pathognomonic of a pseudocyst, especially in a patient with a history of acute or chronic pancreatitis. Additional features of acute pancreatitis in the form of peripancreatic stranding and oedema may be present, or there may be features of chronic pancreatitis with calcification and pancreatic duct dilatation. Abdominal CT scan has a high sensitivity of 90–100% for diagnosis of pancreatic pseudocyst [19]. MRI and magnetic resonance cholangiopancreatography (MRCP) are also sensitive imaging modalities which may provide additional information. MRI provides a better distinction between the fluid and solid components helping to distinguish a pseudocyst from a WOPN. Moreover, MRCP helps delineate pancreatic ductal pathology such as dilatation, irregularity and/or stricture. MRCP may also demonstrate the communication of the pancreatic duct with the pseudocyst and also the point of disruption of pancreatic duct in patients with pancreatic ascites or pancreaticopleural fistula. On MRI/MRCP, pseudocysts may communicate with the pancreatic duct in about 65% of the

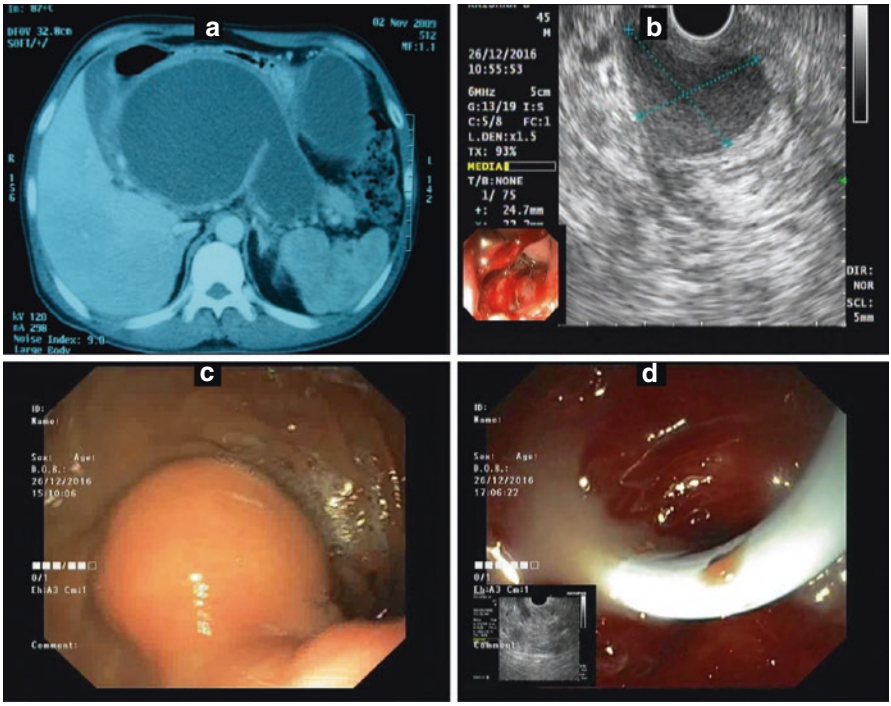

Fig. 11.1 (**a**) Multi-detector computed tomography scan image depicting a large unilocular cystic lesion replacing the pancreas and abutting the stomach. (**b**) EUS image of a pseudocyst with impression along the gastric body proximally. (**c**) Endoscopic view which shows the bulge on the posterior wall of stomach, and (**d**) endoscopic view showing EUS-guided endoscopic puncture and drainage

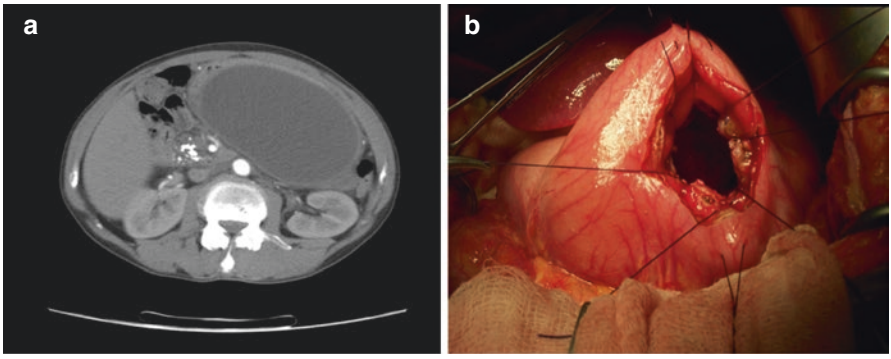

Fig. 11.2 (**a**) Multi-detector computed tomography scan image depicting a chronic pseudocyst. Calcification is seen in the head of the pancreas. (**b**) Operative picture of a wide surgical cystogastrostomy

cases [20]. The limitation of cross-sectional imaging modalities are their inability to definitively differentiate between pseudocyst and cystic tumours of the pancreas. On serial scans, decrease in the size of the lesion may suggest a pseudocyst as cystic tumours are unlikely to regress. It is important to differentiate pseudocysts from IPMNs which can also present with a history of pancreatitis with an associated pancreatic ductal dilatation. In the absence of prior imaging, identification of a cyst in a patient with pancreatitis should lead one to suspect that it may be a case of a cystic tumour causing pancreatitis. Serial imaging where available may suggest the natural history of the disease and differentiate a pseudocyst from a cystic tumour [21].

11.4.2 Natural History of a Pseudocyst

Pseudocysts following an episode of pancreatitis may remain asymptomatic, resolve spontaneously or become symptomatic with or without complications. Size and duration of the pseudocyst are important considerations in the natural history of pancreatic pseudocyst. Cysts <4 cm usually resolve spontaneously without complications. Traditionally, cysts larger than 6 cm and persisting beyond 6 weeks were considered as indications for surgical intervention. Studies charting the natural history of pancreatic pseudocysts have now challenged this traditional approach; 60% of pseudocysts followed over a period of 1 year showed complete resolution. The majority of the pseudocysts could be managed with expectant treatment, and only 10% developed complications with the need for operative intervention [22]. Cysts larger than 6 cm were more likely to develop complications and necessitate surgical intervention, although nonoperative management and follow-up did show resolution in this group of patients [22].

Factors associated with decreased likelihood of spontaneous resolution of pseudocyst lesions [23] are:

1. Number: multiple cysts
2. Location: tail of the pancreas
3. Thick wall (>1 cm)
4. Communication with main pancreatic duct associated with proximal stricture of the duct
5. Increase size on follow-up examination
6. Aetiology: biliary or postoperative
7. Extrapancreatic development in alcoholic chronic pancreatitis
8. Associated with severe acute pancreatitis
9. Extent of pancreatic necrosis >25%

11.4.3 Indications of Treatment in Pseudocysts

Large pseudocysts causing abdominal pain, vomiting and compression symptoms leading to duodenal obstruction are definite indications for intervention. Patients with jaundice due to compression or stenosis of the bile duct and splenic vein

thrombosis with portal hypertension also merit intervention and treatment. Other complications such as secondary infection of the pseudocyst, intracystic bleed due to a pseudoaneurysm and pancreaticopleural fistula are also indications for treatment.

The treatment options include percutaneous catheter drainage, endoscopic intervention or surgical treatment either by laparoscopy or open surgery. Percutaneous drainage of pseudocysts is least invasive and can be used as a temporizing measure in an infirm patient, in the presence of infection or in symptomatic expanding immature cysts [23, 24]. However it has a high failure rate (16%), high recurrence rate (24%) and a complication rate of 18% [25]. Percutaneous drainage of pseudocysts relieves symptomatic gastric outlet obstruction [26]. This comes at the cost of a controlled external pancreatic fistula in 25% of patients, one third of whom may require surgery for definitive management [26]. It is also a useful option in children with successful resolution in 72% [27]. Success of percutaneous drainage is not dependent on size or complexity of the pseudocyst [27].

The aim of endoscopic intervention is to drain the pseudocyst into the stomach or duodenum, depending on the location of the cyst, size of the cyst and proximity/bulge into the gastrointestinal tract. The prerequisites for endoscopic drainage are a distance less than 1 cm between the pseudocyst and the gastric or duodenal wall [28], size of the pseudocyst preferably more than 5 cm and presenting as an indentation on the visceral wall [23, 29]. A mature cyst, with absence of communication with the pancreatic duct, will ensure high success rates [29]. In patients with a pancreatic duct communication, transpapillary drainage is preferred. A cystic tumour and pseudoaneurysm should be excluded before embarking on endoscopic drainage [28]. In a review of endoscopic drainage of uncomplicated pseudocysts, the technical success ranged from 71% to 100%, clinical success of 62–100%, recurrence rate of 4.8–31% and complication rates of 3–37% [30]. The use of EUS improves the technical success rate and decreases the complications (Fig. 11.1b–d). Of all pseudocysts, only 35–40% are ideally suited for endoscopic drainage; 60% have communication with pancreatic duct and 39% have necrotic debris in the cyst; both of these factors may decrease the success of endoscopic drainage. The complications of intervention include infection in 0–15%, bleeding in 0–9%, stent displacement in 4–6% and rarely retroperitoneal perforation; 10–50% of patients may require surgery for failure or complications of endoscopic drainage [31, 32]. In a randomized trial of endoscopic drainage versus surgical drainage [33], of the 110 patients, only 40 (36%) fulfilled the inclusion criteria. The inclusion criteria consisted of a diagnosis of pancreatic pseudocyst on CT, pseudocyst measuring 6 cm in size and located adjacent to the stomach, documented history of acute or chronic pancreatitis, persistent pancreatic pain requiring narcotics or analgesics and symptomatic gastric outlet or bile duct obstruction induced by the pseudocyst. Presence of necrosis on CT, cyst not adjacent to the stomach, multiloculated cyst/multiple cysts, portal hypertension and pregnancy were some of the exclusion criteria. Twenty each were randomized to the endoscopy and surgical arms. There was no difference in the technical success, treatment failure and recurrence rates in the two arms. The hospital stay and cost were higher in the surgical arm [33]. It is clear that in selected patients, endoscopic drainage has equivalent results to surgery in the hands of skilled endoscopists especially with aid of EUS.

Surgical treatment is certainly more versatile, applicable to a much wider spectrum of patients. It provides a wide, durable, long-term drainage. The choice of surgical procedure depends on the location of the cyst (head, body or tail). The cyst can be drained into the stomach (cystogastrostomy), duodenum (cystoduodenostomy) or in the jejunum (cystojejunostomy), ensuring a wide anastomosis in the most dependent area of the cyst (Fig. 11.2b). Additional procedures such as cholecystectomy and/or correction of the pancreatic duct strictures can be performed. A possibility of a CPL, if suspected, can be confirmed by a biopsy of the wall. Surgical drainage can be accomplished with a long-term success rate of 91–97% with 10–15% morbidity. In the era of minimally invasive surgery, laparoscopic drainage has a success rate of 98%, recurrence rate of 3% and complication rate of 9% [34]. A large single-centre series of 108 patients of pancreatic pseudocyst undergoing laparoscopic drainage had 93% success rate and recurrence rate of 0.9% at a mean follow-up of 54 months [34]. In patients with *Type III* cysts, surgical treatment is the option of choice which addresses the pancreatic duct drainage along with drainage of the cyst with or without the head coring (Frey's procedure).

In uncomplicated pseudocysts that require drainage, endoscopy should be the first line of management as it less costly, associated with lesser hospital stay and not inferior to surgery. EUS-guided drainage offers high rates of success and decreases the chances of complications such as bleeding. Surgery may be the first choice in the presence of portal hypertension with extensive collaterals or when concomitant procedures such as a cholecystectomy are needed. For surgical management of a pseudocyst, a laparoscopic approach is feasible in most instances when expertise is available. It is of note that apart from case reports, till date, minimally invasive surgery for pancreatic pseudocysts has been reported only in 253 patients [23].

11.5 Serous Cystadenoma (SCA)

11.5.1 Incidence

SCA accounts for around 20–30% of pancreatic cystic tumours [35]. SCA comprised 16% of 851 CPLs resected over 33 years at the Massachusetts General Hospital [36].

11.5.2 Pathogenesis

Mutation in the Von Hippel-Lindau (VHL) gene plays a central role in the development of SCA. Sporadic cases of SCA have intragenic mutations of VHL (located in the short arm of chromosome 3) or loss of heterozygosity in this gene or close to it [37]. The cysts seen in VHL disease are identical to SCAs; however they are irregularly scattered around the pancreas rather than forming a discrete lesion. The entire pancreas may be replaced with multiple cysts which may be SCA, NET (neuroendocrine tumours) or simple cysts. The frequency of pancreatic involvement in VHL syndrome varies from 17% to 77.2%, and SCAs are reported in about 2.7–9.5% of patients with VHL [38].

11.5.3 Clinical Features

SCAs occur predominantly in females (70%) aged 60–65 years. They can occur anywhere in the pancreas. In the largest multinational study comprising of 2622 SCAs, 61% were asymptomatic [39]. Non-specific abdominal pain was reported in 27% of cases, diabetes mellitus in 5% and biliopancreatic symptoms, including typical pancreatic pain, acute pancreatitis, jaundice and steatorrhoea, in 9% of cases [39]. Common symptoms and signs when present are abdominal pain, weight loss and a palpable mass [40]. Jaundice due to bile duct compression is uncommon [41]. SCAs may present acutely owing to tumour rupture or haemoperitoneum [42]. Tumours more than 4 cm are more likely to be symptomatic when compared to smaller tumours (72% vs. 22%, $p < 0.001$) [42]. A study which followed up 145 patients with annual MRI showed growth rates of 0.1 cm/year for the first 7 years and 0.6 cm/year for the next 3 years [43]. These patients had minimal or no symptoms and hence were initially managed conservatively. Only 23 of them required surgery, at a median of 4 years after diagnosis. Patients with oligocystic SCA and those with a history of extra pancreatic primary malignancy had higher growth rates [43].

Serous cystadenocarcinoma is a malignant variant of the benign SCA. None of the patients developed a serous cystadenocarcinoma on final histopathology. Around 30 cases have been described in literature, and it is extremely rare. There are no factors that can predict malignant behaviour which is solely characterized by invasion of surrounding structures. The risk of malignancy in SCAs has been reported to be around 3% [44].

11.5.4 Cross-Sectional Imaging

Four variants are described: the microcystic, oligocystic, mixed and solid types. Microcystic SCA is the most common type and is seen in more than 70% of patients with SCAs. Typically the tumour is composed of multiple small cysts <2 cm in size arranged around a central fibrous septa giving rise to a honeycomb appearance. (Fig. 11.3a, b). The fine structure of such a lesion entails numerous small, soft-walled cysts forming a cluster around a central scar from which fibrotic bands radiate giving rise to a ‘cyst on cyst’ appearance. It is generally seen as a solitary cystic mass of 2–16 cm in diameter, usually in the pancreatic body or tail. The typical central calcification is seen in about 20–30% of the cases. On contrast-enhanced CT, late enhancement of the fibrotic bands may also help in diagnosis and can be achieved about 5 min after contrast administration [45]. On MRI, the cysts appear hyperintense in T2 phase. The central septa enhances on gadolinium administration in the T1 phase. Calcifications may not be seen on MRI. In SCA there is no pancreatic duct communication with the cyst.

The less common oligo- or macrocystic variant appears as a solitary cyst that is difficult to distinguish from pseudocysts, MCN or unifocal branch-duct IPMNs. A lesion in the pancreatic head with a lobulate contour is likely to be an oligocystic SCA; a thick cyst wall and septa, as well as eggshell calcification, are suggestive of MCN [46]. The oligocystic variant appears lobulated and composed of fewer cysts whose size can be

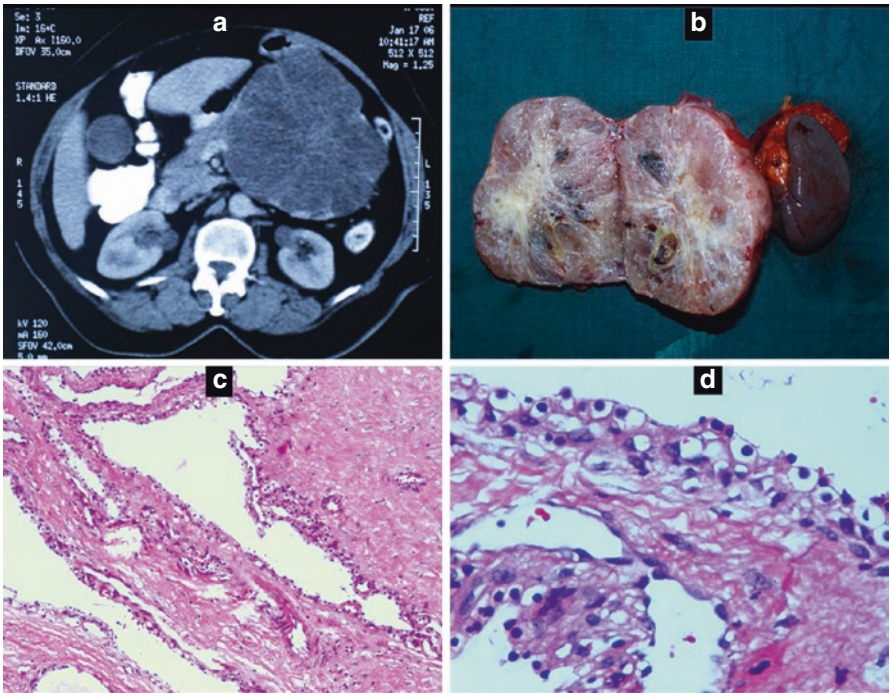

Fig. 11.3 (**a**) Multi-detector computed tomography scan image depicting a lobulated, multicystic tumour in the tail of the pancreas with a central scar and radiating fibrous septa typical of a serous cystadenoma. (**b**) Cut section of the resection specimen with typical gross features of microcystic sponge-like lesion with radiating septa from a central stellate scar. (**c**) (10×) and (**d**) (40×): microscopic view (haematoxylin and eosin) shows the cystic spaces lined by cuboidal cells with abundant clear cytoplasm

up to 6 cm. A sponge-like pattern is found if the cysts increase in size peripherally. The mixed variant has features of both oligocystic and microcystic tumours. The solid variant appears so because of multiple small cysts interspersed with thick septa. The fluid component is not appreciated on CT, but will be seen on MRI [47].

11.5.5 EUS Findings

On EUS, microcysts arranged around a central scar can be clearly appreciated. EUS-FNA of an SCA reveals glycogen-rich cuboidal cells. Cytological examination of EUS-FNA specimens can correctly predict SCA in only 38% of the cases of SCA [48]. When cyst glucose levels of SCAs were compared with those of lesions that were not SCAs (pseudocysts, IPMNs, MCNs and cancer), the median cyst glucose level was significantly elevated. The highest diagnostic accuracy was obtained at a cut-off of 66 mg/dl, with a sensitivity and specificity for differentiating SCAs from lesions that were not SCAs of 88% and 89%, respectively.

Similarly, SCA lesions had significant kynurenine abundance, and the area under the receiver operator characteristic curve was 0.85 (95% CI, 0.66–1.0) [49]. In a prospective study of 87 patients undergoing surgery, vascular endothelial growth factor (VEGF)-A levels of 8500 pg/mL had 100% sensitivity and 97% specificity as an SCA biomarker. VEGF-A and VEGF receptor 2 are overexpressed in SCA cyst tissue. With a cut-off set at 200 pg/mL, VEGF-C identified SCA with 100% sensitivity and 90% specificity [50]. α-Inhibin immunostaining can be useful in detecting a SCA [51]. While cyst fluid assay of glucose, kynurenine, VGEF and α-inhibin are useful adjuncts, they have not found use in routine clinical practice.

A promising development in the assessment of SCA is the use of needle confocal laser endomicroscopy (nCLE) at the time of EUS. nCLE utilizes a microprobe attached to a 19-guage needle and provides microscopic pictures of SCA. A prospective multicentre French study (CONTACT) [52] has found that the detection of a superficial vascular network is a histological feature of SCA, which can be highlighted by nCLE. In a preliminary series of 18 cases, nCLE achieved an overall accuracy of 83%, with a sensitivity of 62.5% and a specificity of 100% for the diagnosis of SCA, with an excellent intraobserver and a good interobserver agreement [52].

In clinical practice, EUS is performed only when the diagnosis of a SCA is not clear after cross-sectional imaging. EUS-FNA and fluid analysis are done in select cases with atypical morphological features when it can differentiate SCA from a mucinous neoplasm, pseudocyst.

11.5.6 Indications for Surgery

Surgical treatment should be considered only if the diagnosis of the CPL remains uncertain despite a complete workup, if the patient has significant symptoms due to the lesion, or there remain concerns, following evaluation, for the coexistence of an underlying malignancy [39]. It is generally agreed that SCAs are benign (1% rate of malignancy) and surgery is indicated in patients who are symptomatic or have tumours larger than 4 cm [53, 54]. It is unclear if the tumour size has any direct impact on malignant potential, but larger tumours are more likely to be symptomatic over a period of time [55]. Location of the tumours in the head of pancreas and size >6 cm are independent risk factors for aggressive behaviour; therefore, surgery is advocated by some authors in this setting [54].

11.5.7 Histopathology

These lesions comprise multiple cysts (usually >6) measuring <2 cm and separated by thin septa lined by epithelial cells. SCA cysts are lined by glycogen-rich cuboidal epithelium (Fig. 11.3c, d). The cysts are filled with serous fluid, and the larger cysts are typically located peripherally, contributing to the lesion's lobulated contour.

11.5.8 Prognosis and Follow-Up

A multinational, retrospective study involving 58 centres in 18 countries showed that the postoperative mortality reported in patients who underwent pancreatic surgery for SCA was 0.8%, while the SCA-related mortality was 0% in patients with a median follow-up period of 3.1 years [39]. The inference drawn from this is that it is safe to 'wait and watch' in patients in whom the diagnosis of an SCA is confirmed beyond doubt. In asymptomatic patients, imaging every 6 months for 2 years and then yearly for 5 years is recommended [5]. After resection, there is no need to follow up the patient as the risk of recurrence in SCA is virtually non-existent.

11.6 Solid Pseudopapillary Tumour (SPT)

11.6.1 Incidence

SPT was first described by Franz in 1959 [56] and comprises 3% of resected CPLs [36]. SPTs are rare and comprise of 0.1–2.7% of all primary pancreatic tumours [57]. They appear to be unique to the pancreas with no tumours of similar lineage reported elsewhere in the body [58]. *Pathogenesis* β-catenin gene mutations are believed to be central to the development of SPT and are commonly observed in most patients [59]. In contrast to patients with pancreatic adenocarcinoma, K-ras, p53 or DPC4 gene mutations are not seen in SPTs [60].

11.6.2 Clinical Features

SPT is found almost exclusively in young women (>80%) with a mean age of 30 years [61].

Less than 10% of the patients with SPT are men [62]. Adjacent organs such as the stomach, duodenum and spleen may be involved, but the common bile duct is usually spared [63]. Obstructive jaundice is a rare feature even in tumours arising from the head of the pancreas [64]. Metastases are described in about 20% of the patients and may occur in the liver, peritoneum or even skin [65].

11.6.3 Cross-Sectional Imaging

SPT predominantly occurs in the body/tail of pancreas. Haemorrhage and necrosis contribute to the solid components in SPT. Calcification is seen in 30% of the patients and is usually peripheral but may be central (Fig. 11.4a) [61]. In SPT, the solid tissue components are generally noted at the periphery, with central areas of haemorrhage and cystic degeneration. After contrast administration, the capsule

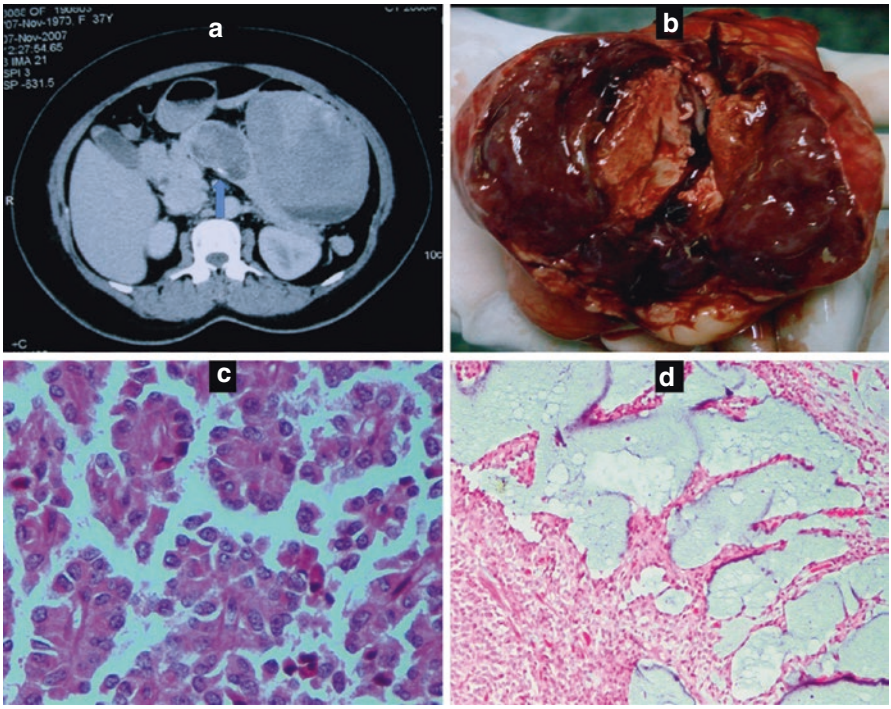

Fig. 11.4 (**a**) Multi-detector computed tomography axial section demonstrating a heterogeneous lesion in the neck and body of the pancreas with peripheral calcification in the capsule (blue arrow). (**b**) The cut section of operative specimen showing cystic areas of haemorrhage, necrosis with solid tumour components. (**c**) Microscopic section (haematoxylin and eosin) shows tumour cells arranged in a pseudopapillary pattern (40×). (**d**) Microscopic section (haematoxylin and eosin) showing the extracellular myxoid stroma characteristic of SPT (10×)

and solid components enhance [66]. A key diagnostic finding of SPT is the presence of a fibrous capsule that encompasses the tumours. Generally, an encapsulated CPL in a young female containing internal haemorrhage is a SPT until proven otherwise (Fig. 11.4b) [67]. On T1-weighted MRI, haemorrhage may be seen as bright areas, while on T2-weighted images, the peripheral fluid component appears bright.

11.6.4 EUS Findings

EUS will typically show a heteroechoic, inhomogeneous mass in the pancreatic tail. Both solid and cystic areas can be appreciated, along with calcification if present. Fluid cytology carries 70–75% accuracy for SPT [68]. EUS-FNA cytological analysis reveals characteristic branching papillae with myxoid stroma, best seen in cell block material [69]. Immunostaining for β-catenin helps in diagnosis.

11.6.5 Indications for Surgery

SPTs are considered premalignant with 2–15% incidence of local invasion or metastatic disease [70]. As these lesions occur mainly in young women and have a malignant potential, the general consensus is to resect these lesions [71, 72]. Presence of metastases is not a contraindication to resection if they can be completely removed; these patients seem to do well, although the actual benefit of metastasectomy in terms of overall survival has not yet been realized.

11.6.6 Histopathology

On histopathology, SPTs contain loosely cohesive cells that form delicate pseudopapillae supported by capillary-sized fibrovascular cores which have an ependymoma-like appearance due to the formation of pseudorosettes (Fig. 11.4c) [59]. Mutation in E-cadherin, β-catenin results in lack of cell to cell cohesion, resulting in this appearance [73]. The stroma can be hyaline or myxoid (Fig. 11.4d). Foamy macrophages are commonly seen; sometimes periodic acid Schiff (PAS) positive globules may also be seen [59]. Adjacent to the cystic spaces resulting from necrosis are foam cells, cholesterol clefts and foreign-body giant cells [74]. Diagnosis is confirmed with immunostaining of characteristic markers, including CD56, CD10, vimentin and nuclear labelling of β-catenin [60, 71]. Neuroendocrine markers such as chromogranin, synaptophysin and pancreatic enzymes are not usually expressed but may be found focally sometimes [63, 75].

11.6.7 Prognosis and Follow-Up

Peritoneal, cutaneous and hepatic metastases have all been reported following SPT excision; however, nodal metastases appear to be rare [76]. A complete margin negative resection confers an excellent long-term survival. Overall, >80% of SPT patients experience long-term survival after surgery [71]. Infiltration into the surrounding pancreatic parenchyma, vascular or perineural invasion, increased mitosis, pleomorphic nuclei and necrosis are histopathological features associated with increased risk of recurrence [59, 77]. Chemotherapy has been reported to be useful in case reports in the setting of recurrent disease after surgery or in a neoadjuvant setting to downsize large tumours. There is no data to support the routine use of adjuvant chemotherapy even in high-risk tumours.

11.7 Cystic Pancreatic Endocrine Neoplasia (CPEN)

11.7.1 Incidence

CPENs occur in equal frequency in men and women and may be found anywhere within the pancreas. They are rare lesions, noted in middle-aged adults. In a

retrospective single-centre review from 1977 to 2006 [78], 29 patients (51% men, mean age 53) were found to have CPENs. They comprised 17% (29 of 170) of all pancreatic NETs and 5.4% of all resected CPLs (29 of 535) [78]. In another large series, CPENs accounted for 7% of resected pancreatic cysts (31/469) and 12% of resected pancreatic NETs (31/255). CPENs are primarily sporadic (94%), solitary (87%), non-functioning (100%) and incidentally discovered (68%) [78–80].

11.7.2 Pathogenesis

Whether they represent a unique tumour type or degeneration of solid tumours is debated. CPEN may also represent a possible de novo cyst formation [78, 79].

11.7.3 Clinical Features

In approximately one fourth of the times, there is an association between MEN syndrome and CPENs [81]. MEN-1 is 3.5 times more common in CPENs than in solid tumours (21% vs. 6%). When compared to solid pancreatic NETs, they are larger (49 mm versus 23.5 mm) and more likely to be non-functional (80% vs. 50%) [78]. Malignancy in non-functioning tumours is determined by local vascular and lymphatic invasion and presence of metastases; there are no predictive histological features [82]. When solid and CPENs were compared, no significant difference was found in location, metastasis, invasion or 5-year survival (87% versus 77%) [78].

11.7.4 Cross-Sectional Imaging

In contrast to solid pancreatic NETs, CPENs occur more frequently in the body and tail of the pancreas [80]. In the series by Bordeianou and colleagues, 10 (34%) were purely cystic, and 19 (66%) were partially cystic [78]. Radiologically, CPENs appear to have solid components (26%) which are hypervascular, with an irregular solid wall, and thick nodular septations (26%), and are round to oval shape, rather than being lobulated. Cyst wall enhancement or a characteristic hypervascular rim is seen in 45% of cases (Fig. 11.5a, b). [78, 79, 83].

11.7.5 EUS Findings

There are no reported ultrasound features that help to discriminate a cystic or necrotic endocrine tumours from other cystic or necrotic tumours of the pancreas. A correct diagnosis on cross-sectional imaging is possible only in a minority of patients (23%) [78]. EUS sampling can be helpful by demonstrating positivity for synaptophysin and chromogranin. Preoperative imaging and/or cytology suggested the diagnosis of CPEN in 61% [78, 79]. EUS-FNA has a 71% diagnostic yield for CPENs [84].

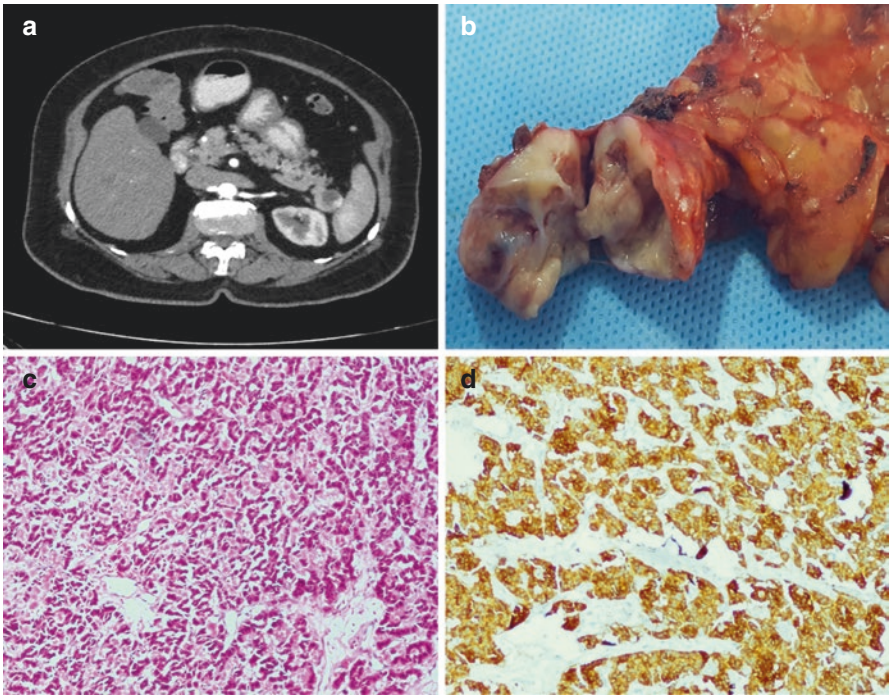

Fig. 11.5 (**a**) Multi-detector computed tomography image showing an exophytic lesion arising from the tail of the pancreas with solid and cystic components with enhancement in the arterial phase. (**b**) The cut section of the resected specimen clearly showing solid and cystic components. (**c**) Microscopic picture (haematoxylin and eosin) shows the characteristic small monotonous round cells arranged in cords (10×). (**d**) Immunohistochemistry (40×) showing diffuse synaptophysin positivity in tumour cells

11.7.6 Indications for Surgery

CPENs portend an 11–14% risk of malignancy and 8–14% risk of nodal or distant metastases, necessitating surgical resection as the only potential curative treatment [85]. Resection is recommended in all patients due to uncertain malignant potential.

11.7.7 Histopathology

CPENs display the characteristic monotonous round cells, rosette patterns and a unique pattern of nuclear chromatin when sampled in their solid areas (Fig. 11.5c). They typically express synaptophysin (100%) (Fig. 11.5d), chromogranin (82%), frequently pancreatic polypeptide (74%) and infrequently cytokeratin (CK)-19 (24%) [78]. Unlike SPT, CPENs stain negative for β-catenin.

11.7.8 Prognosis and Follow-Up

The 1-year survival after surgical resection is reported to be 97% and the 5-year survival 87% [78]. There is a statistically similar long-term outcome after resection of CPEN or other solid pancreatic NETs (5-year disease-free survival: CPEN, 100%, vs. NETs, 86%) [78, 79]. Lymphadenectomy may be beneficial due to uncertain malignant potential [86]. Response to chemotherapy consisting of streptozocin, doxorubicin and 5-flurouracil can be seen in about 40% of patients [87].

11.8 Lymphoepithelial Cyst

Lymphoepithelial cysts (LECs) are rare, non-malignant 'tumours' representing 0.5% of all CPLs, seen predominantly in elderly males [88]. Their pathogenesis is unclear although one theory suggests that LECs represent squamous metaplasia in epithelial inclusions in lymph nodes adjacent to the developing pancreatic anlage [89]. An alternative hypothesis suggests that these result due to fusion of branchial cleft cysts with the developing pancreas [90]. LECs often appear as exophytic cystic lesions (unilocular or multilocular) with enhancing walls on CT scan (Fig. 11.6) [91]. The high keratin in the cysts results in a hypointense signal on T2-weighted MRI images in contrast to other pancreatic cystic neoplasia (Fig. 11.6) [92]. On EUS, it appears heterogeneous (Fig. 11.6), and EUS-guided aspiration shows typical squamous cells and sheets of lymphocytes. Due to the high keratin and cholesterol content, the cyst fluid may appear amorphous, curd like or cheesy [93]. LECs are lined by keratinized stratified squamous epithelium, with subepithelial lymphoid tissue containing T lymphocytes. The architecture is quite similar to lymph nodes with the presence of a capsule, subcapsular sinus and germinal centre [59]. Presence of symptoms or uncertainty about diagnosis is the usual indications for surgery [93].

11.9 Acinar Cell Carcinoma

Cystic acinar cell carcinoma is a very rare epithelial neoplasm, accounting for only 1–2% of pancreatic exocrine neoplasia. The typical presentation is of abdominal pain or an abdominal mass that can be quite large [94]. Multicentricity is common. They are reported to be more frequently encountered in males [95]. These cystic tumours are believed to be formed by the accumulation of pancreatic enzyme secretions in the lumen of the tumour acini rather than as a result in cystic degeneration of a solid tumour. They consist of neoplastic cells which form acini and prominent lumens. The cysts often contain granules rich in pancreatic enzymes [58]. Unlike their solid counterparts, acinar cell cystadenocarcinomas are not associated with elevated serum lipase and do not usually cause the subcutaneous fat necrosis, polyarthralgias and blood eosinophilia [95]. Typical radiological findings consist of well-marginated lesions often with a necrotic centre. Histologically, acinar cell cystadenocarcinomas lack clear cells and mucinous

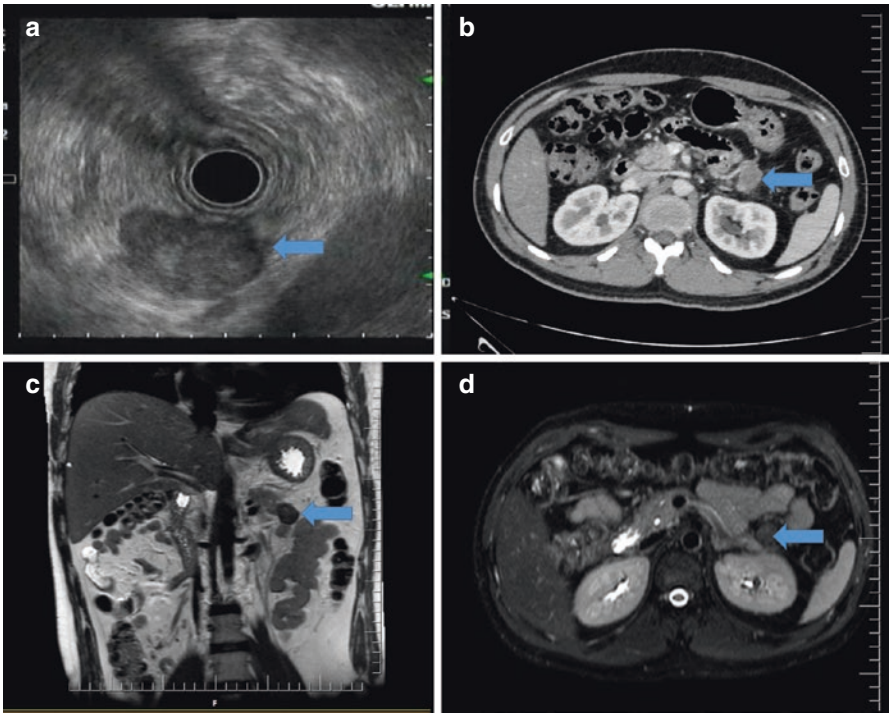

Fig. 11.6 (**a**) Multi-detector computed tomography image showing a heterogeneous exophytic lesion in the tail of the pancreas. (**b**) EUS showing a 2 cm exophytic cyst seen in the distal body of the pancreas with solid debris and hyperechoic contents. T2-weighted MRI in coronal (**c**) and axial section (**d**) showing the hypointense cyst suggesting thick contents. These findings are consistent with a lymphoepithelial cyst (depicted by the blue arrow)

cells, differentiating them from SCA and MCNs, respectively. Cytoplasmic granules are PAS positive and diastase resistant [59]. Expectedly, acinar cell markers such as trypsin, chymotrypsin and lipase are positive on immunohistochemistry [96]. While normal acinar cells do not express cytokeratin 7, tumour cells are positive for this marker [59]. Sometimes, acinar cell cystadenocarcinoma may show prominent intraductal growth and needs to be differentiated from intraductal tubular adenocarcinoma and IPMNs [12, 59]. It has a better prognosis than ductal adenocarcinoma but is still an aggressive disease with liver metastases developing early in its presentation [97].

11.10 Cystic Degeneration of a Pancreatic Adenocarcinoma

Adenocarinomas can undergo cystic degeneration in around 1–8% of cases [98]. Usually large poorly differentiated cancers outgrow their blood supply and undergo cystic degeneration. They appear as heterogeneous tumours with

areas of central necrosis. Diagnosis is usually confirmed by EUS-FNA. Prognosis and treatment follow the lines of management of pancreatic ductal adenocarcinoma.

11.11 Tubular Adenocarcinoma

This is a special variant of adenocarcinoma where the normal pancreatic acini are replaced by large tubular glands, giving it a cystic appearance on imaging. These tumours originate from the lining of the pancreatic duct and result in obstruction and dilatation of the duct [99]. They usually arise in the head of the pancreas; the mean age of presentation is 63 years, with a male to female ratio of 1.5 [100]. Due to their intraductal nature, they resemble IPMNs. On immunohistochemistry, tubular adenocarcinomas stain positive for MUC6, MUC5A, CK7 and CK19. MUC1 and MUC2 are negative except for scattered goblet cells. CK20 and CDX2 stain negative. Prognosis is usually favourable in the absence of invasive cancer due to the slow growth of tumour [59]. Treatment is surgical resection.

11.12 Cystic Metastases

Since they occur in the setting of advanced disease, they may be associated with liver metastases or multiple secondaries elsewhere. Although cystic metastases to the pancreas are most commonly seen with renal cell carcinoma and lung carcinoma, they may be encountered in bowel, breast and prostate cancer. Necrotic metastases occur most often in cases of aggressive tumours such as sarcomas, melanomas or ovarian carcinomas [83, 101]. Metastasectomy of pancreatic secondaries from renal cell carcinoma can result in long-term survival [102].

11.13 Pancreatoblastoma

It is the most common pancreatic tumour in children in their first 10 years of life. Despite this fact, pancreatoblastomas are rare neoplasms with only about 75 cases reported in literature [103]. Patients with Beckwith-Wiedemann syndrome can develop embryonal tumours such as pancreatoblastoma, hepatoblastoma, nephroblastoma and rhabdomyosarcoma [104]. Although most patients are asymptomatic at diagnosis, abdominal pain, anorexia, weight loss, fatigue, nausea or vomiting can be present.

On cross-sectional imaging, pancreatoblastomas exert mass effect; they compress but do not invade adjacent structures. The tumours are so large that in almost half the cases, it may be difficult to discern the organ of origin. Metastases to the liver and lymph nodes may be seen in more than one-third of the cases [105].

11.14 Lymphangioma

Lymphangioma of the pancreas is rare, with only around 60 cases reported in literature. Though congenital in origin, lymphangiomas may occur at any age; they are more common in women and are often localized to the distal pancreas [106]. The lesion can be cavernous or capillary and is composed of multiple spongy cystic spaces which appear bright on T2-weighted images. Microscopically, lymphangiomas comprise of cystic spaces filled with proteinaceous material, lined by endothelial cells, and are positive on immunohistochemistry for endothelial markers CD31, CD34 or D2-40 [107]. Resection is indicated only in symptomatic cases. Cyst fluid from a pancreatic lymphangioma has a characteristic chylous appearance, elevated triglyceride levels and numerous benign lymphocytes [108].

11.15 Other Miscellaneous Rare Tumours

Rarely parasitic cysts such as hydatid cysts may be seen although isolated occurrence in the pancreas is unusual. Enterogenic, retention cysts may also be encountered in the pancreas. Adenosquamous carcinoma and undifferentiated carcinoma with osteoclast-like giant cells are rare tumours that can present with haemorrhagic degeneration [62]. Other rare cystic neoplasias include cystic choriocarcinoma; mature cystic teratoma; pancreatic cystic hamartoma; pancreatic mesenchymal tumours like inflammatory myofibroblastic neoplasm, extra-gastrointestinal stromal neoplasm and solitary fibrous neoplasm; and schwannomas [62].

11.16 Approach to Cystic Pancreatic Lesions

While approaching CPLs, clinical symptoms and signs rarely will lead to a definitive diagnosis. Symptoms such as pain, weight loss or jaundice should alert the clinician to the presence of malignancy and lead to consideration of surgery [109]. Cross-sectional imaging (MDCT/MRI) invariably done as part of the evaluation and interpreted in the right clinical context will often point to the diagnosis. A practical approach is to first confirm that the lesion is located anatomically within, or arising from, the pancreas. This will exclude extrapancreatic lesions such as a retroperitoneal lymphangioma, mesenteric cyst, etc. The next step is to evaluate if the lesion is a pseudocyst or a cystic tumour.

11.16.1 Differentiating CPLs

A single pancreatic cyst of any size detected on cross-sectional imaging is certainly a challenging clinical problem; it could be a pseudocyst, an oligocystic SCA, MCN, branch-duct IPMN, SPT, CPEN or even cystic degeneration of a pancreatic ductal adenocarcinoma. A pseudocyst appears as a well-defined cystic lesion on

cross-sectional imaging with clear fluid, minimal or no debris and absent septae or mural nodules. Imaging features are diagnostic in the setting of a typical history of acute/chronic pancreatitis/trauma. EUS may demonstrate a communication with the pancreatic duct in about *two-thirds* of the cases. EUS-guided aspiration of the fluid will show very high levels of amylase. Once a pseudocyst is ruled out, another most common non-mucinous cystic tumour is a SCA. A lobulated lesion with multiple small cysts arranged around fibrous septa with central calcification in a lady over 60 years is typical of a SCA. SPT occurs in young women (~30 years), with areas of haemorrhage and necrosis. CPEN do not have specific diagnostic features but can demonstrate a capsule which enhances on the arterial phase in about half the patients. Rarely, an adenocarcinoma in the pancreas can undergo necrosis in part leading to cystic degeneration. When definitive diagnosis is not possible on cross-sectional imaging alone, EUS is indicated to enable further characterization and direct sampling that will help in diagnosis and management decisions. Laparoscopic ultrasound offers an advantage over EUS because there is no contamination of the aspirate with gastric or duodenal epithelial cells, which can result in a false-positive cytologic analysis for mucinous cystadenoma [110]. Although it has a potential to provide additional information based on imaging findings/fluid analysis/frozen section of cyst wall, it is always desirable to come to the operation theatre with a definitive plan aided by appropriate use of preoperative diagnostic modalities.

11.16.2 EUS Indications and Contraindications

If the CT clearly indicates a pseudocyst, SCA, SPT or main-duct IPMN, then EUS need not be performed for diagnosis. EUS-FNA is helpful when imaging findings are inconclusive where it helps in differentiating mucinous from non-mucinous tumours and in diagnosing CPEN and SPTs [111, 112]. EUS is indicated when the diagnosis is in doubt or if it is likely to provide additional information that will alter the management decision. For instance, if the imaging features are atypical or non-contributory (e.g. a unilocular cystic lesion), EUS and FNA can contribute towards a definitive diagnosis. If the patient is elderly, infirm and not a surgical candidate, then one may not want to pursue the diagnosis with EUS-FNA even if cross-sectional imaging is not diagnostic. EUS can also be used as a surveillance tool in lesions managed nonoperatively. A raised international normalized ratio (INR) > 1.5, partial thromboplastin time >50 s, platelet count <50,000/μL, acute pancreatitis and the presence of obvious infected necrosis are contraindications to EUS [113].

11.16.3 Comparison of EUS with Cross-Sectional Imaging

EUS offers the advantage of clarity due to proximity of the lesion. EUS is operator-dependent; however wall thickening, nodules and ductal communication can be reproducibly demonstrated. The morphological features that can be seen on CT or MRI can be seen on EUS. Cyst morphology on EUS has an overall accuracy of

50–73%. The sensitivity and specificity for EUS amount to 56–71% and 45–97%, respectively [114]. While evaluating morphological features, not all the nodules found are precancerous. For example, the nodules seen in lymphoepithelial cysts are keratinizing squamous pearls, and mucin globules account for a large percentage of nodules seen during imaging of IPMNs. On EUS, mucin globules are hypoechoic, have smooth edges and hyperechoic rims and move when patients are repositioned or during FNA. In demonstrating multifocal cystic lesions, EUS is superior to both CT and MRI [115, 116]. Overall, the increase in diagnostic yield of EUS and fluid analysis over CT and MRI for prediction of a neoplastic cyst was reported to be 36% and 54%, respectively [117]. When EUS was compared with MRI of the pancreas and MRCP in a prospective study, however, EUS and MRI were equivalent at detecting pancreatic cyst-main duct communications [118]. The need for surgical intervention based on the presence of malignancy cannot be accurately assessed by EUS [119].

11.16.4 Cyst Fluid Analysis for Tumour Markers

The ability to readily perform FNA is a huge advantage of EUS over other diagnostic modalities.

Cysts that are high in amylase (usually >5000) with no mucin or carcinoembryonic antigen (CEA) and negative cytology are likely to be pseudocysts. Cysts that have no mucin, low amylase (<250) and low CEA are likely to be SCA. Cysts high in mucin with high CEA and atypical or malignant cytology are likely to be MCNs [5]. Cyst fluid CEA is the single most important study to differentiate mucinous and non-mucinous lesions. A recent prospective, multicentre study of 112 cysts diagnosed by surgical resection or positive FNA found a CEA level of 192 ng/mL to be 84% accurate in differentiating mucinous from non-mucinous pancreatic cysts (sensitivity 75% and specificity 86%) [113].

In a systematic review of 450 patients from 12 studies, cyst fluid amylase <250 U/L was diagnostic of a serious or mucinous tumour as opposed to a pseudocyst with a sensitivity of 44% and specificity of 98%. A CEA of <5 ng/ml excluded a mucinous tumour with 50% sensitivity and 95% specificity, whereas a CEA > 800 g/ml had a sensitivity of 48% and specificity of 98% for diagnosing a mucinous neoplasm [113]. An amylase level of <250 and CEA >800 essentially excludes a pseudocyst. Likewise, a CEA <5 and CA19-9 <37 virtually excludes a mucinous cyst [48, 120, 121]. Other markers like carbohydrate antigen/CA 19-9, CA 242, etc. have been studied, but their utility is limited.

11.16.5 Cyst Fluid Cytology

Cytology has a sensitivity of 50–60% for the diagnosis of malignancy [122]. However the specificity and positive predictive value are over 90% [112]. When detection of high-grade atypical epithelial cells is included in the diagnostic criteria, the accuracy of cyst fluid analysis increases to 85% [123]. A recently published

meta-analysis, including a total of 18 retrospective and prospective studies, evaluated the accuracy of EUS-FNA for the diagnosis of pancreatic cystic neoplasia and found that cytology has a moderate pooled sensitivity of 54% and a high pooled specificity of 93% [124]. In differentiating histopathologically confirmed mucinous and non-mucinous cysts, EUS-FNA had a pooled specificity of 0.88 (95% CI 0.83–0.93); however the sensitivity was 0.63 (95% CI 0.56–0.70), resulting in a poor negative predictive value [124].

11.16.6 Cyst Fluid Analysis for Molecular Markers

Molecular and genetic markers have utility in the characterization and prognostication of CPLs. Most of these are useful in the setting of mucinous tumours. DNA markers and aneuploidy assessment have been reported to have very high sensitivity and specificity (both close to 95–100%) for SCA and SPT, while having a slightly wider range of both sensitivity and specificity (75–100%) for MCNs [125]. However these are yet to find wide clinical acceptance.

11.17 Management

While formulating a management plan for a CPL, it is imperative to arrive at a diagnosis based on clinical features, radiology, supplemented where needed with cyst fluid analysis and cytology. Once the diagnosis is clear, the further course of action would depend on the natural history of the lesion, its malignant potential and the performance status of the patient. Management of CPLs should ideally avoid unnecessary surgery for benign lesions while also considering the personal and financial costs of prolonged radiologic surveillance in young otherwise healthy patients with premalignant lesions [126]. An important caveat in applying management recommendations for CPLs is that most of the time they are based on the histopathological subtype of the tumour; this is seldom available preoperatively [21]. Most tests including EUS-FNA have high specificity and low sensitivity; hence they will more reliably minimize false-positive results.

An algorithm for the management of CPLs is provided in Fig. 11.7 based on current recommendations available in literature. Surveillance is justified when the patient is a potential surgical candidate and the lesion has uncertain malignant potential. No follow-up is required if the lesion is clearly benign and the patient is not a surgical candidate. This strategy applies to asymptomatic lesions as symptoms generally warrant intervention. In a clearly malignant lesion, surgery is indicated. In large series, the mortality from surgery is less than the risk of malignant transformation of the lesion, justifying the current treatment approach that is adopted in high-volume centres. The mortality associated with pancreaticoduodenectomy in high-volume centres is around 1–2%, while the risk of malignant transformation in lesions initially selected for observation is reported to be around 3% [127].

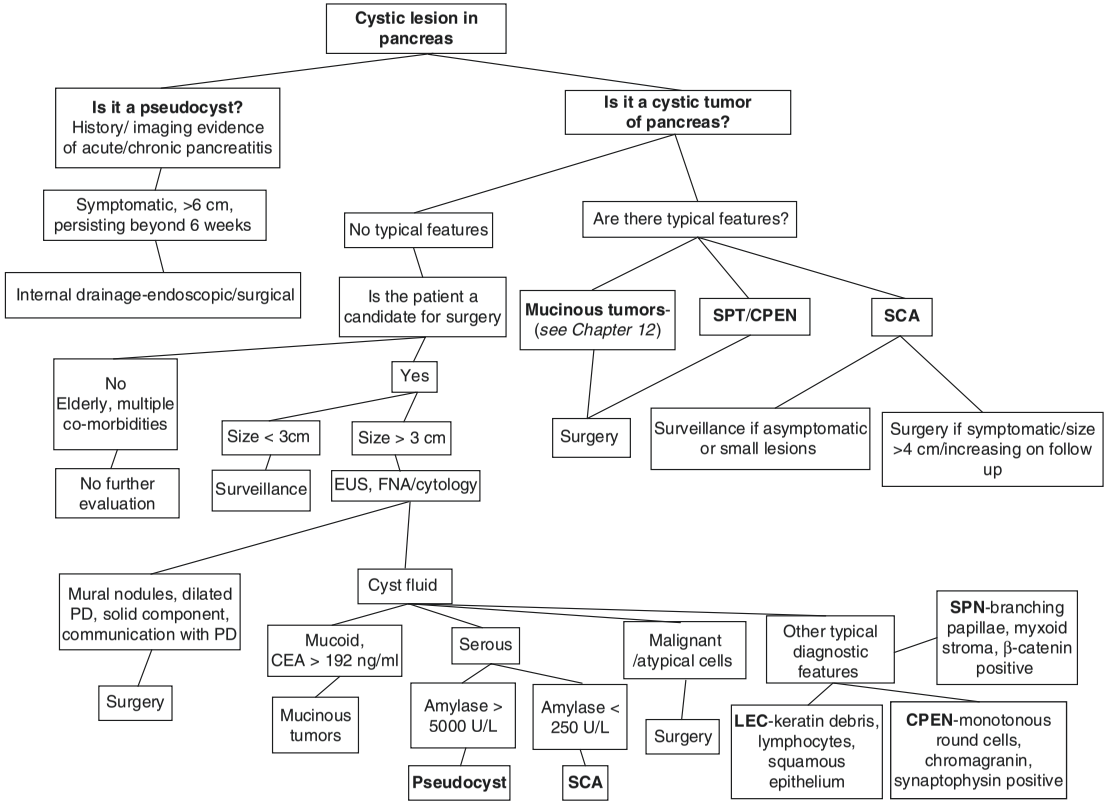

Fig. 11.7 Algorithm depicting management of a cystic pancreatic lesion detected on cross-sectional imaging. *GIST* gastrointestinal stromal tumour, *SCA* serous cystadenoma, *SPT* solid pseudopapillary tumour, *CPEN* cystic pancreatic endocrine neoplasm, *EUS* endoscopic ultrasound, *FNA* fine needle aspiration, *PD* pancreatic duct, *CEA* carcinoembryonic antigen, *LEC* lymphoepithelial cyst

Generally the type of surgery depends on the location of the tumours. Pancreaticoduodenectomy is performed for lesions in the head. For lesions in the body/tail, distal pancreatectomy is performed. Organ-preserving strategies are employed where feasible. For example, central pancreatectomy is a good option in tumours located in the neck. Spleen preservation can be done if there is no local infiltration. Enucleation is generally not a good option as it is associated with high rates of pancreatic fistula and is not recommended on oncological grounds. A formal lymphadenectomy may be required in cystic degeneration of adenocarcinoma and SPT and is not needed in SCA or CPENs. Laparoscopic pancreatic resections, especially for lesions requiring distal pancreatectomy, are becoming the standard of care.

Multidisciplinary input from pancreatic surgeons, gastroenterologists, radiologists and pathologists can help in formulating the appropriate treatment strategy for patients with a CPL. As this entity is increasingly encountered in day-to-day practice, especially in referral centres, having a predefined institutional protocol and care pathways facilitate patient management and data accrual for audit.

11.18 Future Directions

The following are foreseeable developments that might improve current understanding and management strategies for CPLs. (1) Improvements in cross-sectional imaging modalities that will allow non-invasive characterization of small cystic lesions that are incidentally detected. (2) Development of molecular markers that will be available for routine clinical practice at an affordable cost, sufficient sensitivity and specificity to characterize the malignant potential of indeterminate lesions. (3) The role of metabolomics and genetic testing needs to be better defined. (4) Confocal endomicroscopy in clinical practice is under investigation and definitively represents an area of future research [37].

11.19 Salient Points

- CPLs are detected increasingly due to frequent use of cross-sectional imaging.
- It is important to know salient imaging features to make a definitive diagnosis.
- EUS-FNA/cytology can help characterize indeterminate lesions.
- Molecular markers may help clarify preoperative diagnosis and help in better patient selection.
- Of the non-pseudocyst, non-mucinous tumours, SCA is benign, and SPT and CPEN have malignant potential; others are rare and have to be dealt on a patient-to-patient basis.
- Surgery has good results and is the treatment of choice in large (>3 cm)/symptomatic tumours, in those with malignant potential.

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Mucinous Tumours of the Pancreas

12

Rohith G. Rao, Priya Healey, and Christopher M. Halloran

Abbreviations

AJCC	American Joint Committee on Cancer
BD-IPMN	Branch-duct intraductal papillary mucinous neoplasm
CA 19-9	Carbohydrate antigen
CEA	Carcinoembryonic antigen
Cox2	Cyclooxygenase 2
DNA	Deoxyribonucleic acid
EUS	Endoscopic ultrasound
FNA	Fine needle aspiration
GNAS	Guanine nucleotide-binding protein, alpha stimulating
hTERT	Human telomerase reverse transcriptase
IAP	International Association of Pancreatology
IPMN	Intraductal papillary mucinous neoplasm
KRAS	Kirsten rat sarcoma viral oncogene
LKB1	Liver kinase B1
MCL	Mucinous cystic lesions
MCN	Mucinous cystic neoplasm

R. G. Rao, MB BS FRCS
Department of Clinical Cancer Medicine, University of Liverpool, Liverpool, UK

P. Healey, MB BS DMRD FRCR
Department of Radiology, Royal Liverpool University Hospital, Liverpool, UK

C. M. Halloran, BSc MB ChB MD FRCS (✉)
Department of Clinical Cancer Medicine, University of Liverpool, Liverpool, UK

Department of Pancreatobiliary Surgery, Royal Liverpool University Hospital, Liverpool, UK
e-mail: halloran@liverpool.ac.uk

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MD-IPMN	Main-duct intraductal papillary mucinous neoplasm
MDCT	Multi-detector computed tomography
MDT	Multidisciplinary team meeting
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MUC1	Mucin 1
MUC2	Mucin 2
MUC5AC	Oligomeric mucus/gel-forming
O.R.	Odds ratio
p53	Tumour protein p53
Pan IN	Pancreatic intraepithelial neoplasia
PDAC	Pancreatic ductal adenocarcinoma
PET-CT	Positron emission tomography-computed tomography
PJS	Peutz–Jeghers syndrome
PPV	Positive predictive value
SCA	Serous cystadenoma
Shah	Sonic hedgehog
STK11	Serine/threonine kinase 11
TNM	Union for International Cancer Control
USA	United States of America
WHO	World Health Organization

12.1 Introduction

Pancreatic cysts are increasingly diagnosed in patients undergoing cross-sectional imaging, with an estimated 2.6 cysts per 100 patients imaged annually [1–3]. At the outset, it is important to separate pancreatic cysts into those that have arisen following pancreatic inflammation (namely, pseudocysts, secondary to acute pancreatitis) from those which do not. These latter cysts are broadly separated into either serous cystic lesions or mucinous cystic lesions, although exceptions exist, such as cystic adenocarcinomas and cystic neuroendocrine tumours. Quality cross-sectional/interventional gastroenterology and review at regional multidisciplinary team meetings will aid identification. Mucinous cystic lesions (MCL) secrete fluid rich in mucin and are classified into mucinous cystic neoplasms (MCNs) or intraductal papillary mucinous neoplasms (IPMNs). Initially these were confused with each other until the 1996 World Health Organization (WHO) classification made a clear distinction between the two types [4]. Mucinous lesions have an increased risk of malignant potential and will be the focus of the rest of this chapter (Table 12.1).

Table 12.1 Salient features of mucinous cystic lesions

	MCN	IPMN
Age	Fourth and fifth decade	Sixth and seventh decade
Median age	45–48 years	65 years
Sex	Female (>95%) ≫ male	MD-IPMN: male = female BD-IPMN, ~55% female
Site	Body/tail 95%	50–70% in the head of the pancreas
Prevalence	1–2%	2.5%

12.2 Mucinous Cystic Neoplasm (MCN)

Compagno et al. first described MCN in 1978 in a case series [5]. It was observed these mucin-rich lesions were distinct from the glycogen-rich serous cystic lesions that ran an indolent course. These lesions were observed to occur commonly in women in their middle age and were symptomatic. They occurred more frequently in the distal pancreas with areas of calcification and sub-epithelial haemorrhage. Microscopically, MCN contained mucin-secreting columnar epithelium surrounded by ovarian type of stromal tissue with varying degrees of cellular dysplasia [5]. Work by *Zamboni* and colleagues in their series of 56 patients confirmed MCNs were lined by mucinous epithelium being supported by ovarian stroma and importantly lacked a communication with the pancreatic duct [6]. These findings were combined by the WHO (2000) update on histological classification of pancreatic exocrine tumours, which described MCN as epithelial neoplasms, lacking a communication with the pancreatic duct and containing ovarian stroma [7]. MCNs were further classified into adenoma, borderline (low-grade malignancy) and carcinoma (non-invasive or invasive). There are currently three main classification systems. The Japan Pancreas Society classification of MCN [8] is broadly similar to the WHO 2000 guidelines. The Armed Forces Institute of Pathology [9] classified MCN under four categories: MCN with low-grade dysplasia, MCN with moderate dysplasia, MCN with high-grade dysplasia (carcinoma in situ) and invasive mucinous cystadenocarcinoma. The most recent update from WHO 2013 [10] classifies MCN as:

- *MCN with low- or intermediate-grade dysplasia*—previously called mucinous cystadenoma
- *MCN with high grade of dysplasia*—previously called mucinous cystadenocarcinoma, non-invasive
- *MCN with an associated invasive carcinoma*—if there is a component of invasive carcinoma

The classification system advocated by WHO has been adopted by both the European consensus statement and the Fukuoka guidelines [11, 12].

12.2.1 Incidence

As incidental pancreatic cysts are often found following diagnostic cross-sectional imaging for a range of abdominal symptoms, it is difficult to know the true incidence in populations. Of patients who are diagnosed with pancreatic cysts, MCN is estimated to account for up to 10% of these. Furthermore, MCNs eventually account for approximately 1% of pancreatic cancers [13]. MCNs are commonly diagnosed in the fifth decade with mean age at diagnosis between 40 and 50 years [14]. Previously MCN was thought to affect only women; however recent studies are increasingly reporting the existence in men [15–17].

12.2.2 Pathology

MCNs present as solitary lesions and arise frequently in the body and tail of the pancreas [16–18]. Macroscopically, they can reach a large size, have a well-demarcated thick wall and often contain septations [19] (Figs. 12.1 and 12.2). Cysts normally contain mucin but occasionally have haemorrhagic fluid or necrotic material [19, 20]. By definition, they lack any communication with the main pancreatic duct (MPD), although large cysts can occasionally erode into the main pancreatic duct (MPD) resulting in a fistula, which can lead to diagnostic uncertainty [21]. On microscopy, they are lined by columnar epithelium that produce mucin and are surrounded by ovarian stroma. Although debated for many years, the 2000 update by WHO and the *Sendai* guidelines in 2006 [7, 22] underlined the presence of ovarian stroma for diagnostic confirmation. Ectopic ovarian stroma is thought to arise due to abnormal implantation of ovarian tissue on to the pancreas owing to their proximity in early stages of embryological development [14, 20, 23, 24].

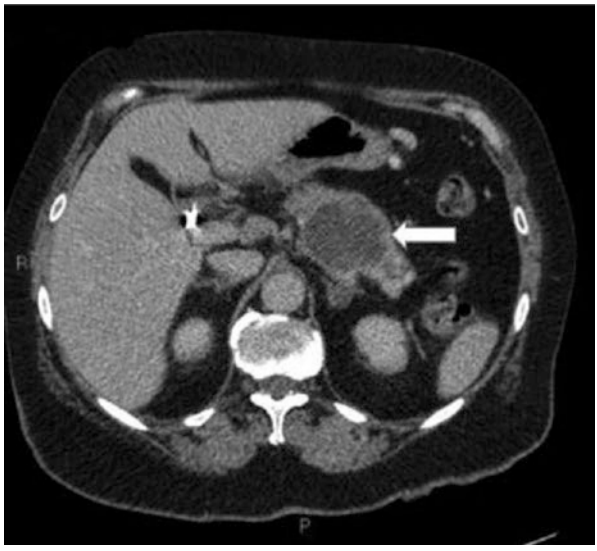

Fig. 12.1 Axial CT scan of a mucinous cystic neoplasm arising from *body of the pancreas* (white arrow)

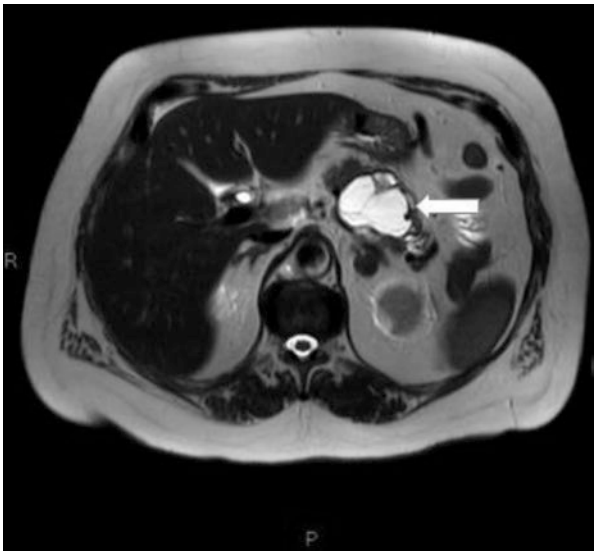

Fig. 12.2 Axial T2-weighted MRI image of the same patient with a mucinous cystic neoplasm arising from body of the pancreas demonstrating septations (white arrow)

12.2.3 Clinical Presentation

Surprisingly, for their position within the pancreas, a significant number of MCNs (up to 65%) are symptomatic at presentation, mostly with abdominal pain, epigastric heaviness, back pain, abdominal fullness or pancreatitis [14, 16, 20]. Occasionally, MCNs may occur within the head of the pancreas and present with jaundice [16]. MCN with neoplastic changes tend to be associated with weight loss, tiredness or diabetes mellitus [14, 20]. The remainder, which are not symptomatic, are diagnosed incidentally on radiological imaging for investigation of other symptoms [17, 20].

12.2.4 Malignant Potential (See Sect. 12.2.5 Also)

The natural history of MCN is unclear, with retrospective studies reporting widely differing prevalences of malignancy, some as high as 51% [20]. However, these earlier studies predated precise definitions of MCN and may have likely combined both MCN and IPMN in their reports. A modern retrospective study undertaken on behalf of the Japan Pancreas Society looked at 156 cases of resected MCN and noted the incidence of malignancy was around 4% (high-grade dysplasia and invasive carcinoma) [17]. However, this contrasted with other large studies that noted higher incidences of malignancy in MCN, notably a retrospective study by Crippa et al., which analysed data from 163 patients with resected MCN as defined by modern WHO criteria. Twelve percent of the specimens contained invasive cancer with 4.5% noted to have high-grade dysplasia (17.5% overall malignancy). However, it should be noted that the majority of cases demonstrated low-grade dysplasia (72%) only [14]. A subsequent meta-analysis by Testini and colleagues noted an

incidence of invasive carcinoma in MCN between 6% and 36% [20]. Another collaborative study from South Korea and the USA looked at 178 MCNs defined by WHO criteria and noted malignancy was present in nearly 24% of the cohort (16.3% invasive carcinoma and 7.3% high-grade dysplasia) [15]. A large multicentre study undertaken in the USA [16] looked at nearly 350 cases of resected MCN as defined by the 2000 WHO criteria and found the incidence of malignancy was approximately 15% (invasive carcinoma 12.6% and HGD 2.3%).

In summary, from the available data, the overall incidence of malignancy in MCN is estimated to vary between 10% and 39%.

12.2.5 Investigation

Specific protocols which utilise modern multi-detector computed tomography (MDCT) and/or magnetic resonance imaging (MRI) are required to confirm the diagnosis and to facilitate formal multidisciplinary team (MDT) discussion and the development of a management plan [25, 26]. MRI with a magnetic resonance cholangiopancreatography (MRCP) sequence can provide a more detailed evaluation of the MPD relationship [25] to the suspected MCN. Endoscopic ultrasound (EUS) is increasingly used to answer diagnostic dilemmas and can be extremely useful in aiding a diagnosis in pancreatic cystic lesions. EUS can identify features predictive of malignancy in MCN (septation, solid component, mural nodules) as well as obtaining fluid from cysts by fine needle aspiration (FNA), for histochemical analysis and measurement of tumour markers [20, 27]. In addition, malignant MCNs tended to contain peripheral calcification with thickened wall, papillary projections and a hyper-vascular pattern on cross-sectional imaging. The presence of a solid component, ductal obstruction or invasion outside the pancreatic margin on EUS was indicative of malignancy with 100% specificity. Testini and colleagues noted elevated levels of CEA >192 ng/ml in cyst fluid on EUS-FNA which was an accurate way of differentiating malignant MCN from non-malignant lesions [20]. Overall, EUS-FNA cytology combined with elevated CEA in cyst fluid has shown the highest accuracy in diagnosing malignant MCN [20, 28].

Testini and colleagues [20] noted from their meta-analysis that high values of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) in peripheral blood had a positive predictive value of between 70% and 100% for malignancy (invasive or preinvasive MCN) preoperatively. A multicentre study [15] looked at nearly 180 cases of resected MCN from South Korea and the USA. Sixty-four percent of patients with malignant MCN were noted to have elevated levels of CA 19-9 (>37 U/L) in their peripheral circulation during preoperative assessment. The size of the cyst (measured at pathological analysis) was also a predictive factor, as the majority of the malignant lesions were over 5 cm (mean size of cyst 9.4 cm). Although four of the MCNs measuring between 3 and 5 cm also harboured malignant change, no malignancy was detected in those MCNs under 3 cm. Presences of mural nodules in cysts were strongly associated with invasive carcinoma in MCN. In this study using a cut-off size of 1 cm for nodules, 23/29 cases with invasive

Table 12.2 Diagnostic markers which identify potential malignancy in mucinous cystic neoplasms

Markers of likely malignancy in MCN	
Serum tumour markers	CEA > 400 ng/mL, CA 19-9 > 37 U/L
Cyst fluid tumour markers	CEA > 192 ng/ml
Size	>5 cm
Radiological signs	Mural nodule, solid component, duct dilatation

carcinoma were noted to have mural nodules >1 cm [15]. Postlewait and colleagues [16] noted male sex, location of cysts (pancreatic head and neck), larger size of MCN, solid component or mural nodule and duct dilation were found to be risk factors of MCN undergoing malignant transformation, in their series of 350 cases. MCN occurring in men carried a higher risk of harbouring a malignancy as compared to women (29% vs. 8%). MCN occurring in the pancreatic head or neck, while uncommon sites, were also noted to have an increased risk of malignancy. Similarly, the presence of duct dilatation, mural nodule or solid component on radiological imaging were significant factors predictive of malignancy [16]. These findings are summarised in Table 12.2.

The role of the specialist MDT is crucial in decision-making and often will decide to intervene in patients with appropriate cross-sectional imaging without EUS ± FNA confirmation. The risks of EUS should not be underestimated, and the performance of an FNA can, on occasion, lead to tumour seeding in intervening organs (namely, the stomach). Thus, EUS should be considered an adjunct to diagnosis and not a prerequisite.

12.2.6 Treatment of MCN

Currently, consensus exists from all international guidelines [11, 12] that MCNs are best treated by resection, unless the patient is unfit for surgery, in which case surveillance could be offered [12]. Surgery would involve a radical left pancreatectomy (with splenectomy) and appropriate lymph node sampling (namely, station 8). Once resected, non-invasive MCNs are deemed curative with no reported recurrences and require no further surveillance. The Fukuoka guidelines [12] recommend a spleen or parenchyma-preserving procedure in MCNs smaller than 4 cm without mural nodules, as well as the use of laparoscopic procedures to resect these lesions.

However, recent observations have questioned these consensus statements: a retrospective study from Seoul [29], looking at their experience of 11 years, noted that the majority of resected MCN were benign. Only 10% of the cohort had high-grade dysplasia or invasive carcinoma with associated elevated CA 19-9 levels in serum. Although CA 19-9 levels >10,000 units/ml in cyst fluid separated malignant MCN from benign cases, it did not reach statistical significance. They concluded that in the absence of symptoms, MCN <3 cm without mural nodules or elevated serum tumour markers had a low prevalence of malignancy and these patients could be

entered into a surveillance programme. A study by Crippa and colleagues [14] noted only 52% of the lesions were in the tail of the pancreas and half of the patients undergoing resection lost a third of their parenchyma putting them at risk of pancreatic insufficiency. In their cohort, cysts >4 cm or the presence of mural nodules was predictive of malignancy. A large multicentre study from the USA noted prevalence of malignancy was 16% in their series of nearly 350 patients. In the absence of worrisome features, it concluded patients could be entered into radiological surveillance programme as not all patients with MCN warranted a resection [16].

In summary, all symptomatic MCNs or those with worrisome features on imaging should be considered for curative resection. However small (<3 cm) asymptomatic incidentally detected MCN could be managed in a surveillance programme after a detailed discussion with the patient. Laparoscopic and parenchymal sparing surgery should be considered in selected cases.

12.3 Intraductal Papillary Mucinous Neoplasms (IPMNs)

Ohashi et al. first reported four patients with pancreatic cancer that had a patulous ampulla with mucous secretion from a dilated MPD (Ohashi et al. 1982). Subsequent reports used a variety of names to describe these cases including intraductal mucin-producing tumour, mucinous ductal ectasia, mucin-hypersecreting neoplasm and intraductal mucin-hypersecreting neoplasm. The nomenclature 'intraductal papillary neoplasm' (IPMN) was first used by Morohoshi [30], after resected pancreas tissue, in six patients examined, and appeared to be nodular, thickened and hard in consistency with an ectatic pancreatic duct. Microscopically, these were found to contain friable intraductal masses secreting mucin with gross dilatation of the main pancreatic duct, but these masses did not seem to invade the pancreatic parenchyma or involve the regional lymph nodes. The masses appeared to be well-differentiated papillary or papillo-tubular cell types with foci of cellular atypia, carcinoma in situ or foci of branch-duct invasion. The group concluded that these lesions (IPMN) were an early stage of invasive adenocarcinoma with a good prognosis. The WHO introduced a terminology to include tumours of uncertain malignant potential [4]. Within this group, mucinous cystic tumour, intraductal papillary mucinous tumour and solid pseudopapillary tumour were included. IPMN was classified under borderline epithelial tumours in later editions [7].

12.3.1 Incidence

Patients with IPMN have a median age of diagnosis of 66 years [23]. While IPMNs of the MPD have no sexual predilection, branch-duct IPMNs are slightly more common in women (~55%) [12, 24]. The true incidence of cystic pancreatic lesions remains unknown, as most of these lesions are noticed incidentally on cross-sectional imaging for a variety of other reasons [31, 32]. Combined image-based studies (CT and MRI) have reported a prevalence for cystic lesions of 2.5%, with

studies involving just MRI scans reporting prevalence between 2% and 38% [23]. A single-centre study looking at CT scans conducted over a year for non-pancreatic symptoms found an incidence of 2.6 cysts per 100 individuals [31]. A county-based epidemiological study conducted in the USA looked at incidence of IPMN in the local population. This was found to be 2.04 per 100,000 person-years for the period of 1984–2005. The prevalence increased with age with most of the diagnoses found incidentally on CT scans [33]. Most recently, a retrospective study of US Surveillance, Epidemiology and End Results (SEER) programme involving over 2600 patients noted increasing incidence of all types of IPMN with reduced incidence of malignant IPMN [34]. Most of these reported studies have noted the incidence increases with advancing age [23, 24].

12.3.2 Classification

IPMNs are classified anatomically based on their site of origin. The 2006 consensus guideline (Sendai) working group of the International Association of Pancreatology (IAP) [22] classifies them into main-duct IPMN (MD-IPMN), if there was segmental or diffuse dilatation of the main pancreatic duct in the absence of distal ductal obstruction, or branch-duct IPMN (BD-IPMN) if there was a mucinous pancreatic cyst communicating with the pancreatic ductal system with an absence of main-duct dilatation. The revised 2012 IAP Fukuoka guidelines [12] (FCG) incorporated the mixed-type IPMN along with main duct and branch duct based on either imaging or histology or both. The definition of mixed-type IPMN requires an existence of lesions bearing features of both, main duct and branch duct, IPMNs. In addition, the Fukuoka guidelines also defined the upper limit of a 'normal' MPD to 5 mm, in the absence of obstruction. Also, all cysts >5 mm in diameter and communicating with main pancreatic duct were classified as BD-IPMN (Figs. 12.3, 12.4, and 12.5).

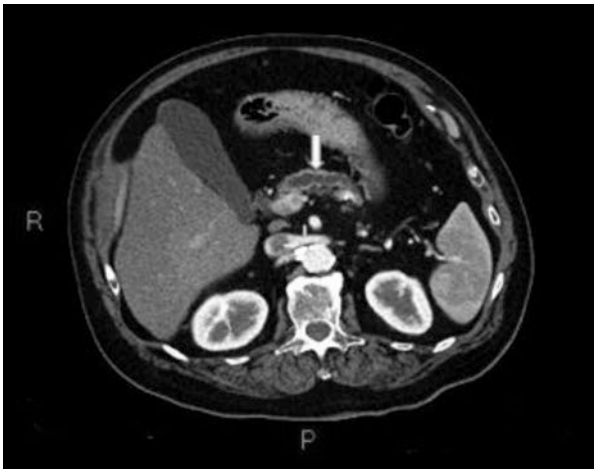

Fig. 12.3 Axial CT scan of a main-duct intraductal papillary neoplasm demonstrating a *dilated main pancreatic duct* (white arrow)

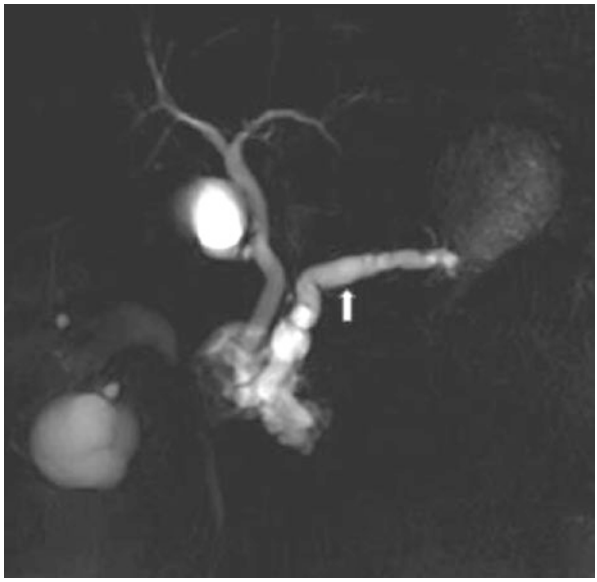

Fig. 12.4 Three-dimensional reconstruction of the pancreatobiliary tree of MRCP (T2) of main-duct intraductal papillary neoplasm demonstrating *dilated main pancreatic duct* (white arrow)

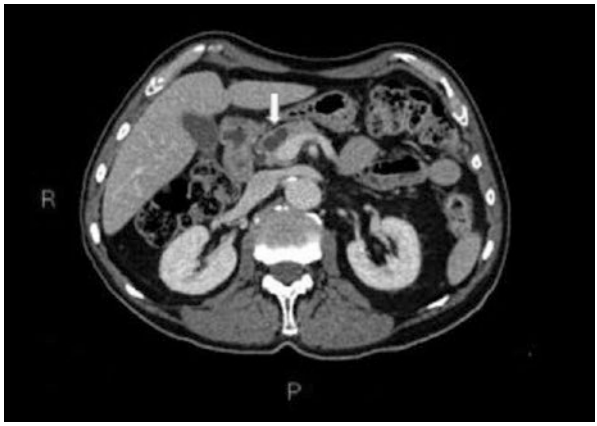

Fig. 12.5 Axial CT scan of a branch-duct intraductal papillary neoplasm arising from the *head of the pancreas* (white arrow)

12.3.3 Pathology

IPMNs account for up to 25% of all cystic lesions of the pancreas. They are exocrine lesions characterised by intraductal papillary growth of mucin-secreting epithelial cells in the MPD or its branches and hence were earlier labelled as 'mucin-producing pancreatic tumours'. Histologically, IPMNs are classified into gastric, intestinal, pancreatobiliary and oncocytic epithelial subtypes (Table 12.3). Furukawa and colleagues [35], based on an analysis of 283 resected IPMNs, described clinical, pathological and prognostic features with each subtype. IPMNs

Table 12.3 Histological subtypes of IPMN and their features

Subtype of IPMN	Features	5-year survival
Gastric type	Associated with BD-IPMN Non-invasive low-/moderate-grade neoplasms No invasion	>90%
Intestinal	Associated with MD-IPMN Invasive colloid carcinomas	>85%
Oncocytic	Affected significantly younger patients Invasive oncocytic carcinomas	>80%
Pancreatobiliary	More common in women, older age group Advanced disease (stage IIb)	>50%

of gastric type usually were associated with branch ducts, had low histological grade, lacked invasion and were associated with good survival; Kaplan–Meier survival rate at 10 years was 93.7% (95% CI 89.2–98.4%). Intestinal-type IPMNs involved the MPD predominantly and were associated with high-grade dysplasia or invasive colloid carcinoma. These intestinal IPMNs had a tendency for recurrence after resection and carried a worse prognosis; Kaplan–Meier survival rate at 5 years was 88.6% (95% CI 81.3–96.5%). Oncocytic type was noted commonly in younger people associated with a high histological grade of dysplasia but with minimal invasion. The survival for this subtype was comparable with the intestinal type: Kaplan–Meier survival rate at 5 years of 83.9% (95% CI 68.4–100%). Finally, the pancreatobiliary type was more common in older women, presented with high-grade dysplasia or invasive tubular carcinoma and carried the worst prognosis; Kaplan–Meier survival rate at 5 years of 52% (95% CI 29.8–90.9%) [35]. Thus, all IPMNs are dysplastic by definition, with the epithelial lining exhibiting varying degrees of dysplasia, before progressing to invasive carcinoma. IPMNs (regardless of their lineage) predominantly occur in the head, uncinate process or neck of the pancreas (>50%) [24, 36] but can occur anywhere in the substance of the gland. Most IPMNs tend to present as solitary lesions but can be multifocal in up to 40% of the cases. Various classification systems existed for IPMN, but the 2010 classification by WHO has been adopted by the 2012 Fukuoka consensus guidelines [36, 37]. By the WHO classification system, IPMNs are categorised as:

- IPMN with low-grade dysplasia
- IPMN with intermediate-grade dysplasia
- IPMN with high-grade dysplasia
- IPMN with invasive cancer

MD-IPMNs have been observed to uncommonly fistulate into adjacent organs like the duodenum, stomach, common bile duct, colon and small bowel. This could be due to malignant invasion of the tumour or mechanical pressure from the IPMN [38].

12.3.4 Malignant Potential

IPMN has an association with Peutz–Jeghers syndrome (PJS). There is evidence to support that the biallelic inactivation of the STK11/LKB1 gene (found in PJS) predisposes to malignant changes in IPMN [39, 40]. In addition, patients with a strong family history of pancreatic cancer (familial pancreatic cancer) are at risk of developing multiple BD-IPMNs as well as pancreatic cancer during surveillance period. Evidence from studies suggests that development of BD-IPMN in these, at risk, individuals may indicate underlying high-grade dysplasia or invasive cancer. Such patients should be recommended for a total pancreatectomy [37].

Overall, MD-IPMNs have the highest frequency of malignancy (23–57%) with lower figures for BD-IPMN (0–31%) [22]. There is evidence to suggest IPMNs are associated with higher incidences of both synchronous and metachronous extra-pancreatic malignancies [41, 42]. A clear aetiology does not exist to explain the development of these malignancies, and they may be due to increased radiological imaging as part of surveillance. Commonly associated extra-pancreatic malignancies include colon, stomach, oesophagus and lung cancer [41]. It is worthwhile noting that IPMNs are frequently diagnosed incidentally after radiological imaging and the extra-pancreatic pathology could have been the trigger factor for those symptoms.

12.3.5 Patient Presentation

Most IPMNs are diagnosed in the seventh decade of life with a reported mean age from 63 to 66 years. Common symptoms of presentation are epigastric pain, abdominal discomfort, nausea, vomiting, back ache and weight loss. Acute pancreatitis can be the presenting feature in up to 20% of IPMN as a result of ductal obstruction by thick mucin. IPMNs with invasive carcinoma often present with jaundice, weight loss and malaise [36, 40].

12.3.6 Diagnostic Markers

Serum CA19-9, a tumour-associated glycoprotein, is the only validated serum biomarker for pancreatic cancer in clinical practice. Currently it is used as an adjunct to diagnosis and to monitor patients for recurrence after surgical resection of the pancreatic tumour. It has a sensitivity and specificity approaching 80% for the diagnosis of pancreatic adenocarcinoma as noted in a recent study [43]. However, CA 19-9 may not be expressed in people who are Lewis antibody negative (although this view is still debated) and may be falsely elevated in benign conditions such as liver cirrhosis, pancreatic inflammation and biliary obstruction [44]. CEA is a cell surface glycoprotein and is elevated in serum of patients with gastrointestinal cancers. Approximately 60% of patients with pancreatic ductal adenocarcinoma (PDAC) have elevated levels of serum CEA, which, in conjunction with CA19-9, have been used to predict survival [45].

A study from Heidelberg has investigated the ability of serum CA19-9 (>37 units/ml) and CEA (>5 μg/l) to distinguish benign and malignant IPMN [45]. They looked at 142 patients who underwent resection of the pancreas for IPMN (37 low-grade dysplasia, 38 moderate-grade dysplasia, 17 high-grade dysplasia and 50 invasive ductal carcinoma in IPMN). The majority of these were of mixed type (52.8%), while the rest were branch duct or main duct (35.9% and 11.3%, respectively). In the invasive carcinoma group, 74% (37/50) had elevated serum CA19-9, and 40% (20/50) had elevated CEA. When both were used in conjunction, serum CA19-9 and CEA were elevated in 80% of the invasive carcinoma cohort compared with 18% of dysplastic group (low, moderate and high grade). A more recent meta-analysis evaluated serum biomarkers in being able to predict malignant transformation in IPMN. Serum CA19-9 was found to be significantly elevated in IPMN with invasive cancer but not in IPMN with high-grade dysplasia. Although it was highly specific, it lacked sensitivity to serve as a stand-alone test to achieve diagnosis [46].

Mutation of Kirsten rat sarcoma viral oncogene (KRAS) has been noted in over 90% of cases of PDAC and is one of the earliest mutations to occur [47]. Recent research has been directed to investigate whether mutations in KRAS play a role in malignant transformation of IPMN and whether it could be used to decide upon clinical management. A retrospective study [48], involving DNA extracted from surgically resected paraffin-embedded IPMN specimens, noted KRAS mutations (codon 12) in 47% of the cohort that was associated with malignancy (high-grade dysplasia or carcinoma) leading to the conclusion that IPMN could use alternate pathways to signal malignant transformation [48]. Nissim and colleagues undertook a meta-analysis looking at eight specific genetic markers in over 80 tissue samples [49] (mucin 1 [MUC1], mucin 2 [MUC2], oligomeric mucus/gel-forming [MUC5AC], KRAS, tumour protein p53 [p53], human telomerase reverse transcriptase [hTERT], cyclooxygenase 2 [Cox2] and sonic hedgehog [Shh]) and their association with malignant transformation in IPMN. Among these, MUC1 (O.R. 3.6), hTERT (O.R. 11.4) and Shh (O.R. 6.9) overexpression was strongly associated with malignant IPMN. However, analysis of 285 samples from 13 different studies did not show KRAS mutation to be as strongly associated with malignant IPMN (O.R. 2). A more recent meta-analysis [50] noted prevalence of KRAS mutation to be around 61% and 'guanine nucleotide-binding protein, alpha stimulating' (GNAS) mutation to be 56% in IPMN, respectively. The frequency of these mutations did not differ significantly across the three subtypes of IPMN dysplasia (low, intermediate and high grade) nor in the presence of invasive adenocarcinoma. Combined detection of KRAS and GNAS mutation served to distinguish IPMN from other cystic lesions of the pancreas but failed to demonstrate any association with malignant transformation within IPMN. This study highlights that KRAS mutation was more frequent in IPMN with low-grade dysplasia than malignant cases. Hence, KRAS could be used as a diagnostic biomarker to distinguish between IPMN and MCN in the case of diagnostic uncertainty, but not to predict malignant transformation in IPMN [50].

In summary, combining serum diagnostic markers appears to provide good sensitivity and specificity for identifying malignant transformation within IPMN. Although molecular markers can differentiate MCN from IPMN, there is

still uncertainty as to which single marker or combination of markers can determine which cysts are at risk of malignant progression versus those that are not.

12.3.7 Imaging

MDCT will offer detailed views of the surrounding anatomy, morphology of the cyst, its relation to the MPD and the presence of calcification [26], with an overall accuracy to differentiate malignant cystic lesions of the pancreas from benign cysts of 64–82% [51–53]. Although all these studies have looked at cystic lesions of the pancreas in general rather than specifically at IPMN, a pancreas protocol CT has been shown to have a high accuracy in identifying worrisome features in IPMN predictive of malignancy [26].

MRI with MRCP is being increasingly utilised to evaluate cystic lesions of the pancreas due to its excellent soft tissue and contrast resolution. It can analyse cystic lesions in detail and importantly demonstrate its relationship to the ductal system (which differentiates BD-IPMN from MCN) (Figs. 12.6 and 12.7). MRCP has an

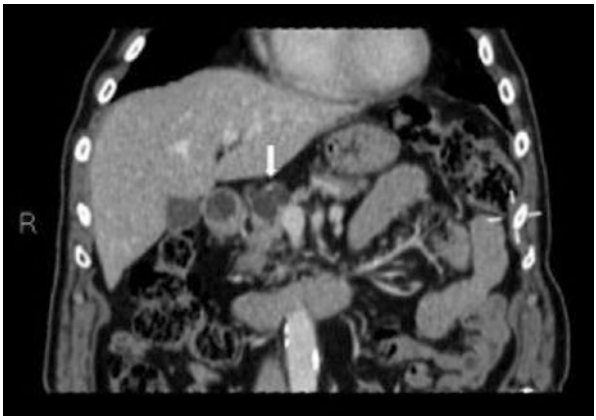

Fig. 12.6 Coronal CT scan of a branch-duct intraductal papillary neoplasm communicating to the main pancreatic duct in the *head of the pancreas* (white arrow)

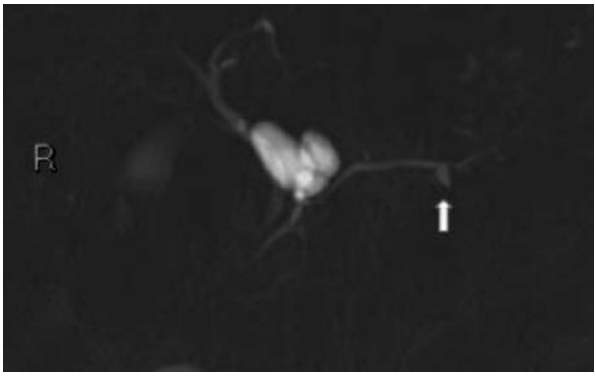

Fig. 12.7 Three-dimensional reconstruction of the pancreatobiliary tree of MRCP (T2) demonstrating branch-duct intraductal papillary neoplasm in the *tail of the pancreas* (white arrow)

advantage, providing that patients do not suffer from claustrophobia, as it does not expose them to ionising radiation, a fact to be considered when patients enter a surveillance pathway. The delineation of the pancreatic duct and side branches is increased by the administration of secretin. This enzyme stimulates the production of the pancreatic enzymes and increases the tone of the sphincter of Oddi, resulting in an increase in the calibre of the pancreatic duct. The increase in calibre can be seen by 1 min post administration of secretin by slow intravenous injection and reaches a maximum by 3–5 min, returning to normal by 5 min. Dynamic MRCP sequences are obtained every 30 s for 10 min postinjection. This transient increase in pancreatic duct diameter improves the depiction of the ductal anatomy and allows differentiation of a side-branch IPMN from a mucinous tumour with a high degree of accuracy [54].

Recent advances in MDCT that use very thin slices have put both CT and MRCP on par in terms of diagnostic accuracy [26]. Although a recent meta-analysis failed to identify an advantage of MDCT compared to MRCP in identifying predictors of malignant transformation in IPMN [46], it has shown the usefulness of positron emission tomography–computed tomography (PET-CT) in identifying malignant changes in IPMN. However, false-negative results with borderline lesions, false positivity in patients with previous attacks of pancreatitis or those who have undergone a biopsy are common [26]. The recently concluded PET-PANC trial [55] will confirm the value of PET scan imaging in IPMN.

EUS is increasingly used as an adjunct in diagnostic workup of IPMN and allows close visualisation of any 'worrisome features' within the cyst. In addition, it allows sampling of fluid for tumour markers and provides tissue for cytological, pathological or genetic analysis. It has been shown to accurately identify and quantify mural nodules, demonstrate thickened septa and depict the relation of IPMN to the pancreatic duct [56]. EUS has shown the highest accuracy in identifying malignant transformation within IPMN, especially in early pancreatic cancer where other radiological modalities have a diagnosis rate of <45% [56].

The 2012 Fukuoka guidelines [12] suggested all cysts >1 cm in diameter can be evaluated with either a pancreatic protocol CT or a gadolinium-enhanced MRI/MRCP. If frequent scans are to be undertaken as part of surveillance, then MRI (with an MRCP sequence) is recommended to minimise radiation exposure. If a cyst demonstrates any 'high-risk stigmata' (see Sect. 12.3.8) on either CT or MRI, the guidelines recommend resection without any further evaluation of IPMN. EUS evaluation was advised for smaller cysts with 'worrisome features' or cysts >3 cm with no 'worrisome features' (see Sect. 12.3.8). Recent studies have highlighted some limitations with the 2012 Fukuoka guidelines. A systematic review evaluated nearly 1400 patients with 2012 guidelines (FCG) and noted a positive predictive value (ppv) of 66% for the high-risk cohort; however, 10.5% (40/382) of malignant IPMN fell into the low-risk criteria. The authors felt that this finding was due to discordant results of a particular study and, when excluded, went down to 5.8% (14/241) [57].

12.3.8 Stigmata at Risk of Malignant Progression

The 2006 Sendai IAP guidelines [22] recommended resection of all MD-IPMN due to the risk of progression to invasive cancer. Although studies had noted that the presence of mural nodules and pancreatic duct dilatation >15 mm were significant predictors of malignancy, some cases with adenocarcinoma did not demonstrate either of these signs. For BD-IPMN in which the risk of malignant transformation is lower, resection was recommended for lesions >3 cm or for smaller BD-IPMN if they were found to have mural nodules, dilation of main pancreatic duct or abnormal cytology on sampling. Otherwise patients were offered surveillance either with CT or MRI scan [22].

The 2012 Fukuoka guidelines [12] made some revisions to the existing *Sendai* consensus guidelines. The classification system was expanded to include mixed-type IPMN alongside existing main-duct and branch-duct variety. All cystic lesions >1 cm were recommended for duct evaluation by CT or MRCP. To achieve a radiological diagnosis of MD-IPMN, the threshold calibre for a normal MPD was reduced from 10 mm to 5 mm in the absence of obstruction. This was felt to increase the sensitivity of achieving a radiological diagnosis without compromising specificity. MPD dilatation >10 mm, obstructive jaundice with a cystic lesion in the head of the pancreas, an enhancing solid component within a cyst and a main pancreatic duct dilatation >10 mm were considered 'high-risk stigmata', and these patients were recommended to undergo resection if surgically fit. MPD dilatation between 5 and 9 mm, cyst size equal or greater to 3 cm, cyst wall thickening or enhancement, presence of a non-enhancing mural nodule and sudden change in calibre of pancreatic duct with distal atrophy and lymphadenopathy were classified as 'worrisome features'. This latter group of patients was recommended to undergo further evaluation with EUS to identify mural nodules, define cyst relation to main pancreatic duct and obtain tissue for cytological analysis. In this group if there was an absence of any 'high-risk stigmata', further surveillance was recommended [12], summarised in Table 12.4.

Surveillance for IPMN with 'worrisome' features was defined including choice of imaging modalities. CT and MRCP were imaging modalities of choice for surveillance combined with clinical examination and measurement of serological biomarkers. Shorter intervals were required if there was a family history of PDAC or in patients with 'high-risk stigmata', who were not keen on surgery. The interval

Table 12.4 2012 IAP Fukuoka guidelines to classify IPMN [12]

Worrisome features (evaluate further)	High-risk stigmata (offer resection)
Main pancreatic duct 5–9 mm	Main pancreatic duct ≥10 mm
Non-enhancing mural nodules	Enhancing solid component in cyst
Abrupt change in calibre of main duct with atrophy of the distal pancreas	Jaundice in patient with cystic lesion in the head of the pancreas
Cyst size of ≥3 cm	
Cyst wall thickening and enhancement	

between scans could be extended if there were no change after 2 years, but a rapid increase in cyst size was a strong indication for resection. Patients with small 'simple' BD-IPMN were offered surveillance based on the size of the largest cyst.

In addition, these guidelines recommended the use of the term high-grade dysplasia instead of carcinoma in situ to describe neoplastic transformation as suggested by WHO. Staging of IPMN with invasive carcinoma was felt to be better served using AJCC (American Joint Committee on Cancer)/TNM (Union for International Cancer Control) [12] systems to bring about uniformity in reporting. It also stressed inclusion of histological subvariety of carcinomas (colloid vs. tubular) as it carried prognostic implications [12].

Controversially, there are further guidelines from the American Gastroenterological Association [58]. There is much debate over indications, contained within the three sets of published guidelines, regarding indications for high-risk IPMN. Although the Fukuoka and European guidelines are broadly similar [11, 12], there is concern that the AGA guidelines may put patients at risk by missing malignancy within lesions [59]. More concerningly, the AGA recommends that in the absence of change within a pancreatic cyst, patients can be discharged after 5 years of surveillance, irrespective of age. Practically, surveillance should continue up to the point that individuals are no longer deemed fit to undergo pancreatic surgery.

In summary, the Fukuoka guidelines, constructed by an international panel, provide the clearest guidance on diagnosis, surveillance and treatment of IPMN. Consequently, most pancreatic units base their IPMN management on this consensus view.

12.3.9 Treatment

MD-IPMNs are associated with a high incidence of malignancy. The Fukuoka working group [12] undertook a review of published evidence and concluded the mean frequency of malignancy was 61.6% with invasive malignancy in 43.1% of these IPMNs. In the absence of reliable factors to identify malignant transformation, it is strongly recommended that all suitably fit patients with a suspected MD-IPMN be offered surgical resection. It is worthwhile noting that the 5-year survival for MD-IPMN with invasive malignancy is between 31% and 54%. The European consensus statement [11] recommends resection of all main-duct and mixed-type IPMN, given the prevalence of malignancy in these subtypes of up to 60%. Right-sided resections are favoured initially, as extension of the resection margin to the left is technically easier [12]. Segmental resections require frozen section sampling of the transection margin, whereas a globally dilated MPD is best served by a total pancreatectomy.

BD-IPMNs have a lower rate of malignancy compared to MD-IPMN, with a mean frequency of malignancy between 15% and 25% and that of invasive cancer around 17.7%. *Fukuoka* guidelines [12] recommend surgery for patients with BD-IPMN in the presence of 'high-risk stigmata' as detailed in Table 12.4.

The European guidelines [11] recommend resection if BD-IPMNs are associated with mural nodules, MPD >6 mm diameter or the presence of specific symptoms—abdominal pain, pancreatitis, new-onset diabetes mellitus and jaundice. Rapidly increasing size of cyst >2 mm annually or elevated levels of CA 19-9 were relative indications to consider surgery. If no risk factors were present, BD-IPMN could be kept under surveillance until they reach a size of 4 cm, when resection would be offered to the individual [11]. Both European consensus statement and Fukuoka guidelines recommend that surgery is considered in a young patient (<65 years) without any risk factors due to cumulative risk of malignancy [11, 12].

Despite these recommendations there is considerable debate about the optimum management of BD-IPMN. A study from Heidelberg looked at their cohort of over 500 patients over an 8-year period and recommended all BD-IPMN should be resected [60]. Histopathological analysis of resected specimens noted 67 cases misdiagnosed as BD-IPMN had in fact involvement of the main duct. Reviewing BD-IPMN without any risk factors, malignancy (high-grade dysplasia or adenocarcinoma) was noted in 18% (26/141) of cases. Specifically, small sub-centimetre BD-IPMN, which would be classified as low risk, had a 34% rate of malignancy (high-grade dysplasia or adenocarcinoma) on histopathological analysis, and the authors felt the size of the cyst did not correlate with risk of malignancy.

In summary, the management pathway for MD-IPMN and mixed type is well defined with resection being offered to all surgically fit patients. Controversy exists for the management of lower-risk BD-IPMN as there is no single test that can reliably predict malignant transformation with the possibility of a MD-IPMN being misdiagnosed as a branch-duct variety. Given the cumulative risk of malignancy, a personalised tailored approach should be formulated after an honest discussion with the patient.

12.3.10 Follow-Up

Recurrence of IPMN in the post-operative setting has been reported in the literature with estimates as high as 20% [11, 12]. Debate exists about the true recurrence, as a dilated MPD could be secondary to an anastomotic stricture. European expert's consensus statement recommends an annual follow-up with preferable imaging by EUS or MRI for non-invasive IPMN. All invasive IPMNs are to be considered as pancreatic cancer and followed up as per appropriate guidelines [11]. The Fukuoka guidelines divide IPMN into three groups based on their resection margin histology. Normal or non-dysplastic pancreatic tissue (PanIN1A/PanIN1B) in resection margin is recommended a follow-up at 2 and 5 years for recurrence. Dysplasia in resection margin (low, moderate and high grade) is advised to undergo six monthly follow-ups with MRCP. The presence of adenocarcinoma mandates management and follow-up as a PDAC [12], which, paradoxically, in most healthcare systems, is less than that recommended for non-invasive IPMN.

12.4 Conclusion

Our understanding of pancreatic cysts has increased in the last few decades. Consensus statements notably the *Sendai* and *Fukuoka* guidelines have greatly improved standardisation of diagnosis, imaging and treatment of mucinous cystic lesions. All symptomatic MCNs or those with worrisome features on imaging should be considered for curative resection. The role of surveillance for MCN < 3 cm or the role of parenchyma-sparing surgery is not yet fully established and should only be considered in carefully selected patients. Main pancreatic duct IPMN, mixed-duct IPMN or BD-IPMN with high-risk features should be primarily treated by resection. Surveillance can be undertaken in IPMNs that have been assessed and do not show either worrisome or high-risk features and is based on the size of the largest cyst. Follow-up should be for as long as patients are fit enough to undergo resection.

12.5 Future Directions

Both serum and cyst biomarker research will be central to elucidating the invasive potential of MCN and BD-IPMN. Randomised trials of modern CT vs. MRI (MRCP) need to be undertaken to determine the optimum method of cross-sectional diagnosis. The role of PET-CT is up and coming in the diagnosis of invasive IPMN and may usurp other modalities. Endoscopic techniques such as needle-based confocal laser endo-microscopy hold significant promise but need to be carefully evaluated in multicentre clinical trials.

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Pancreatic Neuroendocrine Tumours

13

Domenico Tamburrino, Stefano Partelli, and Massimo Falconi

13.1 Introduction

Neuroendocrine tumours (NETs) are neoplasia that can exhibit a range of features such as the production of neuropeptides, the presence of large dense-core secretory vesicles, and the lack of neural structures [1–3]. NETs can be found in many body regions including the head, neck, lungs, and abdomen. Gastroenteropancreatic (GEP) NETs can be functioning or nonfunctioning, depending on whether hormones are secreted [4]. While the majority of NETs are sporadic, a smaller portion can be related to genetic syndromes such as multiple endocrine neoplasia (MEN), von Hippel-Lindau (VHL), and neurofibromatosis (NF). Compared with their epithelial counterparts, NETs have usually better outcomes [5]. Surgical resections, ranging from enucleation to standard pancreatectomy and lymphadenectomy, play a key role in the management of these lesions, even in advanced disease. Long-term outcomes are correlated with the grading of the disease. Among GEP-NETs, small intestinal NETs (Si-NETs) have a higher incidence than pancreatic neuroendocrine tumours (PanNETs) [6]. This chapter focuses on epidemiological, clinical, and pathological aspects of PanNETs emphasizing the role of surgery in these tumours.

13.2 Epidemiology and Risk Factors of PanNETs

PanNETs are rare tumours that account for <3% of all pancreatic neoplasms [7–9]. Autopsy studies have indicated that these tumours are much more common, ranging from 0.8% to 10% in patients undergoing post-mortem examination [10, 11]. The

D. Tamburrino · S. Partelli · M. Falconi (✉)
Pancreatic Surgery Unit, Pancreas Translational and Clinical Research Centre, San Raffaele Scientific Institute, 'Vita-Salute' University, Milan, Italy
e-mail: falconi.massimo@hsr.it

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incidence of PanNETs in the United States has been estimated to be 0.4 per 100,000 inhabitants per year with a prevalence of approximately 25–30 per 100,000 inhabitants. In the last two decades, the apparent incidence of PanNETs has dramatically increased by 710% due to the widespread use of cross-sectional imaging techniques [8, 12]. Some risk factors associated with PanNETs have been investigated although they remain largely unknown. A history of diabetes and a first-degree family history of cancer seem to be associated with an increased risk of developing PanNETs, while a possible role of alcohol abuse and smoking has been suggested, but these remain unproven [13–16].

13.3 Pathology and Pathophysiology

PanNETs are usually classified as functioning (F-PanNETs) or nonfunctioning (NF-PanNETs) based on the presence or absence of a clinical syndrome associated with hormone hypersecretion. Most PanNETs express neuroendocrine markers, such as synaptophysin, neuron-specific enolase (NSE), and chromogranin A (CgA).

Molecular alterations and overexpression of different types of genes have been implicated in the pathogenesis of PanNETs [17]. Several of these genetic alterations, such as mutations in death domain-associated protein gene (DAXX) or ATR-X gene (ATRX), have been detected in 40% of PanNETs [18]. Loss of DAXX or ATRX seems to correlate with shorter survival [19]. PanNETs exhibit a wide range of biological behaviour and associated prognosis. PanNETs have usually a more indolent behaviour compared with pancreatic adenocarcinoma, although 60–70% of patients have metastatic disease [8, 20, 21]. In 2010, the World Health Organization (WHO) proposed a classification of PanNETs that reflects a proliferation-based grading system in conjunction with the traditional histopathologic diagnostic criteria [22]. A three-tier grading system designating tumours as well-differentiated PanNETs or poorly differentiated neuroendocrine carcinomas (PanNECs) has been proposed. Well-differentiated PanNETs are further divided into grade 1 (Ki-67 < 2%) and grade 2 (Ki-67 of 2–19%), whereas PanNECs are classified as grade 3 (Ki-67 ≥ 20). Recently the WHO has updated the classification of PanNETs, and the new grading system will be published soon by Kloppel et al. In the revised classification, grade 1 will include Ki-67 < 3% and grade 2 a Ki-67 of 3–20%, and PanNECs will include a Ki-67 > 20%. The European Neuroendocrine Tumor Society (ENETS) and the American Joint Committee on Cancer (AJCC) proposed two different TNM staging systems for PanNETs [23]. These two systems differ as regards the definition of pT3 and pT4. The AJCC classification distinguishes pT3 from pT4 by the recognition of major vascular invasion, whereas the ENETS classification is based on tumour size. Several authors have shown the superiority of the ENETS classification compared with UICC/AJCC/WHO 2010 TNM in predicting survival [24, 25].

13.4 Classification and Clinical Presentation

Functioning PanNETs (F-PanNETs) are associated with hormone hypersecretion, such as gastrin, insulin, and glucagon. Among F-PanNETs, 30–50% are insulin-producing PanNETs (insulinomas), which cause hypoglycaemia that is typically reversible with glucose administration. Hypoglycaemia can be diagnosed by 'Whipple's triad' which consists of (1) symptoms consistent with hypoglycaemia, (2) a low plasma glucose concentration measured by an accurate method, and (3) relief of the symptoms when the plasma glucose level is raised [26, 27]. Gastrin-producing tumours (gastrinomas) constitute 20–40% of F-PanNETs. Gastrinoma is associated with Zollinger-Ellison syndrome which typically includes refractory peptic ulceration(s) and secretory diarrhoea [28]. Other rare F-PanNETs include VIPomas and glucagonomas. VIPomas secrete *vasoactive intestinal polypeptide* (VIP) and cause watery diarrhoea, hypokalaemia, and achlorhydria (WDHA syndrome or Verner-Morrison syndrome) [29]. The most common presentation of glucagonomas is a dermatitis known as necrolytic migratory erythema. Sometimes called the '4Ds' syndrome, glucagonomas can also be associated with diabetes, depression, and deep venous thrombosis [30]. Less than 5% of PanNETs are somatostatinomas that often produce several nonspecific and seemingly unrelated symptoms including steatorrhoea (or diarrhoea), recent-onset diabetes mellitus, cholelithiasis, anaemia, weight loss, and features of hypochlorhydria, known as 'somatostatinoma syndrome' [31].

The majority of patients with localized nonfunctioning PanNETs (NF-PanNETs) are diagnosed incidentally [8, 9, 12]. The clinical presentation of NF-PanNETs is usually related to their location and a mass effect due to their size [32]. When large PanNETs are located in the head of the pancreas, the most frequent presenting symptoms are jaundice, abdominal pain, vomiting, and weight loss [33].

Although most PanNETs occur sporadically, nearly 10% of them are associated with genetic syndromes. These hereditary syndromes include type 1 MEN (MEN1), VHL, type 1 NF (NF-1), and tuberous sclerosis complex (TSC) [34]. These patients are usually younger with a family history of endocrine disorders. The combination of primary hyperparathyroidism, pancreatic islet cell tumours, and anterior pituitary tumours is a characteristic of MEN1. In patients with MEN1 these tumours are most often NF-PanNETs (30–80%), gastrinomas (50%), and insulinomas (18%) [35].

13.5 Preoperative Imaging and Staging

High-quality cross-sectional imaging, such as computed tomography (CT) and magnetic resonance (MR) scan, is routinely used in the staging of PanNETs. Both techniques have high sensitivity in the detection of pancreatic lesions and liver metastases. Usually, PanNETs present as a hypervascularized mass on arterial phase CT scan (Fig. 13.1) with a high signal intensity on T2-weighted images on MR. MR

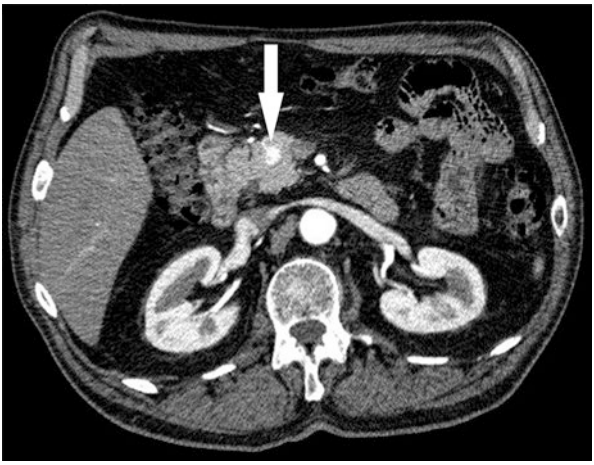

Fig. 13.1 Multidetector computed tomography axial section in arterial phase demonstrating hypervascular NF-PanNET lesion in pancreatic head (marked by a white arrow)

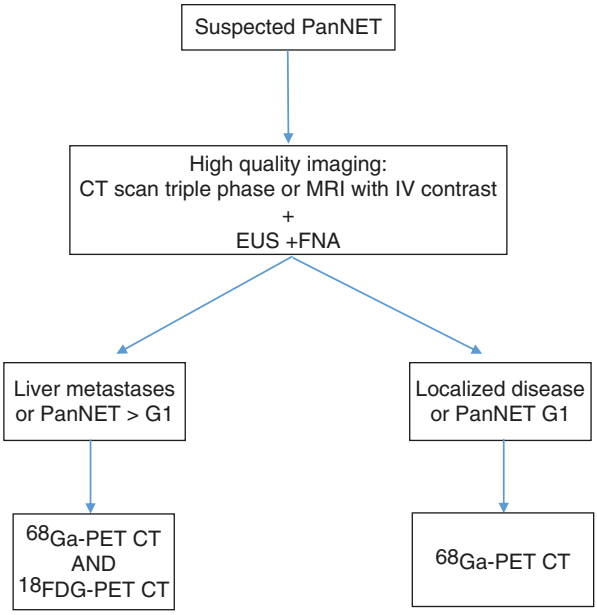

Fig. 13.2 Flow chart depicting the algorithm for the preoperative assessment of patients with suspected PanNET

has a greater sensitivity compared with CT scan in the detection of liver metastases [36]. Endoscopic ultrasound (EUS) is helpful in the assessment of vascular involvement, and it is essential for the achievement of a certain diagnosis with fine-needle aspiration (FNA) or biopsy (FNB) [37, 38]. Along with cross-sectional and endoscopic imaging modalities, 68-gallium-positron emission tomography CT (^{68}Ga-PET CT) is routinely performed in patients with PanNETs in our institution. ^{68}Ga-PET CT can guarantee the highest accuracy in detecting the primary PanNETs and possible distant metastases [39]. In particular, ^{68}Ga-PET CT is extremely accurate for

low- and intermediate-grade PanNETs, whereas 18-fludeoxyglucose (^{18}FDG) CT is more accurate for high-grade PanNET/Cs [39–41]. The combination of morphological and functional imaging techniques, with FNA or FNB, can currently identify with high accuracy the tumour grading before surgery and facilitates a more tailored treatment strategy [42–44]. In our experience, the preoperative assessment of patients with suspected PanNETs includes high-quality imaging (CT or MRI) followed by EUS+FNA and ^{68}Ga-PET CT. In selected patients, usually with advanced and/or suspected metastatic disease, a combined ^{68}Ga-PET CT and ^{18}FDG-PET CT can be helpful in choosing the best treatment strategy (Fig. 13.2).

13.6 Treatment of PanNETs

13.6.1 Functioning PanNETs: Insulinomas

Insulinomas are the most common functioning PanNETs. They usually present as a small, well-demarcated, solitary nodule that may arise in any part of the gland [45]. Most insulinomas are low-grade tumours, and for this reason enucleation and/or parenchyma-sparing procedures (PSP), such as middle pancreatectomy (MP), could be considered as curative treatment, with a 5-year disease-free survival (DFS) rate of 100% [46].

13.6.2 Nonfunctioning PanNETs in the Setting of Localized Disease

Along with incidental diagnosis [46], tumour size and tumour grading are the most powerful predictors of long-term survival and recurrence [47–50]. Based on this data, the ENETS guidelines suggested active surveillance rather than surgery for patients with incidental NF-PanNETs that are <2 cm [51]. A recent systematic review demonstrated that surveillance of asymptomatic small NF-PanNETs is safe at least in selected patients although the quality of available studies is still too low to draw firm conclusions [52].

Regardless the size of the primary tumour and the absence of symptoms, a G2 or G3 PanNET/Cs should be treated with resection. Surgery still remains the gold standard in patients with NF-PanNET >2 cm. The type of resection depends on the location of the lesion. In the presence of head lesions, Whipple's procedure is the treatment of choice, while distal pancreatectomy and splenectomy is recommended in body-tail lesions. Regardless the type of surgery, a standard lymphadenectomy should be performed. The role of lymphadenectomy during surgical resection for PanNETs is still unclear; however, several authors have shown that the presence of lymph node metastases is associated with poor prognosis; therefore, lymphadenectomy is very helpful in the staging of the disease, but there is no evidence to support an extended lymphadenectomy. The risk of lymph node metastases increases with the increasing size of the primary lesion. Therefore, a standard lymphadenectomy,

which consists of peripancreatic lymph node dissection along major pancreatic vessels, should always be performed [53–55]. Recent evidence on the role of conservative management of small PanNETs and the risk of node involvement in PanNETs >2 cm have now significantly limited the role of PSP in NF-PanNETs. These procedures that include enucleation and MP are now limited to patients with small, asymptomatic PanNETs in whom a conservative approach is contraindicated because of young age or for patient's willingness. Despite a clear benefit in terms of long-term risk of developing pancreatic insufficiency, PSP has a similar morbidity and mortality to standard pancreatic resections [56, 57].

13.6.3 Nonfunctioning PanNETs in the Setting of Locally Advanced and Metastatic Disease

Before planning a possible surgical strategy in the presence of advanced PanNETs, tumour biology and grading should be taken into account. In G1-G2 PanNETs with nearby organ or vascular invasion, an aggressive surgical approach is associated with a survival benefit [58]. As demonstrated by several authors, a tumour-free resection margin (R0 resection) is of paramount importance for achieving a good long-term survival [59, 60].

The majority of patients have liver metastases (LMs) at the time of diagnosis (Fig. 13.3) [21, 61]. Surgery is indicated in patients with LMs in the presence of resectable primary tumour, with G1-G2 grading, estimated mortality rate <5%, absence of peritoneal deposits, or extra-abdominal disease [61]. The type of resection should take into account the number of liver lesions along with patient conditions and liver remnant. If the criteria are met, ENETS guidelines suggest a therapeutic algorithm based on LMs distribution [61]. A curative surgical resection

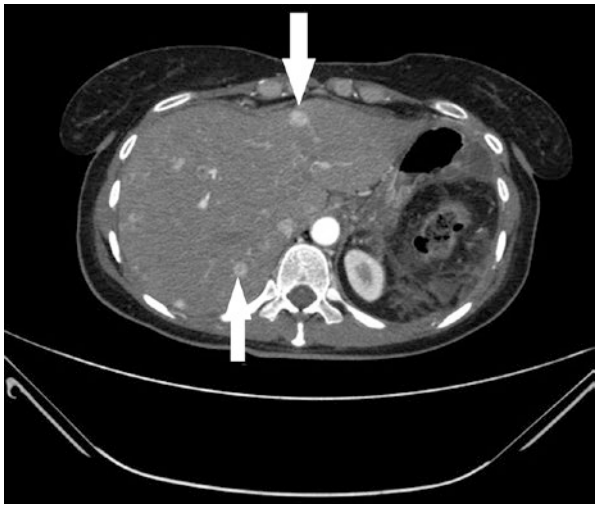

Fig. 13.3 Multidetector computed tomography axial section demonstrating hypervascular NF-bilobar liver metastases from PanNET (marked by white arrows)

should always be attempted in the presence of resectable liver metastases. In the presence of potentially resectable disease, a two-step approach including embolization of portal vein or ALPPS (two-stage hepatectomies associated with liver partition to portal vein ligation) represents valid options [62, 63].

The resection of primary tumour or debulking surgery in patients with unresectable liver metastases is still under debate. Although several studies demonstrated an advantage in terms of survival in patients with primary tumour resection, firm recommendations cannot be made due to the poor quality and the retrospective design of these studies [64, 65]. However, because PanNETs are associated with a prolonged life expectancy also when LMs are present, resection of primary tumour may be helpful for symptom control and life-threatening complications.

13.6.4 Liver Transplantation

Liver transplantation (LT) has been performed for symptom control, potential for cure, and removal of tumour burden. Specific criteria for LT for NET with unresectable LMs have been proposed including a Ki-67 <5%, portosystemic tumour drainage, age <55 years, stable disease in the previous 6 months, pre-transplant R0 resection, liver involvement <50% of total liver volume, and absence of extrahepatic disease [66]. The correct timing of transplantation (e.g. whether stable disease needs to be observed for a certain amount of time) and selection criteria, including the development of patient-specific biomarkers for the identification of those who gain a long-term benefit from the procedure, still remain debated. Liver transplantation for metastatic NETs under restrictive criteria can guarantee a good long-term outcome. The selection of patients should take into account the predictors of poor outcome such as hepatomegaly, age more than 45 years, and any amount of resection concurrent with LT [67]. Well-planned management based on a good patient selection can achieve a 5-year OS between 60% and 80% and a 10-year survival of 97% and 89% [67, 68].

13.6.5 Surgery for PanNETs in MEN1 Syndrome

The indication for surgery is mainly based on primary tumour size. Patients with lesions >2 cm are exposed to a higher risk of malignancy [69, 70]. In this setting, surgery remains the treatment of choice in MEN1 patients with NF-PanNETs >2 cm [51]. Regarding the management of patients with NF-PanNETs ≤2 cm, several authors have shown that these neoplasms are usually indolent with a negligible oncological risk. For this reason surgical treatment of these tumours at initial diagnosis is rarely justified in favour of a ‘wait and see’ attitude [51, 71, 72].

Gastrinomas are often associated with MEN1 syndrome [73]. The risk of LM is related to the size of primary lesion, and for this reason surgical resection is always recommended if the biochemical diagnosis is unequivocal and in the presence of lesion >1 cm [70, 74].

The appropriate resection of MEN1-associated gastrinomas is still a matter of debate. Thompson et al. [75] proposed a simple enucleation of duodenal gastrinomas, through a longitudinal duodenotomy associated with lymphadenectomy along the hepatic artery and the peripancreatic area and the body-tail pancreatic resection (Thompson's procedure). The advantage of this procedure is to preserve the head of the pancreas, avoiding a pancreaticoduodenectomy that is associated with higher morbidity and mortality. On the other hand, several authors suggest pancreaticoduodenectomy as the first-line procedure for duodenal gastrinoma in MEN1 [70, 76, 77]. In our institution, we strongly support this approach for two reasons. First, approximately 90% of MEN1 gastrinomas arise in the duodenum, and proliferative gastrin cells in the normal duodenal mucosa are the precursors of these tumours. Second, pancreaticoduodenectomy allows radical treatment of the peripancreatic nodal lesions that are involved in the vast majority of cases, and it includes a complete clearance of the so-called gastrinoma triangle [77].

13.7 Future Directions

The incidence of PanNETs is increasing markedly, and for this reason the surgical treatment of these neoplasms is gaining increasing importance. There remain unanswered questions, and prospective randomized clinical trials are needed to provide answers to many of the debated issues such as the appropriate management of small, asymptomatic PanNET and the role of surgical treatment in advanced forms.

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Hilar Cholangiocarcinoma

14

Bradley N. Reames and Timothy M. Pawlik

14.1 Introduction

Cholangiocarcinoma, or primary malignancy of the bile duct epithelium, is a rare cancer that accounts for 3% of all gastrointestinal malignancies. It is the second most common primary liver tumour behind hepatocellular carcinoma (HCC) and accounts for 10–15% of all hepatobiliary malignancies [1]. Cholangiocarcinoma is traditionally classified according to its anatomical location: intrahepatic or extrahepatic. Extrahepatic disease is further classified as hilar or distal (Fig. 14.1). Intrahepatic cholangiocarcinoma is distinguished from hilar disease by the involvement of the second-order bile ducts and accounts for 5–10% of all diagnoses. Hilar lesions (also called Klatskin tumours) are the most common type of cholangiocarcinoma and account for 60–70% of all established diagnoses. Distal lesions of the extrahepatic bile duct (defined by the insertion of the cystic duct) account for 20–30% of all diagnoses [2]. Although these lesions exist along a spectrum of disease, they are considered distinct entities, as they exhibit significant differences in biology, presentation, management and prognosis. In this chapter, we will specifically focus on the presentation, management and prognosis of hilar cholangiocarcinoma.

B. N. Reames
Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: breames1@jhmi.edu

T. M. Pawlik (✉)
The Urban Meyer III and Shelley Meyer Chair in Cancer Research, Department of Surgery, The Ohio State University, Wexner Medical Center, Columbus, OH, USA
e-mail: Tim.Pawlik@osumc.edu

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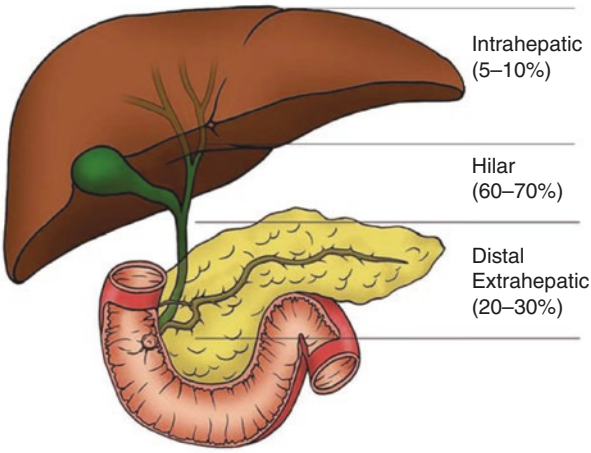

Fig. 14.1 Anatomic location of intrahepatic, hilar and distal cholangiocarcinoma (with permission, adapted from [175])

14.2 Epidemiology

Cholangiocarcinoma typically presents during the seventh decade and rarely occurs before age 40. The incidence is higher in men versus women (M:F ratio of 1.2–1.5:1) and varies substantially by geographic region. The incidence, overall, appears to be increasing over time, though individual studies evaluating intrahepatic and extrahepatic disease are conflicting [3]. Differentiating the epidemiology and risk factors of intrahepatic and extrahepatic cholangiocarcinoma can be difficult for multiple reasons. First, the rare nature of hepatobiliary malignancy overall requires many population-based studies to combine cholangiocarcinoma with other malignancies, such as HCC and gallbladder carcinoma. Second, differentiation among the types of cholangiocarcinoma can be challenging in advanced stages of disease. In addition, coding revisions in the second version of the International Classification of Diseases for Oncology (ICD-O) resulted in the misclassification of many hilar lesions as intrahepatic, instead of extrahepatic [4, 5].

The highest incidence of cholangiocarcinoma worldwide is found in northeast Thailand, where the rate is as high as 113 per 100,000 for men and 50 per 100,000 for women [6, 7]. This stands in stark contrast to age-standardized incidence rates in developed countries, which appear to be 50- to 100-fold lower. For example, the age-standardized rate in Europe is less than 1.5 per 100,000, while in Australia the rate is 0.2 and 0.1 per 100,000 for men and women, respectively [3, 8]. In the United States, recent data from the Surveillance, Epidemiology, and End Results (SEER) programme suggests the annual incidence is 0.58 per 100,000 for intrahepatic cholangiocarcinoma and 0.88 per 100,000 for extrahepatic cholangiocarcinoma between the years 2000 and 2005 [3]. Published trends in incidence over time are difficult to interpret, given the difficulties discussed above in differentiating intrahepatic and extrahepatic cholangiocarcinoma in population-based studies. For example, while many studies have reported an increasing incidence of intrahepatic disease and

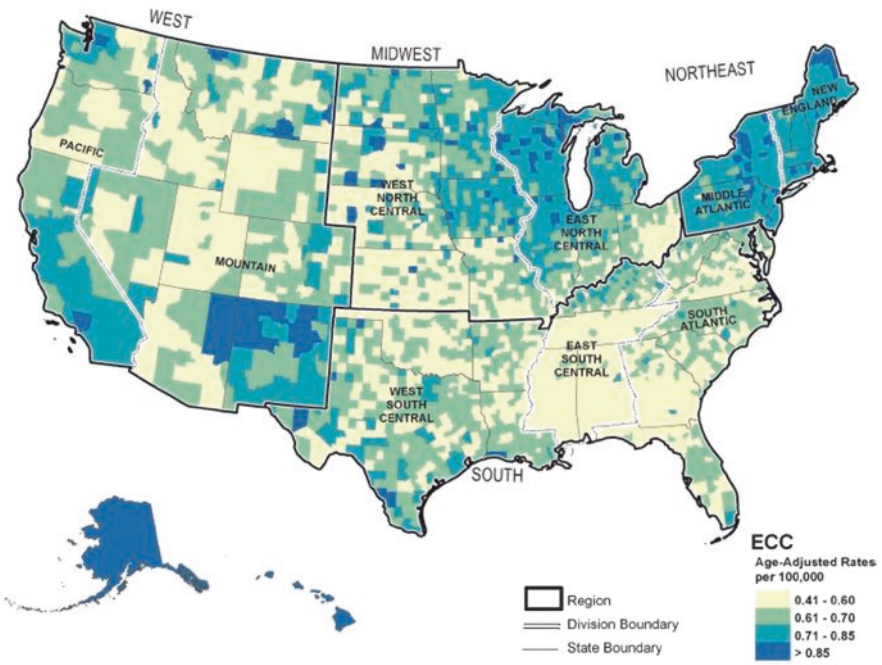

Fig. 14.2 Geographic variation in the modelled incidence of extrahepatic cholangiocarcinoma in the United States between the years 2000 and 2009 (with permission, from [14])

stable or decreasing extrahepatic disease, other studies have reported stable incidences for both, while yet others have reported reversed trends [9–12].

The incidence of cholangiocarcinoma varies greatly by geographic location and is largely thought to be secondary to variation in risk factors for the disease. In northeast Thailand, for example, high rates of cholangiocarcinoma are closely correlated with infection by the liver fluke *Opisthorchis viverrini*, which is endemic in the region [13]. In the United States, rates of extrahepatic cholangiocarcinoma are highest in the northeast and Upper Midwest and in the southwest and Pacific regions (Fig. 14.2). Though high rates in the southwest and Pacific regions may be related to increased populations of Asians and Pacific Islanders living in those areas, reasons for increased rates in the northeast and Upper Midwest remain unclear [14].

14.3 Risk Factors

While the majority of cholangiocarcinomas are sporadic, several risk factors have been reported. Though numerous mechanisms have been suggested, a detailed understanding of the biology of malignant transformation is not well known given the rarity of disease. As a result, much of what is known regarding established and possible risk factors comes from retrospective population-based research.

Table 14.1 Evidence-based risk factors for intra- and extrahepatic cholangiocarcinoma (*CCA* cholangiocarcinoma, *CI* confidence interval, *MA* meta-analysis, *CC* case-control, *IH* intrahepatic, *EH* extrahepatic; for study references please see original publication) (with permission, adapted from [1])

Risk factor	Study author	Type of study	Type of CCA	Risk estimate (95% CI)
Liver flukes				
O. viverrini or *C. sinensis*	Shin	MA	CCA	4.7 (2.2–9.8)
Biliary tract conditions				
Choledochal cysts	Welzel	CC	EH-CCA	47.1 (30.4–73.2)
	Welzel	CC	IH-CCA	36.9 (22.7–59.7)
Hepatolithiasis	Lee	CC	EH-CCA	16.5 (1.9–146.3)
	Donato	CC	IH-CCA	6.7 (1.3–33.4)
Choledocholithiasis	Shaib	CC	IH-CCA	8.8 (4.9–16.0)
	Welzel	CC	IH-CCA	22.5 (16.9–30.0)
	Welzel	CC	EH-CCA	34.0 (26.6–43.6)
Hepatic disorders				
Hepatitis B	Palmer	MA	IH-CCA	5.1 (2.9–9.0)
	Zhou	MA	IH-CCA	3.2 (1.9–5.3)
	Li	MA	IH-CCA	3.4 (2.5–43.7)
Hepatitis C	Palmer	MA	IH-CCA	4.8 (2.4–9.7)
	Zhou	MA	IH-CCA	3.4 (2.0–6.0)
Cirrhosis	Palmer	MA	IH-CCA	22.9 (18.2–26.8)

Recognized risk factors for cholangiocarcinoma include parasitic biliary tract infections, disorders of the biliary tract such as choledochal cysts and primary sclerosing cholangitis, hepatic disorders such as hepatolithiasis and viral hepatitis and toxins. Other proposed, but less well-established, risk factors include obesity, diabetes, inflammatory bowel disease, genetic polymorphisms, smoking and alcohol (Table 14.1) [3]. A common theme among recognized and proposed risk factors is chronic biliary tract inflammation [15, 16].

Opisthorchis viverrini and *Clonorchis sinensis* are parasitic liver flukes prevalent in the Far East and Southeast Asia. Humans are a definitive host, and infection occurs by eating raw, pickled or undercooked fish. Adult worms attach to the mucosa of the biliary tree and are associated with numerous hepatobiliary diseases in addition to cholangiocarcinoma, including cholelithiasis, cholecystitis, obstructive jaundice, cholangitis and hepatomegaly [17]. Numerous studies have reported strong associations between fluke infection and cholangiocarcinoma [13, 18]. A recent meta-analysis by Shin and colleagues reported a pooled relative risk of 4.8 (95% confidence interval [CI] 2.8–8.4) for the development of cholangiocarcinoma in liver fluke infection [19].

Choledochal cysts are congenital cystic dilations of the biliary tree. Over time, these lesions develop bile stasis and pancreatic enzyme reflux, which leads to chronic inflammation and can promote malignant transformation. Choledochal cysts are classified into five types based on anatomic location, and Types I (solitary,

fusiform, extrahepatic) and IV (intra- and extrahepatic) have the strongest association with cholangiocarcinoma. Ten percent to thirty percent of adults with choledochal cysts will be diagnosed with malignancy [20]. A case-control study by Welzel and colleagues examining the association with extrahepatic cholangiocarcinoma reported an odds ratio of 47.1 (95% CI 30.4–73.2) [21].

Primary sclerosing cholangitis (PSC) is an autoimmune disease that causes cholestasis and chronic biliary inflammation, ultimately leading to stricturing of the intra- and extrahepatic bile ducts. The incidence of cholangiocarcinoma in PSC is reported to be 8–13% [22–24]. Patients with PSC diagnosed with cholangiocarcinoma are generally younger than patients with sporadic disease, and the diagnosis is usually made within a year of PSC diagnosis in a majority of cases [24].

Other hepatobiliary disorders, such as stone disease, toxins and hepatitis, have also been associated with cholangiocarcinoma. A single-institution case-control study by Lee and colleagues reported that the odds ratio for hilar cholangiocarcinoma in hepatolithiasis was 16.5 (95% CI 1.8–146.3) and 9.4 (95% CI 1.1–79.7) in choledocholithiasis [25]. In the study by Welzel, the odds ratio for choledocholithiasis was 34.0 (95% CI 26.6–43.6) [21]. Thorotrast, a carcinogenic radiographic contrast agent used before 1960, was strongly associated with the development of cholangiocarcinoma, with a 300-fold increased risk in exposed patients [26]. While chronic viral hepatitis B and C, cirrhosis and alcohol have also been implicated as risk factors for intrahepatic cholangiocarcinoma, less is known about their association with extrahepatic cholangiocarcinoma [1]. The associations between cholangiocarcinoma and other proposed risk factors such as smoking, diabetes, obesity and genetic polymorphisms are less clear, as data are mixed [3].

14.4 Pathology

Though the detailed mechanisms underlying the pathogenesis of hilar cholangiocarcinoma are still being elucidated, recent studies have highlighted certain genetic mutations that may play a role in malignant transformation. Mutations in p53, for example, have been identified in up to 94% of resected specimens stained for the tumour suppressor gene [27, 28]. Similar to other gastrointestinal cancers, K-ras mutations have been reported in up to 60% of specimens and are more likely to be found in patients with tumours larger than 3 cm and in those with lymph node metastases [29–32]. Other mutations that have been implicated in pathogenesis include C-myc, *Bcl-2*, BRAF, NRAS, EGFR, APC, DPC4/*Smad4* and E-cadherin [16, 32]. It is important to note, however, that the specific mutations identified in individual tumour specimens vary substantially.

Pathological analysis of tumour specimens yields three distinct morphologic subtypes of hilar cholangiocarcinoma: sclerosing, nodular and papillary (Fig. 14.3). Sclerosing tumours are most common and account for 70% of specimens, while papillary tumours are rare and account for 5–10% [33, 34]. Appreciation of these subtypes is essential, as each subtype is anatomically distinct and can have

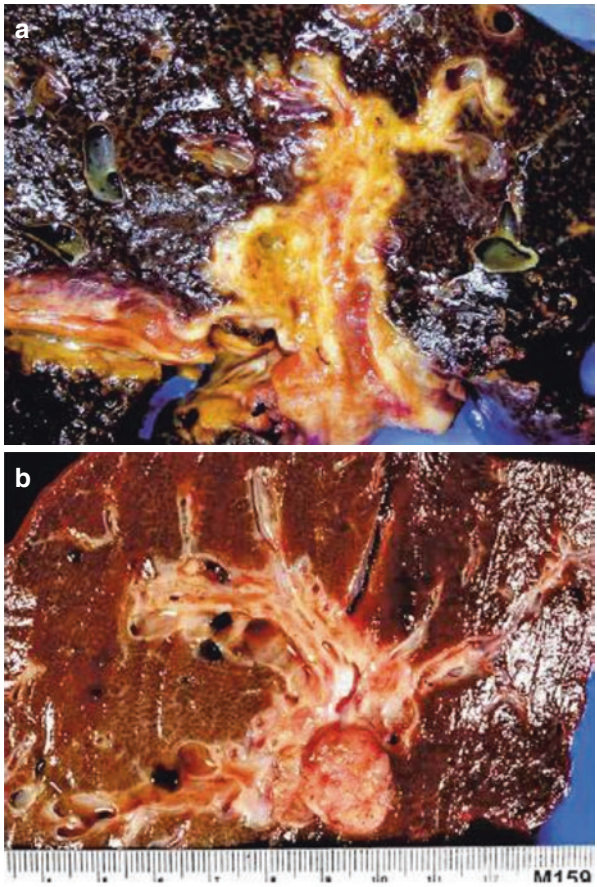

Fig. 14.3 Examples of morphologic subtypes of hilar cholangiocarcinoma: (**a**) nodular-sclerosing and (**b**) papillary (with permission, adapted from [37])

important implications for operative technique and patient prognosis. Sclerosing tumours, which are frequently found at the hilum, are firm and cause annular thickening of the bile duct with longitudinal and radial infiltration. As such, these lesions can invade surrounding neural tissue and vessels, leading to periductal inflammation and fibrosis. While also firm, nodular cholangiocarcinomas, on the other hand, grow as irregular nodules that project into the lumen of the duct. Specimens that have features of both subtypes are termed "nodular-sclerosing". Papillary tumours, which are commonly found in the distal bile duct and rarely at the hilum, are soft and friable polypoid masses that often arise from a well-defined stalk. This growth pattern allows papillary tumours to be freely mobile within the lumen and expand the duct (as opposed to subtypes with infiltrative growth patterns that frequently constrict the duct) [33]. Papillary tumours have the best prognosis, as these tumours usually have a well-differentiated histology, are less invasive and are more often resectable [35, 36]. Consequently, the preoperative identification of a papillary (vs. non-papillary) tumour is important, as it may lead the surgeon to be more aggressive in technical considerations.

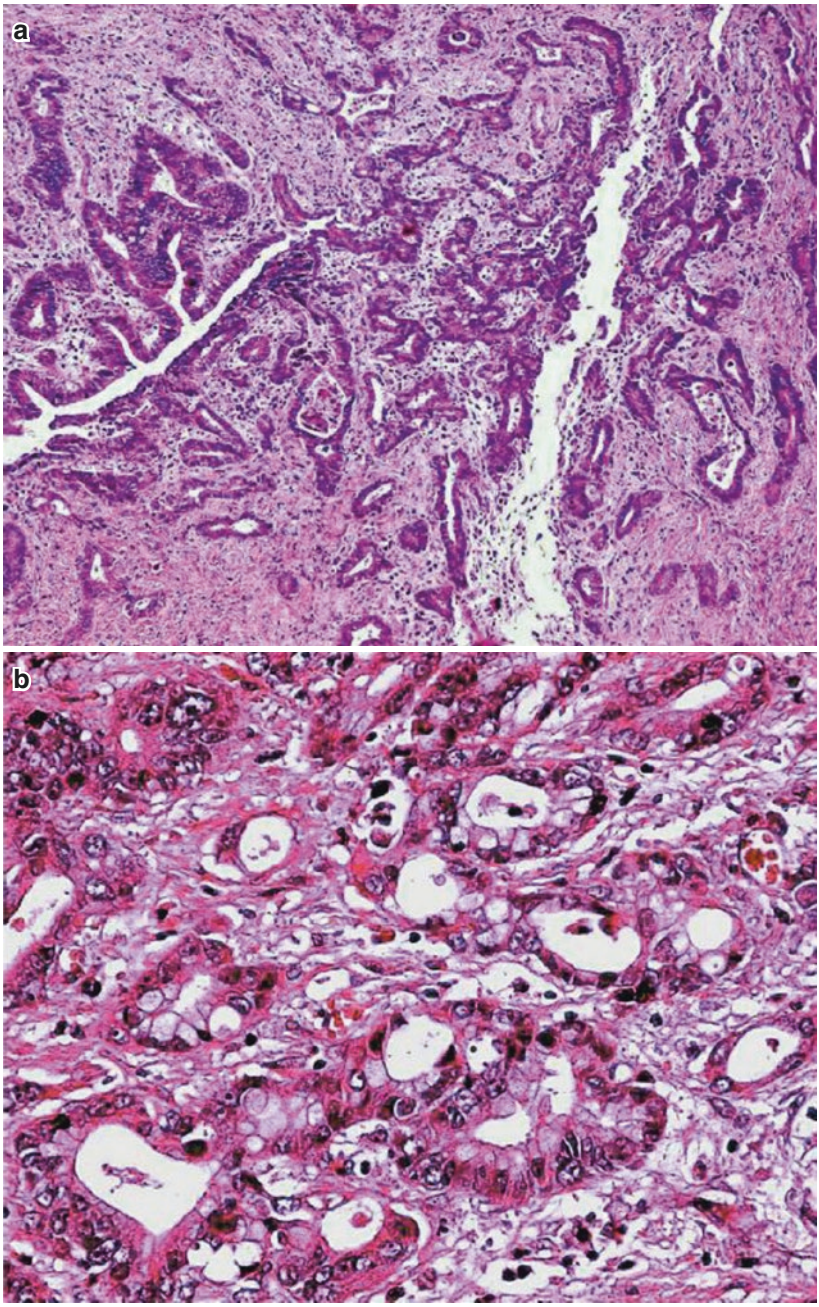

Fig. 14.4 Examples of three common differentiations of adenocarcinoma causing hilar cholangiocarcinoma: (**a**) pancreaticobiliary, identified by atypical glands infiltrating periductal tissues associated with a densely desmoplastic stroma; (**b**) intestinal, characterized by atypical infiltrating glands containing cytoplasmic vacuoles of mucin; and (**c**) gastric, characterized by the presence of distinct areas of gastric-type mucosa with oxyntic cells (with permission, adapted from [37])

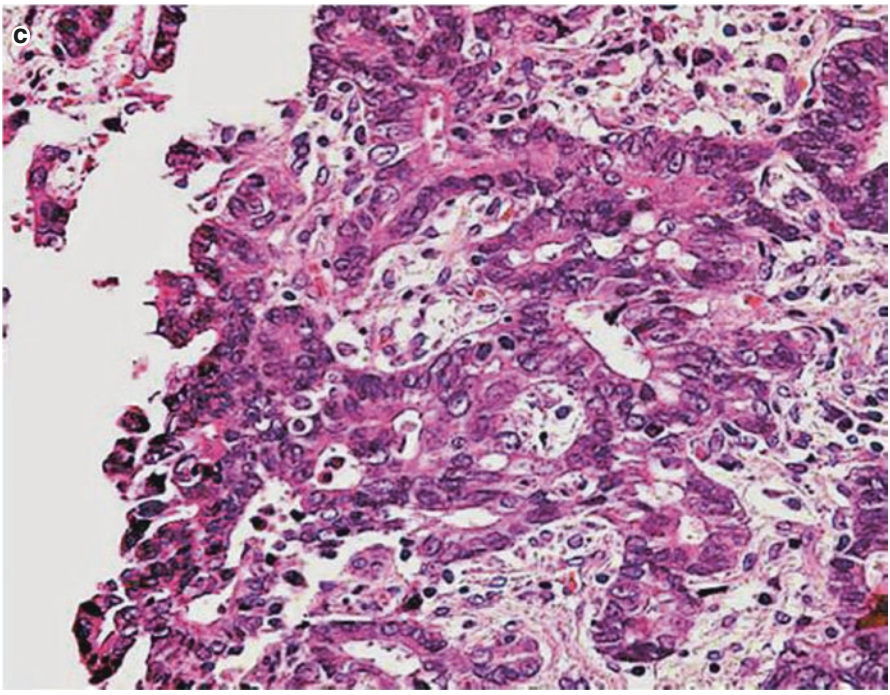

Fig. 14.4 (continued)

Microscopically, most hilar cholangiocarcinomas are moderate or well-differentiated adenocarcinomas, characterized by tubules or glands in a desmoplastic stroma surrounded by a variable inflammatory response. Tumour cells are columnar or cuboidal, with a moderate amount of clear or eosinophilic cytoplasm and generally small nuclei [35]. The histological grade is determined by the degree of glandular or tubular differentiation, with ≥95% corresponding to a well-differentiated grade and <50% or <40% corresponding to poorly differentiated grade, depending on the classification system used (College of American Pathologists or World Health Organization, respectively). The vast majority of adenocarcinomas are mucin producing, and though pancreaticobiliary differentiation is most common, intestinal or gastric differentiation is also possible. A clear distinction between histologic types of adenocarcinoma can sometimes be difficult, as features often overlap (Fig. 14.4) [37]. Immunohistochemically, nearly all hilar cholangiocarcinomas stain for cytokeratin (CK) 7, and a majority (80%) also express CK20 [35]. Other histologic types are rare and include adenosquamous carcinoma, squamous cell carcinoma, clear cell carcinoma, signet ring cell carcinoma, papillary carcinoma, small cell (oat cell) carcinoma, undifferentiated carcinoma, carcinosarcoma, leiomyosarcoma and embryonal rhabdomyosarcoma [34, 35].

14.5 Classification

Over time, numerous classification and staging systems have been devised to aid in the evaluation and management of patients with hilar cholangiocarcinoma. Accurate determination of resectability and disease stage is critical to identify patients that will benefit from resection, while sparing morbidity in patients with advanced disease. Though early systems focused on an anatomic classification of tumour location, subsequent studies failed to demonstrate an association with survival. As a result, more recent systems have focused on clinical and pathologic aspects of the disease to better predict resectability and survival.

The first classification scheme of hilar cholangiocarcinoma was published by Bismuth and Corlette in 1975 and updated in 1992 [38, 39]. This system stratifies tumours into four types based on anatomic location within the proximal bile duct and the degree of periductal infiltration (Fig. 14.5). Type I lesions involve the common hepatic duct distal to the bifurcation, while Type II lesions involve the bifurcation of the right and left hepatic ducts but do not extend into intrahepatic ducts. Type III lesions also involve the bifurcation but extend into the right (IIIa) or left (IIIb) hepatic ducts. Type IV lesions involve the bifurcation and extend into secondary biliary radicals bilaterally or are multifocal. Though originally devised to aid

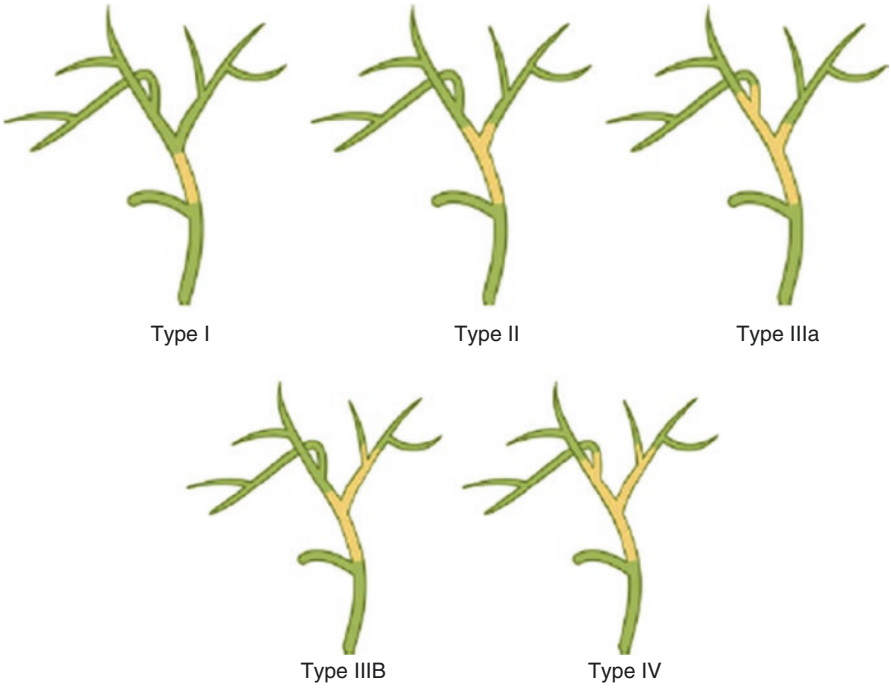

Fig. 14.5 Bismuth-Corlette classification Types I through IV (with permission, from [176])

Table 14.2 T stages of the Blumgart classification (with permission, from [177])

Stage	Criteria
T1	Tumour involving biliary confluence ± unilateral extension to second-order biliary radicles
T2	Tumour involving biliary confluence ± unilateral extension to second-order biliary radicles AND ipsilateral portal vein involvement ± ipsilateral hepatic atrophy
T3	Tumour involving biliary confluence + bilateral extension to second-order biliary radicles OR unilateral extension to second-order biliary radicles with contralateral portal vein involvement OR unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy OR main or bilateral portal venous involvement

Table 14.3 Survival outcomes of selected case series involving surgical resection of more than 100 hilar cholangiocarcinoma tumours (for references, see original publication) (with permission, from [63])

Author	Year of publication	Number of patients	Overall 5-year survival
Wang	2015	204	23.7% (radical resection)
			4.5% (palliative resection)
Higuchi	2015	239	9.3% (1974–1988)
			41.1% (1989–2003)
			55.6% (2004–2008)
Regimbeau	2015	331	53%
Furusawa	2014	144	33% (1990–2000)
			35% (2001–2012)
Nagino	2013	574	32.5%
Cho	2012	105	34.1%
Cannon	2012	110	17.7%
Matsuo	2012	157	37.5%
Song	2012	230	33%
DeJong	2012	305	20.2%
Nuzzo	2012	440	25.5%
Lee	2010	302	32.5%
Shimizu	2010	224	28.3% (left hepatectomy)
			30.3% (right hepatectomy)
Unno	2010	125	34.7%

determination of resectability, the lack of detailed information regarding vascular encasement and hepatic morphology has limited its use in this regard, while the lack of information regarding regional and distant metastasis has limited its ability to predict prognosis. Indeed, multiple recent reports have failed to show an association between Bismuth-Corlette classification and survival [40–43] (Tables 14.2, 14.3, 14.4 and 14.5).

To address these limitations, staging systems that include clinical prognostic information have been devised by the American Joint Committee on Cancer

Table 14.4 Conditional survival of patients with hilar cholangiocarcinoma undergoing surgery with curative intent (with permission, from [129])

	If the patient has survived… (%)						
Total survival time, year	1 year	2 year	3 year	4 year	5 year	6 year	7 year
1							
2	60.8						
3	44.9	73.9					
4	35.0	57.5	77.8				
5	23.9	39.3	53.2	68.4			
6	17.6	28.9	39.2	50.4	73.6		
7	14.7	24.2	32.7	42.1	61.5	83.6	
8	13.0	21.4	28.9	37.2	54.4	73.9	88.4

Note: Each column represents the actual time survived/elapsed from the date of surgery, while each row represents the survival estimates for surviving additional time. For example, if a patient has already survived 3 years, the probability of surviving to 5 years is 53.2%

Table 14.5 Common procedure-specific complications and associated treatments in patients undergoing resection for hilar cholangiocarcinoma

Common complications	Treatment
Biliary leak	Percutaneous external drainage Internal-external transhepatic biliary drainage Re-exploration
Cholangitis	Antibiotics and biliary drainage
Intra-abdominal fluid collection or abscess	Antibiotics and percutaneous drainage
Portal vein thrombosis	Anticoagulation when appropriate
Hepatic insufficiency	Best supportive care

(AJCC) and the Japanese Society of Biliary Surgery (JSBS). The recently revised eighth edition AJCC staging system utilizes the traditional tumour, node, metastases (TNM) model and is the most commonly used staging system worldwide [44]. The tumour (T) is defined according to whether the tumour is confined to the bile duct (Tis or T1), invades surrounding adipose tissue or adjacent hepatic parenchyma (T2a or T2b), invades branches of the portal vein or hepatic artery (T3) or has bilateral vascular involvement or unilateral vascular with contralateral secondary biliary radical involvement (T4). Nodal disease (N) is categorized by the number with metastatic disease with 1–3 metastatic nodes being N1 versus four or more metastatic nodes being N2. The presence of distant metastasis is M1 disease. Using this information, patients are stratified into one of four stages to differentiate patients by prognosis (Table 14.6). While some recent studies have supported the prognostic value of the seventh edition, other studies have questioned its accuracy [45–47]. For example, de Jong and colleagues suggested that depth of tumour invasion might better predict patient outcome compared with AJCC seventh edition T criteria [47].

Table 14.6 American Joint Committee on Cancer 8th Edition Prognostic Groups for Hilar Cholangiocarcinoma (with permission, from [44])

Prognostic stage		Tumour (T)	Regional lymph nodes (N)	Distant metastasis (M)
Stage 0		Tis	N0	M0
Stage I		T1	N0	M0
Stage II		T2a–b	N0	M0
Stage III	A	T3	N0	M0
	B	T4	N0	M0
	C	Any T	N1	M0
Stage IV	A	Any T	N2	M0
	B	Any T	Any N	M1

Importantly, while the seventh edition was substantially modified from previous editions to divide hilar and distal cholangiocarcinoma into distinct staging subgroups, recent modifications to the eighth edition have further improved prognostic accuracy. First, the definition of Tis was expanded to include high-grade biliary intraepithelial neoplasia, and bilateral second-order biliary radical invasion was removed from the T4 category. In addition, the nodal category was reclassified and no longer focuses on node location (hepatoduodenal or retroperitoneal) and instead is defined by the number of involved nodes. Furthermore, the prognostic stage groups were modified: T4 tumours are now considered IIIB (formerly IVA), and N1 is now IIIC (formerly IIIB) while the N2 category is IVA (Table 14.6) [44].

An alternative TNM staging system was proposed by JSBS in 1981 and recently updated to the fifth edition in 2003 [48]. In this staging system, additional details are included in the T and N classifications in order to improve prognostic accuracy. The T classification includes the depth of invasion according to histologic landmarks of the bile duct wall, the distance (in millimetres) of penetration into adjacent structures and the macroscopic appearance of the tumour, while the N classification includes the location of both the node and the tumour (Table 14.7). The resulting staging system is complex and difficult to use and as a result has not been widely adopted outside of Japan, despite research suggesting improved prognostic accuracy compared to the current AJCC system [48].

While the above staging systems may accurately predict survival, neither has been shown to accurately and consistently predict resectability. Given that curative resection remains the only therapy associated with prolonged survival, multiple authors have attempted to devise a classification scheme to assist in the preoperative determination of resectability. The classification by Gazzaniga and colleagues, first proposed in 1985, attempted to differentiate tumours by the degree of extrabiliary involvement (Fig. 14.6) [49]. An alternative system, reported by Blumgart and colleagues, tried to expand the Bismuth-Corlette classification by stratifying patients into one of three T stages after accounting for tumour location, bile duct and portal vein involvement and lobar atrophy (Table 14.2). While subsequent studies of both classifications have reported accurate predictions of resectability, their association with predicted survival is less clear [50, 51].

Table 14.7 Japanese Society of Biliary Surgery Staging for Hilar Cholangiocarcinoma, 5th Edition (with permission, from [48])

pT classification					
pT	Contents				
pT1	m, fm, hinf0, panc0, pv0, a0				
pT2	ss, hinf1, panc1, pv0, a0				
pT3	se, hinf2, panc2, pv1, a1				
pT4	si, hinf3, panc3, pv2, pv3, a2, a3				
Lymph node grouping					
Lymph node (site number)	Group				
	Hilar and proximal	Middle	Distal		
Infrapyloric LN (6)	pN3	pN3	pN3		
LN around the common hepatic artery (8)	pN2	pN2	pN2		
LN at the splenic hilum (10)	pN3	pN3	pN3		
LN along the splenic artery (11)	pN3	pN3	pN3		
LN at the hepatic hilum (12h)	pN1	pN2	pN2		
LN along the hepatic artery (12a)	pN1	pN2	pN2		
Periportal LN (12p)	pN1	pN2	pN2		
Pericholedochal LN (12b)	pN1	pN1	pN1		
LN around the cystic duct (12c)	pN1	pN1	pN1		
Posterior superior pancreaticoduodenal LN (13a)	pN2	pN2	pN2		
Posterior inferior pancreaticoduodenal LN (13b)	pN3	pN3	pN3		
LN along the superior mesenteric artery (14)	pN3	pN3	pN2		
Para-aortic LN (16)	pN3	pN3	pN3		
Anterior superior pancreaticoduodenal LN (17a)	pN3	pN3	pN3		
Anterior inferior pancreaticoduodenal LN (17b)	pN3	pN3	pN3		

(continued)

Table 14.7 (continued)

Stage grouping					
	H(−) and P(−) and M(−) pN0	pN1	pN2	pN3	H(+) and/or P(+) and/or M(+) and any N
pT1	I	II	III	IVa	IVb
pT2	II	III	III	IVa	IVb
pT3	III	III	IVa	IVb	IVb
pT4	IVa	IVa	IVb	IVb	IVb

m invasion limited to the mucosa; *fm* invasion limited to the fibromuscular layer, *ss* invasion limited to the subserosa; *se* invasion of serosal surface; *si* invasion beyond the serosa and invasion of other organs or structures; *hinf0* no direct invasion of the liver, or direct invasion limited to the fibromuscular layer of intrahepatic bile ducts; *hinf1* direct invasion of fibromuscular layer of intrahepatic ducts and/or liver parenchyma which invasion is not more than 5 mm in depth; *hinf2* direct invasion of liver parenchyma, of which invasion is 5 mm or more but not more than 20 mm in depth; *hinf3* direct invasion of liver parenchyma, of which invasion is 20 mm or more in depth; *panc0* no invasion of the fibromuscular layer of the inferior bile duct; *panc1* invasion of the fibromuscular layer of the inferior bile duct and/or pancreatic parenchyma, of which invasion is not more than 5 mm in depth; *panc2* invasion of the pancreatic parenchyma of which invasion is 5 mm or more but not more than 20 mm in depth; *panc3* invasion of the pancreatic parenchyma, of which invasion is 20 mm or more in depth; *pv0* no invasion of portal vein; *pv1* invasion of the adventitia; *pv2* invasion of the media, *pv3* invasion of the intima; *a0* no invasion of hepatic arteries; *a1* invasion of the adventitia; *a2* invasion of the media; *a3* invasion of the intima; *LN* lymph node; *H(−)* no liver metastasis; *H(+)* liver metastasis; *P(−)* no peritoneal metastasis; *P(+)* peritoneal metastasis; *M(−)* no distant metastasis; *M(+)* distant metastasis

14.6 Clinical Presentation

The clinical presentation of patients with hilar cholangiocarcinoma largely depends on the anatomic location of the mass, tumour size and the degree of biliary obstruction. While a majority of patients with hilar cholangiocarcinoma are asymptomatic, a minority of patients will first experience non-specific symptoms such as fatigue, weight loss, anorexia and abdominal pain. As a result, few tumours are identified early unless found incidentally. As the tumour grows and biliary obstruction develops, patients will gradually become jaundiced, which is the presenting symptom in more than 90% of patients [52, 53]. Associated symptoms may include nausea and vomiting, pruritis, steatorrhoea and bilirubinuria. Fever is uncommon and usually occurs in the setting of cholangitis, which may also be accompanied by chills, hypotension and altered mental status in severe cases [54].

Similar to the clinical presentation, positive findings on physical examination are largely determined by the degree of biliary obstruction. Though usually painless, patients may occasionally experience abdominal tenderness. As obstruction progresses, patients will develop scleral icterus and jaundiced skin, and severe pruritis may lead to multiple skin excoriations. Hepatomegaly may be appreciated, and in later stages, liver palpation may reveal a firm consistency. While the gallbladder is not usually palpable, the presence of a palpable gallbladder (*Courvoisier's sign*) may indicate distal extension of a hilar tumour or a distal cholangiocarcinoma [55].

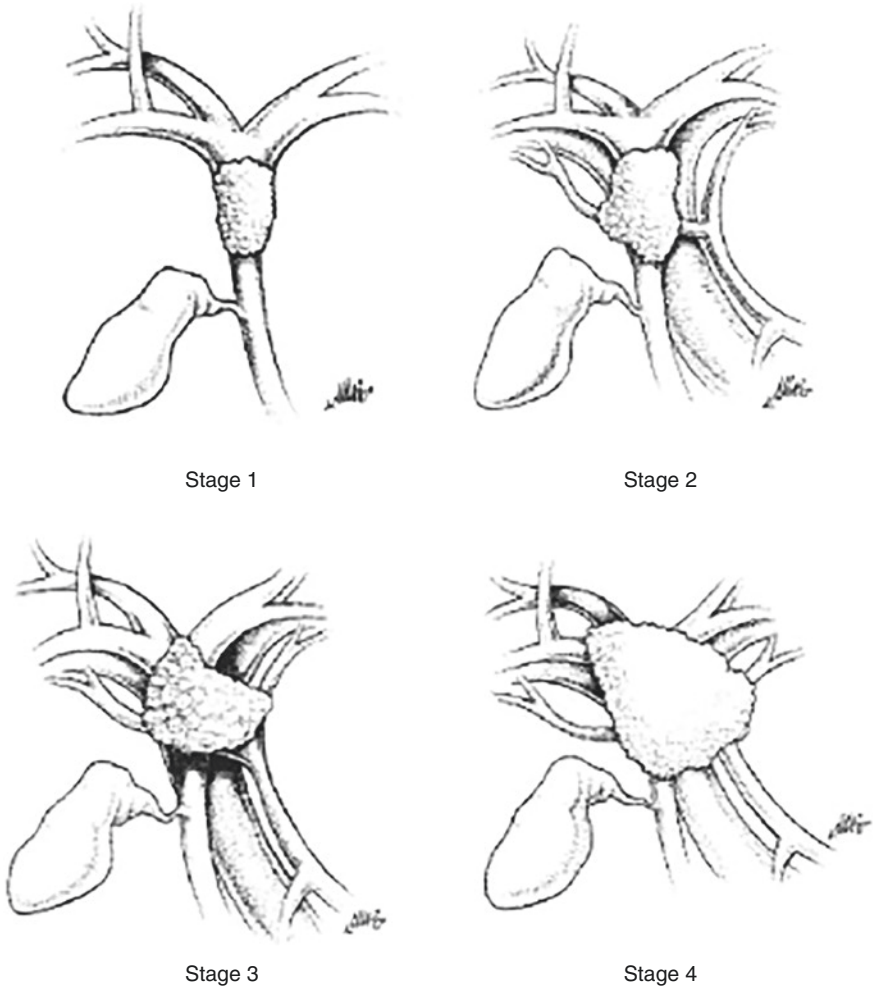

Fig. 14.6 Stages of the Gazzaniga classification (with permission, from [177])

Laboratory evaluation of patients with hilar cholangiocarcinoma will typically reveal biochemical evidence of biliary obstruction. The most common abnormality is a conjugated hyperbilirubinaemia, and this may be associated with elevations in alkaline phosphatase, gamma glutamyl transpeptidase and aminotransferases. Large single-institution series from the United States and France reported average serum bilirubin levels of 5.7 mg/dL (hilar cholangiocarcinoma) and 17.8 mg/dL (extrahepatic cholangiocarcinoma), respectively [52, 53]. In late stages, biochemical evidence of metastatic disease and malnutrition may be present, such as anaemia, hypoalbuminaemia, fat-soluble vitamin deficiencies, elevations in prothrombin time and abnormalities in lactate dehydrogenase, erythrocyte sedimentation rate and C-reactive protein [56].

14.7 Preoperative Evaluation

14.7.1 Initial Evaluation

A thorough evaluation is required of any patient who presents with symptoms or signs concerning for hilar cholangiocarcinoma. In addition to a complete history and physical and basic laboratory evaluation, current National Comprehensive Cancer Network (NCCN) guidelines recommend obtaining serum tumour markers to establish a baseline high-quality cross-sectional abdominal imaging for cholangiography and to assess vascular invasion (ideally prior to endobiliary stenting if needed) and chest computed tomography to evaluate for metastatic disease [57]. Other investigations considered in select instances include duplex ultrasound, endoscopic ultrasound with fine-needle aspiration and positron emission tomography with 18-fluorodeoxyglucose.

Serum tumour markers potentially elevated in hilar cholangiocarcinoma include carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA). In patients without PSC, the sensitivity of CA 19-9 value >100 U/ml is 53%, while the specificity for differentiating biliary malignancy from non-malignant liver disease and benign biliary stricture was 76% and 92%, respectively [58]. In patients with a concurrent diagnosis of PSC, the sensitivity (67–89%) and specificity (80–89%) may be increased [59–61], though studies are conflicting [62]. A higher cut-off (>180 U/ml) in PSC patients may improve specificity (98%) with little effect in sensitivity (67%), while the combination of elevated CA 19-9 (>180 U/ml) and CEA (>5.2 ng/ml) increases sensitivity to 100%, with a specificity of 78.4% [23]. The sensitivity and specificity of CEA alone, on the other hand, vary widely and have been reported between 33–84% and 33–100%, respectively [63]. Retrospective analyses of both CA 19-9 and CEA in hilar cholangiocarcinoma patients have reported associations between increasing tumour marker levels and more advanced stages of disease [64]. However, 10% of patients may be Lewis antigen non-producers and therefore not secrete CA 19-9 [58]. Moreover, it must be remembered that CA 19-9 and CEA can be elevated in a wide variety of gastrointestinal, pancreatic and gynaecologic malignancies, and as a result, abnormalities must be interpreted carefully in the context of all available clinical and diagnostic information.

Though not recommended for the targeted evaluation of hilar cholangiocarcinoma, duplex ultrasound (DUS) is commonly used in the evaluation of abdominal pain and biliary obstruction given its availability, convenience and cost (Fig. 14.7). In addition to identifying non-malignant causes of symptoms such as hepatocellular and biliary stone disease, DUS may define the location of biliary obstruction, may identify a biliary mass and possible extension and may reveal portal vein involvement causing lobar atrophy or contralateral hypertrophy [65]. In patients with obstructive jaundice, the sensitivity and specificity of DUS in defining the location of obstruction are 94% and 96%, respectively [66]. In a study evaluating ultrasound in patients with hilar cholangiocarcinoma reported by Hann and colleagues, DUS isolated bile duct tumours in 87% of patients. Moreover, in patients proceeding to surgery, ultrasonography accurately determined the full extent of biliary

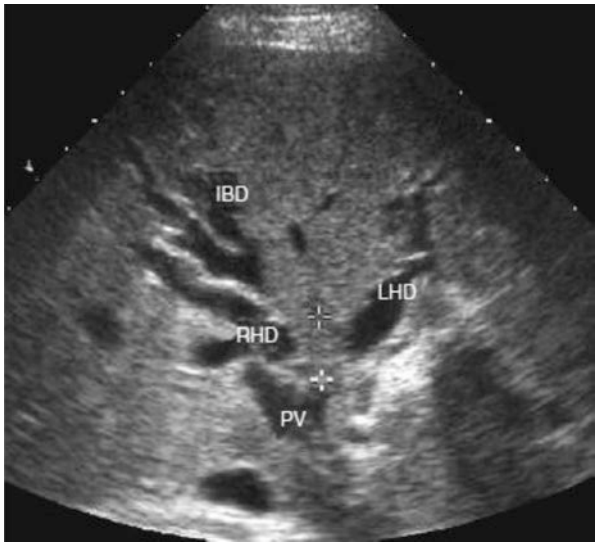

Fig. 14.7 Duplex ultrasound image of hilar cholangiocarcinoma (edges denoted by +) at the biliary confluence (*LHD* left hepatic duct, *RHD* right hepatic duct, *PV* portal vein, *IBD* intrahepatic bile ducts) (with permission, from [81])

involvement in 94% of cases and correctly identified portal vein involvement in 86% of cases [67]. However, it must be noted that these findings occurred within a specialized research protocol, and the sensitivity and specificity of duplex ultrasound are highly operator dependent. As a result, more detailed abdominal imaging is required whenever a diagnosis of hilar cholangiocarcinoma is suspected.

14.7.2 Cross-Sectional Imaging

Multidetector contrast-enhanced helical computed tomography (MDCT) is commonly used to obtain high-quality cross-sectional imaging in patients with hilar cholangiocarcinoma. MDCT is useful in identifying the location of biliary obstruction, tumour extension, vascular involvement, hepatic lobar atrophy, regional lymphadenopathy and distant metastasis. Specific findings on MDCT depend on the morphology of the tumour (Fig. 14.8). Sclerosing tumours appear as focally thickened ductal walls obliterating the lumen, and a majority (80%) are hyperattenuating relative to liver. Nodular tumours are identified as a low-attenuation hilar mass with peripheral rim enhancement, and the size and growth pattern can make it difficult to discern the exact origin in the biliary tree. Papillary tumours are seen as intraductal soft tissue masses that are hypoattenuating relative to liver, and these lesions are often multiple or disseminated within the biliary system. The sensitivity and accuracy of MDCT for diagnosing hilar cholangiocarcinoma are both greater than 90% in recent series [68–71]. In one such series, the reported accuracy of MDCT was 96% for portal vein invasion, 93.3% for hepatic artery invasion and 96% for longitudinal invasion. Moreover, the sensitivity, specificity and accuracy of predictions of resectability were 95.7%, 82.1% and 90.7%, respectively [69]. However,

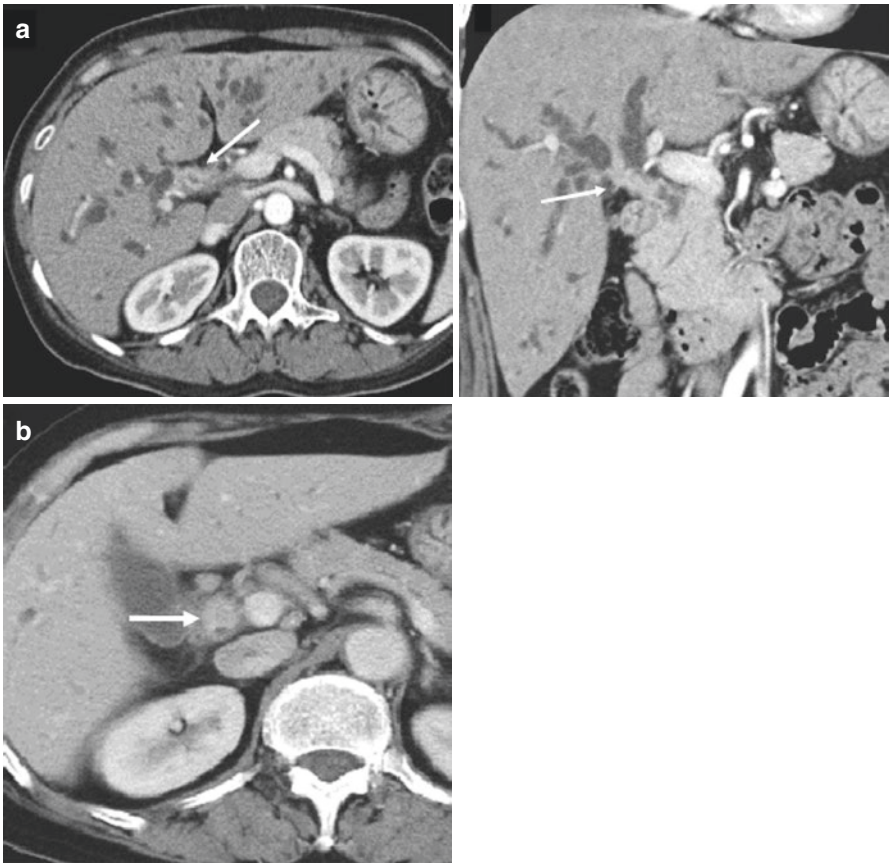

Fig. 14.8 Computed tomography images of hilar cholangiocarcinoma: (**a**) axial (left) and coronal (right) images of infiltrating hilar tumour (arrows) with intrahepatic biliary dilatation; (**b**) axial image showing nodular-type tumour (arrow) below the hilum (Bismuth-Corlette Type I) (with permission, adapted from [176])

multiple reports have suggested that the accuracy of MDCT to detect nodal and distant metastasis is substantially lower (<60%) [70, 71].

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are alternative methods of cross-sectional imaging in patients with hilar cholangiocarcinoma. In comparison to MDCT, the technique of MRI can produce a multitude of enhancement sequences that better differentiate the involved soft tissues (bile ducts, vessels, hepatic parenchyma and surrounding adipose). On MRI/MRCP, tumours appear mild to moderately hypointense (compared to liver parenchyma) on T1-weighted images and isointense to mildly hyperintense on T2-weighted images (Fig. 14.9) [72]. A meta-analysis of 67 studies revealed the sensitivity and specificity of MRCP for detecting biliary malignancy were 88% and 95%, respectively [73]. Similar to MDCT, the accuracy of MRI to diagnose arterial

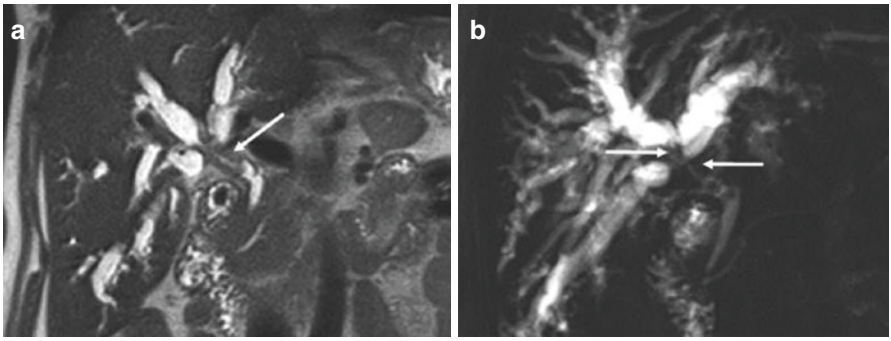

Fig. 14.9 Magnetic resonance imaging of hilar cholangiocarcinoma: (**a**) coronal T2-weighted image of irregular ductal wall thickening (arrow) at the confluence; (**b**) two-dimensional magnetic resonance cholangiography image of a hilar mass (arrows) (with permission, adapted from [176])

or portal venous invasion was 89% for both in one report [74], and the accuracy to define resectability ranged from 72% to 83% [75]. Park and colleagues performed a direct comparison of MDCT and MRI/MRCP in extrahepatic cholangiocarcinoma and reported that accuracy rates for predicting involvement of secondary biliary confluences were 90.7% for MRI/MRCP and 85.1% for MDCT ($p > 0.05$) [76]. Numerous studies have reported diagnostic equivalence between MRI/MRCP and invasive cholangiography (either endoscopic or percutaneous), and consequently, MRI/MRCP has largely supplanted these tests for diagnostic evaluation in current practice [68].

Though studies on its performance are mixed, positron emission tomography (PET) may also be considered in the evaluation of hilar cholangiocarcinoma. Reports of sensitivity range from 59% to 92%, with decreased sensitivities reported in small (<1 cm), infiltrating (vs. mass forming) and hilar (vs. intrahepatic or distal) tumours [77–79]. The specificity of PET, on the other hand, has been reported as high as 93% in a cohort of all cholangiocarcinoma types [77]. Furthermore, while PET may accurately detect distant metastasis (sensitivities ranging from 56% to 100%), the detection of lymph node metastasis is poor (sensitivities ranging from 12% to 42%) [77–80]. Moreover, use of PET is limited in states of chronic biliary inflammation such as cholangitis and PSC (increased false positives) and in patients with mucinous tumours secondary to decreased fluorodeoxyglucose uptake (increased false negatives) [68].

14.7.3 Endoscopic and Percutaneous Evaluation

While non-invasive, high-quality cross-sectional imaging is usually sufficient for diagnosis of hilar cholangiocarcinoma, invasive cholangiography, either via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), may be necessary to decompress obstruction or obtain a tissue biopsy. It is important to note, however, that both modalities can be limited in

the evaluation of the entire biliary tree in obstructed patients: ERCP may fail to assess proximally, while PTC may be limited distally [68]. Furthermore, with their use comes a non-trivial risk of complications, including pancreatitis, haemorrhage, cholangitis and biliary leak. As a result, the choice of modality is frequently institution- and patient-dependent. Pertinent findings on cholangiography include an abrupt, irregular and eccentric biliary stenosis with proximal biliary dilatation or may occasionally show a mobile mass within the lumen in tumours with papillary morphology [81]. The accuracy of both ERCP and PTC is 95%, with sensitivities and specificities ranging from 75–85% to 70–75%, respectively [68]. If tissue biopsy is desired and invasive cholangiography is unsuccessful, endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) is another technique that may be utilized to aid diagnosis. The sensitivity and specificity of this technique are reported to be 77–89% and 100%, respectively, but the negative predictive value is low (29%), meaning a diagnosis of malignancy cannot be excluded [82, 83]. In addition, EUS with transperitoneal FNA carries a significant risk of peritoneal metastasis (86% in one study), and performance of this technique may exclude patients from consideration for subsequent therapy (liver transplantation) [84]. As a result, it should only be considered in patients for whom nonoperative management is planned.

14.7.4 Preprocedural Assessment and Future Liver Remnant

In addition to confirming the diagnosis and evaluating the extent of disease, the preoperative assessment of patients with hilar cholangiocarcinoma must also determine the patient's ability to tolerate potential therapies. Important factors that may influence a patient's procedural risk include overall health and co-morbid conditions, performance status and available social support. Moreover, if consideration is given to significant liver resection as a part of the treatment plan, preoperative evaluation will also require an assessment of the potential future liver remnant (FLR).

A complete assessment of liver function should include information on synthetic function as well as anatomical information regarding the distribution of liver as it relates to the proposed resection. In the absence of obstruction, synthetic liver function may be determined through measurements of serum bilirubin and albumin, platelet count and prothrombin time (international normalized ratio), while measurements of serum aminotransferases and alkaline phosphatase can provide an insight into prior or ongoing liver damage secondary to hepatocellular disease [85]. Scoring systems, such as the Child-Pugh score and the Model for End-Stage Liver Disease (MELD), have also been developed to assist in the assessment of liver function and risk of morbidity and mortality following liver resection [85]. Patients considered Child-Pugh class A and those with a MELD score <9 have a low risk of hepatic failure following resection [86, 87]. Another alternative to assess quantitative liver function is the indocyanine green (ICG) clearance test. ICG is a water-soluble, inert, anionic compound selectively taken up and excreted by hepatocytes [85]. Measurement of the percent retained in the circulation at 15 minutes (ICG-R15) can estimate hepatic function, with levels

>15% indicating high risk for post-hepatectomy complications [88]. Other metabolic quantitative liver function tests, such as galactose elimination capacity, are infrequently used to assess synthetic function but are beyond the scope of this chapter [85]. Regardless of the test used, results should be interpreted with caution in the setting of mechanical biliary obstruction, and a greater emphasis should be placed on anatomic assessment.

Preoperative volumetric assessment is important because functional capacity is patient-dependent and not distributed uniformly within the liver. Currently, CT volumetry is the most frequently used modality for anatomic assessment of a FLR [89]. In this technique, three-dimensional reconstruction software is used to determine the total liver volume and the FLR is estimated by subtracting the volume demarcated by the proposed resection [85]. Alternative approaches to estimating FLR entail the use of mathematical formulae based on body surface area. However, these are not widely used [85, 90]. In patients with healthy livers, a FLR volume ≤20% is a strong predictor of hepatic insufficiency and is therefore a significant risk factor for postoperative liver failure and death [91–93]. Patients with known liver disease, on the other hand, have a significantly increased risk of hepatic insufficiency. As a result, these patients should be carefully selected, and the FLR should be 40% or greater [94, 95]. If uncertainty exists regarding the presence or severity of liver disease, additional investigations may be pursued. Though not routinely used due to their invasive nature, these include percutaneous biopsy for histologic analysis of diseased parenchyma, upper gastrointestinal endoscopy to evaluate variceal disease and the measurement of portal venous wedge pressure by venography [85]. Regardless of the technique used for volumetric assessment, surgeons must realize that anatomic volume does not necessarily correlate with synthetic function, and consequently each result must be carefully interpreted in the context of all available clinical and diagnostic information, in order to determine the optimal management approach.

14.8 Arriving at a Diagnosis and Management Plan

Solidifying the diagnosis of hilar cholangiocarcinoma requires a careful consideration of all available clinical information. A thorough history and physical examination, with additional directed evaluation as indicated, will assist in determining medical appropriateness for major abdominal surgery. A full laboratory and imaging evaluation is critical to stage the disease, assess liver function and plan the operative approach. While biopsy may assist in select patients, especially those with unresectable disease, it is not a requirement. In cases of indeterminate or non-diagnostic pathology, surgeons should consider proceeding to resection in appropriately selected patients with suspicious lesions on imaging, even in the absence of tissue diagnosis. In the authors' practice, MRCP is the preferred imaging modality for diagnosis and operative planning. In patients with hyperbilirubinaemia greater than 7 mg/dL, biliary drainage (either endoscopic or percutaneous, as feasible) is achieved for decompression. Once adequately decompressed below 7 mg/dL, CT

volumetry is performed to determine FLR. In patients with normal liver function and a FLR ≤20%, portal vein embolization (PVE) is pursued. Extirpation is scheduled once sufficient hypertrophy of the remaining liver segments is confirmed by imaging.

14.9 Management

The successful therapeutic management of hilar cholangiocarcinoma requires thoughtful multidisciplinary collaboration from surgical oncologists, medical oncologists, radiation oncologists, gastroenterologists and diagnostic and interventional radiologists. Accurate staging of the disease and thorough assessment of overall health, co-morbidities and performance status are critical to the determination of an appropriate evidence-based treatment plan. Preoperative optimization may require control of biliary obstruction and/or PVE for a borderline or inadequate FLR. In patients deemed to have resectable disease, surgery with negative margins constitutes first-line therapy. Though not standard of care, neoadjuvant therapy may be considered in patients with borderline or questionable resectability. Select patients with unresectable tumours and those with PSC may be eligible for orthotopic liver transplantation and should be referred to a transplant centre early in their evaluation. Patients with locally advanced or metastatic disease should be referred to gastroenterology or interventional radiology for consideration of biliary decompression, followed by early consultation with medical and radiation oncology for consideration of definitive chemotherapy and/or radiotherapy. Ultimately, the management approach taken for an individual patient will be highly dependent on specific characteristics of the tumour and patient, available specialty expertise and institutional resources. Given the rarity of hilar cholangiocarcinoma, selective referral to high-volume centres should be considered early in the evaluation if providers or institutions are not equipped to handle the complexity of management.

14.9.1 Preoperative Therapy

Preoperative preparation of patients with hilar cholangiocarcinoma may require biliary decompression to relieve symptoms of obstruction and decrease periprocedural risks. At this time, there is little evidence regarding the ideal level of serum bilirubin or the duration of decompression to guide clinicians in preoperative management [63]. In addition, there are few randomized controlled trials evaluating preoperative biliary drainage in the setting of hilar cholangiocarcinoma. A 2002 meta-analysis of randomized and non-randomized studies evaluating routine preoperative drainage in malignant biliary obstruction reported increased rates of postoperative complications among patients undergoing drainage [96], and this was corroborated by a recent systematic review of non-randomized studies in hilar cholangiocarcinoma [97] and a randomized trial in pancreatic head malignancy [98]. As a result, routine preoperative biliary drainage is not recommended, but there is

widespread consensus that drainage is appropriate in the following situations: patients with symptomatic jaundice or cholangitis, states of hepatic or renal insufficiency or severe malnutrition, as an adjunct to systemic therapy and in preparation for PVE [99, 100].

Biliary drainage can be accomplished internally (via ERCP) or externally (via PTC), and there are advantages and disadvantages to each. While internal drainage prevents bile loss from the enterohepatic circulation and may be easier for patients, it causes contamination of the sterile biliary tree and can be technically challenging due to tumour location and extension. As a result, it frequently does not allow for selective biliary drainage and may not adequately drain the proximal biliary tree. Complications of endoscopic drainage include cholangitis, haemorrhage, duodenal perforation and acute pancreatitis. External drainage by PTC, on the other hand, is more invasive but allows for proximal and selective biliary drainage and better delineation of endobiliary tumour spread and has higher technical success rates in hilar cholangiocarcinoma [100]. Complications of percutaneous drainage include occlusion and tube dysfunction, cholangitis, portal vein injury and thrombosis, biloma and haemobilia. Though metastatic tumour seeding was previously thought to be rare following PTC, recent series have suggested rates as high as 5.2% [101], although no influence on survival has been appreciated [102]. Retrospective studies of internal versus external drainage in hilar cholangiocarcinoma are mixed; while some have reported equivalent rates of success and complications, others have suggested endoscopic approaches have higher rates of periprocedural complications [103–105]. Randomized controlled trials evaluating internal and external approaches in various types of malignant biliary obstruction have yielded mixed results [106–108]. Though results are not yet available, a randomized trial of endoscopic versus percutaneous approaches in hilar cholangiocarcinoma patients is currently ongoing [109]. Ultimately, the approach chosen is highly dependent on patient and tumour characteristics and institutional resources and expertise and varies across institutions and internationally [99].

PVE should be considered in patients with an estimated FLR less than 30–40% due to increased risks of postoperative hepatic insufficiency and failure [100]. The technique of PVE typically entails the injection of embolic materials into select portal venous branches via a percutaneous transhepatic approach. Commonly used embolic materials include fibrin glue, polidocanol foam, gelatin sponge, metallic coils and cyanoacrylate [63]. Common complications following PVE include abdominal discomfort, fever and nausea or vomiting (post-embolization syndrome), while rare complications include cholangitis, liver abscess, portal vein thrombosis or haematoma and vascular injury [110]. PVE is most frequently performed prior to extended right hepatectomy, as more than 90% of patients undergo embolization of segments 4 or 5 through 8 [111]. Multiple reviews have reported that FLR hypertrophy ranges from 8% to 37%, while clinical success (defined as proceeding to resection) varies from 85% to 96% [110, 111]. Most centres wait 4–6 weeks following PVE to reassess FLR, though the waiting times may vary between individual centres. Although no randomized trial evidence exists in hilar cholangiocarcinoma, multiple studies have reported that the perioperative morbidity and mortality and long-term median survival of patients undergoing PVE are equivalent to patients with adequate liver volumes [91,

112–114], while patients with decreased FLR who do not receive PVE do worse than similar patients who do undergo the procedure [115]. If the degree of hypertrophy following technically successful PVE is ≤5% or the new FLR is ≤20%, most authors agree that surgery should be considered high risk and may be contraindicated [116].

14.9.2 Surgical Resection

Surgical resection with negative margins is the treatment of choice in medically appropriate patients with hilar cholangiocarcinoma, as it offers the best chance of cure and long-term survival. Unfortunately, due to its insidious growth and lack of early symptoms, many patients present with advanced disease, precluding resection. Among patients in whom resection is considered, a detailed preoperative evaluation of co-morbidities, performance status, synthetic hepatic function and FLR must be completed to determine overall fitness for a major operation and to estimate individualized perioperative risks of morbidity and mortality.

Many authors suggest staging laparoscopy should be routinely performed prior to resection for hilar cholangiocarcinoma. Recent studies suggest that almost 50% of patients undergoing surgery with curative intent are found to have unresectable disease or metastases at the time of surgery [117, 118]. Thus, roughly 14–41% of laparoscopies reveal metastases (liver or peritoneal) precluding laparotomy, and a recent pooled analysis of these studies reported a yield rate of 27% (95% CI 17–37%) [118]. Exploratory laparoscopy in this setting includes assessment of the peritoneum, liver and greater omentum. The lesser omentum may be incised to inspect celiac lymph nodes, and any lymphadenopathy identified (celiac or hepatoduodenal) may be excised. Assessment of local unresectability, on the other hand, is difficult laparoscopically, and hence such decisions are best made preoperatively by high-quality imaging. Extent of proximal biliary involvement, concurrent lobar atrophy and arterial involvement (if present) ultimately determine the feasibility of complete resection.

The primary goal of surgery for hilar cholangiocarcinoma is resection with negative margins. Modern series suggest that median and 5-year survival can be increased up to twofold when negative margins (R0) are achieved [100]. Thus, it is not surprising that studies examining the characteristics of surgery for hilar cholangiocarcinoma over time have shown that rates of limited extrahepatic bile duct resection have decreased substantially in modern practice (68% of surgeries performed in 1974–1988 vs. 14% in 2004–2014) [119]. The type of resection performed is determined by the anatomic location of the tumour and the proximal and distal extent of biliary and vascular involvement. Intraoperative frozen section is frequently used to aid in the determination of clear margins. The presence of a positive distal biliary margin should prompt consideration of a pancreatoduodenectomy for complete resection if additional clear margins cannot be obtained. While combined liver, extrahepatic bile duct resection and pancreatoduodenectomy can be performed safely, it is often associated with increased complications and therefore should be undertaken with caution. Obtaining an additional proximal bile duct margin, while difficult, is sometimes needed and can be done with further resection of the

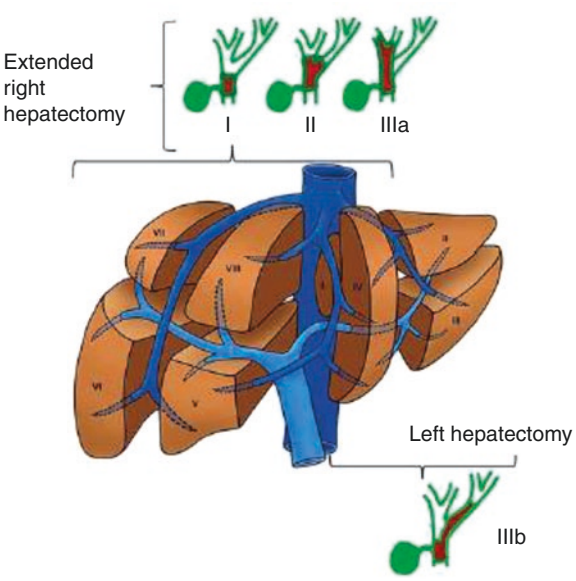

Fig. 14.10 Proposed operations for hilar cholangiocarcinoma according to Bismuth-Corlette type (with permission, from [175])

proximal biliary tree. Resection of proximal bile duct margins is ultimately limited by duct calibre. Despite its frequent use in current practice, literature to date is unclear regarding the survival benefit of additional margins [120, 121].

The Bismuth-Corlette classification system can be helpful in operative planning (Fig. 14.10). In general, limited resection of the extrahepatic biliary tree has been shown to increase the likelihood of R1 or R2 resection [122] and therefore should be avoided in hilar cholangiocarcinoma except in select instances of clearly localized Type I lesions amenable to hepaticojejunostomy (Fig. 14.11). In this instance, intraoperative frozen sections should be obtained to confirm clear proximal and distal margins. Outside of this small subset of patients, the majority of patients with hilar cholangiocarcinoma should undergo a left- or right-sided hepatectomy, extrahepatic bile duct resection and lymphadenectomy. Though several studies have not demonstrated a survival benefit with lymphadenectomy, removal of nodes along the cystic duct, common bile duct, hepatic artery and portal vein is critical to accurate staging (Fig. 14.12). Evidence of disease in celiac, pericaval or para-aortic (N2) nodes is typically considered a contraindication to resection given the prohibitively poor prognosis.

Typically the laterality of hepatic resection is determined by the extent of proximal biliary involvement, but lobar atrophy and vascular involvement must also be considered. Because a right-sided resection often allows for improved biliary margins due to increased extrahepatic length of the left hepatic duct, an extended right hepatectomy is often considered for Type I, II and IIIa lesions, while a left hepatectomy is typically performed for Type IIIb lesions (Fig. 14.10). In addition, routine caudate lobectomy should be performed to improve survival and decrease local recurrence [122], as the close proximity of the caudate lobe to the hilum can lead to

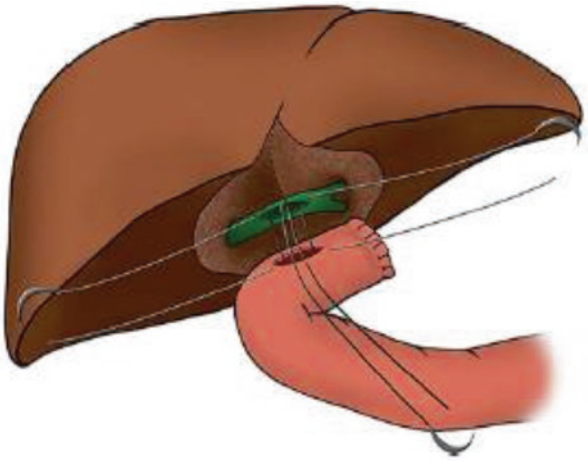

Fig. 14.11 Hepaticojejunostomy for limited resection of extrahepatic cholangiocarcinoma (with permission, from [175])

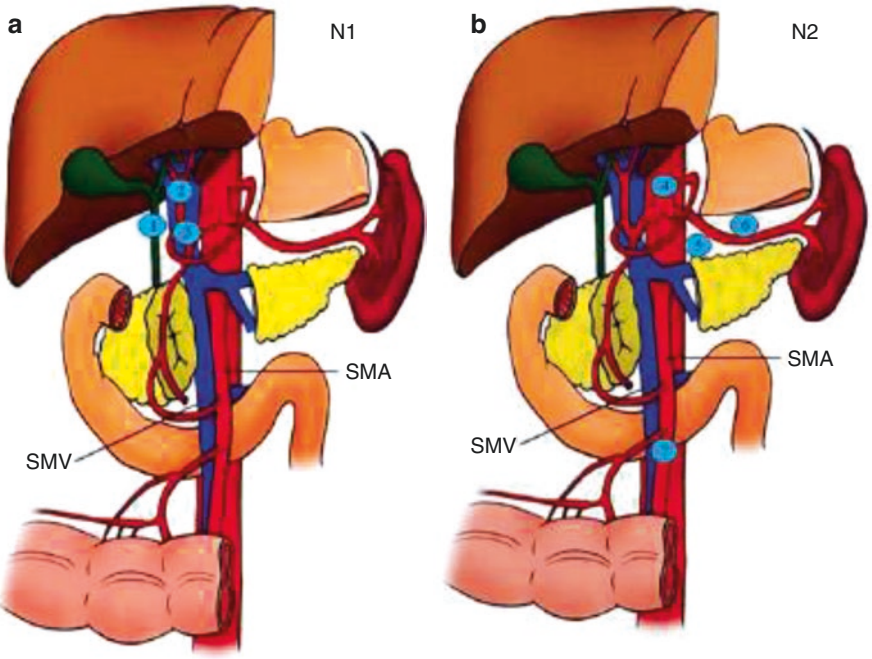

Fig. 14.12 Nodal stations for hilar cholangiocarcinoma: (**a**) N1 nodes include cystic duct, common bile duct, hepatic artery and portal vein lymph nodes (#1–3); (**b**) N2 nodes include celiac artery, pericaval, periaortic and superior mesenteric artery lymph nodes (#4–7) (with permission, from [175])

tumour involvement by local extension. While a subset of patients with Type IV lesions may be considered for a right or left trisectionectomy, these patients should also be considered for a transplantation protocol early in their clinical evaluation.

In the authors' practice, a few important intraoperative technical considerations are worth noting. A "no-touch technique", which calls for routine portal vein resection, is not routinely used. Instead, portal vein resection should be considered for cases with vessel involvement as long-term survival can be achieved with an R0 resection achieved by portal vein resection. Whether routine portal resection should be undertaken as part of a "no-touch" technique is more controversial and not universally performed by many liver surgeons. Early in the operation, the full extent of the tumour is defined to assess vessel involvement, prior to committing to resection. Traditional contraindications to resection are used to guide intraoperative determinations of resectability, which include main portal vein involvement or encasement, bilateral involvement of hepatic artery or portal vein branches, involvement of secondary biliary radicals bilaterally, unilateral hepatic artery involvement with contralateral venous or biliary involvement and evidence of distant lymphadenopathy or metastasis. Non-standard resections, such as limited hepatic resection or central hepatectomy, are rarely considered. And in most cases, transection of the bile ducts is performed intrahepatically during transection of the liver parenchyma.

The role of combined vascular resection in patients with hilar cholangiocarcinoma is not clearly defined. Though portal vein resection has been shown to lead to increased 30- and 90-day postoperative mortality [42], a recent meta-analysis reported equivalent survival in patients who did and did not undergo portal vein resection, despite more advanced disease in the portal vein resection group [123]. Thus, given the survival benefit of successful R0 resection, portal vein resection should be considered in appropriately selected otherwise resectable patients. Hepatic artery reconstruction, on the other hand, has not been shown to improve survival and is associated with increased morbidity and mortality [124, 125]. Consequently, this is not considered standard practice.

If unresectable or metastatic disease is first appreciated at open surgery, performance of a bilioenteric bypass may be considered depending on the age, comorbidities, performance status and life expectancy of the patient. At this time, no randomized data is available to guide this decision, but recent observational data suggests no survival benefit and a higher complication rate [126]. Given the hilar location of the tumour, the technique of operative bypass usually requires exposure of the proximal intrahepatic biliary tree. The left hepatic ducts may be exposed through the umbilical fissure or the ligamentum teres or via a partial excision of the left lateral segment (Longmire procedure). Bypass of the right lobe may be performed to the right anterior or posterior sectoral ducts. In general, segment III bypass is preferred unless technically unfeasible or the left lobe is atrophic or involved with tumour [127].

As noted, R0 resection offers the best chance for long-term survival in hilar cholangiocarcinoma patients. However, recent studies suggest only 25–35% of patients present with resectable disease [50, 128, 129]. The overall 5-year survival of all patients with hilar cholangiocarcinoma is reported as high as 30% [53], while the estimated 5-year survival of patients with advanced and metastatic disease is 5–10% [130]. In patients undergoing resection, 5-year survival approaches 53% in highly selected patients (Table 14.3) [63], and median survival is 34 months (range 13–64 months) [118]. Estimated prognosis improves significantly when patients are stratified by resection status. For patients with hilar cholangiocarcinoma undergoing margin negative (R0) resection, median and 5-year survival in the literature range from 27 to 58 months and 27–47%, respectively. Conversely, among patients undergoing margin positive (R1 or R2) resection, outcomes are substantially worse: median and 5-year survival range from 12 to 21 months and 0 to 23%, respectively [100]. Unfortunately, the recurrence rate following resection ranges from 50 to 70%, while rates of metastases following resection, with or without local recurrence, are as high as 40% [131, 132]. Despite these grim statistics, recent analyses of conditional survival following resection for hilar cholangiocarcinoma are encouraging. This type of analysis yields a more accurate estimate of long-term survival, as it illustrates that the probability of survival improves as the length of survival increases. For example, while actuarial overall survival decreased from 26.6% at 4 years to 9.9% at 8 years following surgery, 3-year conditional survival increased from 35% at 1 year to 54.4% at 5 years following surgery (Table 14.4 and Fig. 14.13) [129].

14.9.3 Liver Transplantation

In patients with unresectable hilar cholangiocarcinoma and those with a concurrent diagnosis of PSC, neoadjuvant chemoradiotherapy followed by orthotopic liver transplantation has evolved to become the preferred management approach in appropriately selected patients. Though early studies of transplantation alone reported dismal survival with 5-year rates below 30% at many centres [133, 134], recent protocols utilizing preoperative external beam radiotherapy (EBRT) and 5-fluorouracil (5-FU)

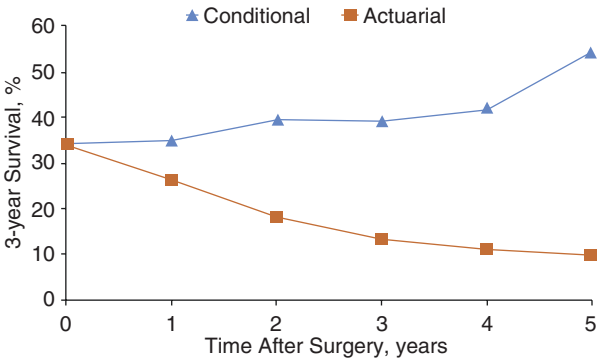

Fig. 14.13 Comparison of 3-year actuarial and conditional survival of all patients undergoing curative intent surgery for hilar cholangiocarcinoma (with permission, from [129])

chemosensitization have generated a renewed interest in the approach. Using this management strategy, 5-year recurrence-free and overall survival rates in highly selected patients have been reported to range from 65% to 82%, equalling and surpassing survival rates for patients undergoing successful R0 resection [135–137].

In 2006, the United Network for Organ Sharing published standardized criteria for MELD exception points in liver transplant candidates with hilar cholangiocarcinoma [138]. Patients with a concurrent diagnosis of PSC are also included in most protocols because the presence of multifocal intrahepatic disease and extensive periductal fibrosis frequently precludes successful resection [100]. Indeed, studies of liver transplantation in this cohort have reported improved outcomes and survival compared with resection alone [135, 137]. Exclusion criteria commonly used by many centres include (1) metastatic disease (lymph nodes, multifocal or extrahepatic), (2) prior malignancy <5 years, (3) previous abdominal radiotherapy, (4) uncontrolled infection, (5) previous resection or direct tumour biopsy and (6) mass > 3 cm. In a recent large prospective multicentre study, 25% of patients overall dropped out of the protocol and the average dropout rate increased by 11.5% every 3 months. Disease progression was the cause of dropout in a majority of patients [136]. These inclusion and exclusion criteria are important to understand. Patients with unresectable hilar cholangiocarcinoma benefit from early referral to a transplantation centre, and an unnecessary tissue biopsy (e.g. by EUS with FNA) or ill-advised attempt at resection may preclude otherwise eligible patients from consideration for transplant.

While the specific neoadjuvant protocol varies between centres, standard therapy includes EBRT given to a total dose of 4500 cGy (30 fractions of 150 cGy twice daily for 3 weeks) with concomitant infusion of 5-FU for the duration. This is followed by an endoluminal brachytherapy boost (iridium-192 seeds) with oral capecitabine maintenance (2000 mg/m2 of body surface area in two divided doses for 2 weeks, every 3 weeks until transplantation). Though low-dose brachytherapy was previously used, recent protocols utilize high-dose brachytherapy of 1200–1600 cGy in 2–4 fractions [100]. The majority of complications following neoadjuvant chemoradiotherapy are the sequel of radiation toxicity on various tissues, such as fatigue (41%), gastroduodenal ulcers (34%) and gastrointestinal dysmotility (18%), as well as portal vein (23%) and hepatic artery (12%) friability leading to stenosis and/or thrombosis. While many centres perform staging surgery prior to and separate from transplantation, some complete this step during transplantation. Many centres will routinely biopsy hepatic artery and pericholedochal lymph nodes, as positive findings will preclude transplantation. In addition, intraoperative bile duct frozen sections are used to determine the need for pancreatoduodenectomy for R0 resection of the distal bile duct [136]. Combined liver resection and pancreatoduodenectomy should be considered in light of the possible higher morbidity and perioperative mortality.

14.9.4 Nonoperative Management

Unfortunately, a majority of patients are not eligible for curative resection owing to advanced disease. Nonoperative therapies such as chemotherapy, radiation and

photodynamic therapy have traditionally been reserved for the adjuvant setting and cases of advanced or unresectable disease. However, recent studies have begun to investigate potential uses of these treatments in the neoadjuvant setting.

Because the hilar cholangiocarcinoma most commonly recurs loco-regionally, adjuvant therapy is recommended for patients with positive margins and nodal disease. Historically, 5-FU, either alone or in combination, has been the most extensively studied chemotherapeutic agent in biliary malignancy. Agents frequently used in combination included cisplatin, adriamycin, epirubicin and mitomycin C. However, response rates ranging from 0% to 40% and median survival ranging from 2% to 12 months have led to the investigation of other agents. Recently, gemcitabine, alone or commonly in combination with a platinum agent such as cisplatin or oxaliplatin, has been favoured for adjuvant use in cholangiocarcinoma [139]. Unfortunately, at present, evidence to guide recommendations in the adjuvant setting is sparse, as few randomized trials are reported, and most retrospective studies are small and include multiple types of biliary malignancies. Although two small retrospective studies on adjuvant chemotherapy alone in patients with hilar cholangiocarcinoma have reported improvements in survival [140, 141], the only randomized controlled trial with results currently available reported no survival benefit at 5 years [142]. However, numerous clinical trials evaluating the use of adjuvant chemotherapy in biliary malignancy are currently ongoing or have yet to present results [130].

Similarly, studies of adjuvant radiotherapy (most commonly with EBRT) show mixed results and are limited by size and heterogeneity [143]. A recent meta-analysis of adjuvant therapies for biliary malignancy reported no statistically significant benefit for adjuvant radiotherapy alone [144]. Thus, combined chemotherapy and radiation is currently the adjuvant therapy of choice [100]. This recommendation is supported by a meta-analysis of adjuvant chemoradiotherapy, as well as multiple retrospective studies of mixed biliary malignancy, suggesting that the survival in patients undergoing an R1 resection followed by adjuvant therapy was similar to patients undergoing an R0 resection and no further adjuvant therapy [144–146]. Moreover, a recently reported single-arm phase II trial of adjuvant capecitabine and gemcitabine followed by capecitabine chemoradiotherapy in biliary malignancy (SWOG s0809) confirmed feasibility and reported no difference in 2-year survival rates between patients undergoing R0 and R1 resection (67% vs. 60%, respectively) [147].

Similar regimens are used for patients with unresectable and metastatic hilar cholangiocarcinoma. In unresectable patients ineligible for transplant, definitive chemoradiation with or without intraluminal brachytherapy has been reported to improve local control of disease [148]. A small randomized trial of radiotherapy (brachytherapy and EBRT) and drainage versus drainage alone reported modest improvements in survival for the radiotherapy arm (12.9 vs. 9.9 months, $p < 0.05$) [149].

Radiation therapy is not generally used in the setting of recurrence following resection due to risks of radiation toxicity to the jejunal reconstruction, and instead chemotherapy alone is pursued [100]. The chemotherapy regimen of choice in locally advanced, recurrent and metastatic hilar cholangiocarcinoma is dictated by results of the Advanced Biliary Tract Cancer (ABC)-02 trial, which was a phase III study evaluating gemcitabine and cisplatin versus gemcitabine alone in patients

with advanced stage biliary malignancy. The authors reported significantly improved median survival (11.7 vs. 8.1 months, $p < 0.001$), progression-free survival and tumour control in the combination arm [150]. Recent randomized phase II trials evaluating the addition of targeted therapies, such as cetuximab and cediranib, among others, have yielded disappointing results in patients with non-resectable, recurrent or metastatic disease [122, 151, 152].

Outside of a liver transplantation protocol, currently there is little evidence supporting the use of neoadjuvant therapy in hilar cholangiocarcinoma. Two case reports of neoadjuvant gemcitabine chemotherapy have reported successful downstaging and resection of previously unresectable tumours, resulting in at least 18 months of recurrence-free survival [153]. However, a retrospective review of neoadjuvant gemcitabine in 28 patients reported a decreased median survival in the neoadjuvant group and recommended against neoadjuvant therapy in resectable patients [154]. A single small retrospective review of neoadjuvant EBRT suggested improved control of implantation metastasis following ERCP [155]. Two studies of neoadjuvant therapy evaluated chemoradiotherapy with EBRT and 5-FU in unresectable patients and reported R0 resection rates ranging from 92% to 100% [156, 157]. In addition, multiple studies have reported the safety and utility of photodynamic therapy in the neoadjuvant setting. Thus, at this time, while neoadjuvant therapy for hilar cholangiocarcinoma is not standard, it may be considered in select patients with advanced disease when potential tumour downstaging is desired prior to resection.

Photodynamic therapy (PDT) has recently been proposed as a possible treatment for unresectable hilar cholangiocarcinoma. In this approach, a non-toxic photosensitizing drug is systemically administered and preferentially taken up by tumour cells. Two or three days later (depending on the drug administered), high-energy laser light is administered intraluminally via an endoscopic procedure. Light activation of the photosensitizing agent leads to the formation of oxygen free radicals, which cause the destruction of tumour cells through apoptosis [158]. Prior to PDT, endobiliary decompression is achieved to relieve obstruction, and cholangioscopy is performed to define the precise locations of tumour extension. Complications of PDT include phototoxicity, biliary stenosis and cholangitis [158]. In the setting of unresectable hilar cholangiocarcinoma, numerous retrospective studies have reported significant improvements in median days of survival (ranging 130–270 days), biliary decompression and quality of life when PDT and drainage were compared to drainage alone [159–162]. These results have been confirmed by two randomized trials comparing PDT and drainage versus drainage alone. In the study by Zoepf and colleagues, median survival for the PDT group was 630 days, compared to 210 days in the drainage-only group ($p < 0.05$) [158, 163]. In addition, prospective studies of PDT and drainage have shown significantly improved 1-year survival when compared to chemotherapy and drainage [164, 165]. Few studies have examined the use of PDT in the adjuvant and neoadjuvant settings [166, 167]. A small phase II study of neoadjuvant PDT in hilar cholangiocarcinoma reported a R0 resection rate of 100% and a 1-year recurrence-free survival rate of 83% [166]. Overall, PDT has a limited role in treating most patients with hilar cholangiocarcinoma.

14.9.5 Palliation in Hilar Cholangiocarcinoma

Because most patients present with locally advanced or unresectable disease, palliation is an important component of the management of hilar cholangiocarcinoma. In addition to consideration of the systemic therapies discussed above in medically appropriate patients, palliation in all patients with unresectable disease should focus on quality of life, symptom control and relief of biliary obstruction. Biliary decompression in this cohort may be achieved through endoscopic, percutaneous or operative approaches. The approach chosen largely depends on anatomic considerations of the tumour, medical fitness of the patient and available institutional resources and expertise.

Minimally invasive approaches (endoscopic or percutaneous) are preferred if the presence of locally advanced or metastatic disease is determined prior to operation. The choice of approach is controversial, as the current evidence addressing this issue is mixed. While an early randomized trial of endoscopic versus percutaneous approaches demonstrated a higher success rate and lower mortality for plastic stents by the endoscopic approach, a subsequent trial reported a higher therapeutic success rate and median survival with the use of self-expanding metal stents by the percutaneous approach [106, 107]. Ensuing retrospective studies have supported this latter finding [168]. Though plastic stents cost less, randomized evidence in hilar cholangiocarcinoma suggests that plastic stenting results in higher rates of cholangitis, failure and need for reintervention [169]. Recent guidelines recommend palliative use of a self-expanding metal stent in patients with a life expectancy longer than 3 months, while plastic stenting is considered for a life expectancy less than 3 months [99]. Though previous reports asserted drainage of 25% of liver volume was necessary to achieve adequate control of obstructive symptoms [170], recent research suggests ≥50% is best [171]. Though retrospective reports are mixed, the only randomized trial to evaluate unilateral versus bilateral drainage reported increased technical success (89% vs. 77%, $p = 0.041$) and decreased rates of complications (19% vs. 27%, $p = 0.026$) and cholangitis (9% vs. 17%, $p = 0.013$) for unilateral drainage [172]. Current recommendations suggest either is acceptable, as long as adequate drainage is achieved [99].

14.10 Perioperative Care and Outcomes

The operative and nonoperative management of hilar cholangiocarcinoma requires focused multidisciplinary collaboration and an institutional commitment to the complex care of these patients. Surgery for hilar cholangiocarcinoma is high risk even in the healthiest of patients and requires unremitting vigilance for the detection of complications to rescue patients from domino complications that can lead to mortality.

Although outcomes have substantially improved over time, complications remain common following surgery for hilar cholangiocarcinoma (Table 14.5). Compared to patients from the years 1974 to 1988, patients presenting between 2004 and 2014 are

older and more likely to have Bismuth Type III and IV tumours. Rates of concurrent major hepatectomy with extrahepatic bile duct resection have increased, while rates of limited biliary tract resection have decreased. As technology and surgical technique have improved, intraoperative blood loss and rates of transfusion have significantly decreased over time, rates of R0 resection have increased (82% in 2004–2014 vs. 26% 1974–1988, $p < 0.001$), and rates of morbidity (41% vs. 76%, $p < 0.001$) and mortality (4.4% vs. 26%, $p < 0.001$) have shown substantial improvements [119].

Recently published institutional series have highlighted the risks of morbidity and mortality during the modern era (after the year 2000). As expected, procedure-related complications depend on the type of surgery performed; extrahepatic bile duct resection combined with major hepatectomy has a greater risk of complications than limited bile duct resection alone. Recent institutional series suggest 75–85% of modern resections for hilar cholangiocarcinoma include a major hepatectomy [129, 173]. Reported complication rates in the literature range from 31% to 63%, while mortality rates range from 0% to 8% [118]. In addition to general postoperative complications and those associated with general anaesthesia, important procedure-specific complications following surgery for hilar cholangiocarcinoma include biliary leak, haemorrhage, intra-abdominal fluid collections and abscesses, cholangitis, portal vein thrombus and hepatic insufficiency. The most common complication following surgery for hilar cholangiocarcinoma is postoperative fluid collections and abscesses, reported to occur in 21.8% and 18.6% of cases, respectively [129].

Complications following resection for hilar cholangiocarcinoma must be promptly identified, as a delay in diagnosis may lead to the development of sepsis, liver failure, multi-system organ failure and ultimately death (Table 14.5). Infectious complications such as fluid collections, abscesses and cholangitis should be treated with early antibiotic therapy and source control. Broad-spectrum antibiotics covering gram-positive, enteral gram-negative and anaerobic bacteria should be started initially and, with clinical improvement, can subsequently be tailored to sensitivities from previously collected cultures. Source control may often be obtained with percutaneous transabdominal drainage, but reoperation must be considered in the setting of peritonitis, haemodynamic instability or failure to obtain source control with drainage. A biliary leak that cannot be controlled with percutaneous transabdominal drainage may require percutaneous transhepatic cholangiography with stenting across the leak and internal-external drainage. Massive biliary leaks that cannot be controlled by percutaneous means and those causing peritonitis or haemodynamic instability may require operative re-exploration. Depending on the timing and clinical circumstance, postoperative haemorrhage from the liver edge may be treated by conservative therapy with resuscitation and transfusion or may require re-exploration for definitive control. Hepatic insufficiency is best managed by early recognition and best supportive therapy. Management in an intensive care unit setting would be ideal in this scenario. Fluid balance and nutrition should be optimized, and signs of worsening hepatic function, such as coagulopathy and thrombocytopenia, should be addressed with early goal-directed therapy. A thorough diagnostic evaluation should be completed to rule out reversible causes of insufficiency (biliary obstruction, portal vein thrombosis), and all hepatotoxic drugs should be avoided.

14.11 Future Directions

Though substantial progress has been made in the biological understanding and clinical management of hilar cholangiocarcinoma, many unresolved questions remain. Further improvements in the long-term survival of patients with hilar cholangiocarcinoma will require a better understanding of the molecular mechanisms of malignant progression, which will aid the development of more effective systemic therapies to be used in the neoadjuvant and adjuvant settings. As discussed above, photodynamic therapy is a promising new therapy under investigation. Multiple targeted agents, such as the tyrosine kinase inhibitors erlotinib, cetuximab and sorafenib, and the vascular endothelial growth factor inhibitor bevacizumab, among others, are actively being studied in patients with cholangiocarcinoma [122]. Active immunotherapy is another potential treatment for cholangiocarcinoma in early experimental phases [174]. And finally, in concert with general trends in personalized medicine throughout oncology, a more complete elucidation of the genetic mechanisms of hilar cholangiocarcinoma may eventually allow for the use of systemic regimens specifically targeted to an individual tumour's unique genetic mutations.

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Gallbladder Cancer

15

Vikram Chaudhari, Manish Bhandare, and Shailesh V. Shrikhande

Abbreviations

AJCC	American Joint Committee on Cancer
APBDJ	Anomalous pancreaticobiliary duct junction
BMI	Body mass index
CA19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
CT	Computed tomography scan
EC	Extended cholecystectomy
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasonography
FDG	[18F]-2-deoxy-D-glucose
FNAC	Fine-needle aspiration cytology
GB	Gallbladder
GBC	Gallbladder cancer
GI	Gastrointestinal
HPD	Hepatopancreaticoduodenectomy
LC	Laparoscopic cholecystectomy
LFT	Liver function tests
MRA	Magnetic resonance angiography
MRCP	Magnetic resonance cholangiopancreatography

V. Chaudhari · M. Bhandare · S. V. Shrikhande (✉)
GI and HPB Services, Department of Surgical Oncology, Gastro Intestinal Disease Management Group, Tata Memorial Hospital, Mumbai, India

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MRI	Magnetic resonance imaging
NACT	Neoadjuvant chemotherapy
OS	Overall survival
PD	Pancreaticoduodenectomy
PET	Positron emission tomography
RCT	Randomized controlled trial
RR	Relative risk
TNM	Tumour, node, metastasis
UGI	Upper gastrointestinal
USG/US	Ultrasonography/ultrasound
VEGF	Vascular endothelial growth factor

15.1 Introduction

Gallbladder cancer (GBC) was first described by Maximillian de Stoll in two autopsy cases in 1777. The first documented GBC resection was performed by Keen in 1891 [1]. Late presentation, limited treatment options, poor prognosis and survival have traditionally been associated with this lethal cancer. Less than 10% patients have disease limited to GB wall on presentation. At least 45% patients have lymph node involvement, more than 60% of the patients exhibit local advancement with invasion of liver and/or adjacent organs and as many as 54% patients present with metastatic disease [2]. Asymptomatic early stage, neglect due to similarity of pain with more common benign disorder of the same organ (chronic cholecystitis), absence of serosal layer in gallbladder wall, lack of access to healthcare, low incidence of cholecystectomy in a particular population and the inherent aggressive nature of the disease contribute to the delayed presentation of the disease [3].

Surgery is the only curative treatment option. Improvements in surgical techniques, systemic chemotherapy and increased cholecystectomy rates after the advent of laparoscopy resulting in indirect early detection have improved results recently [4, 5].

15.2 Epidemiology

GBC is the sixth most common gastrointestinal malignancy. It is the most common biliary tract cancer and represents around 80–95% of all biliary tract cancers [6]. Incidence of this malignancy varies significantly across the globe and among the races. It is a result of differences in environmental exposure, genetic predisposition and risk factors which vary geographically and among ethnic groups [7]. More than 64% GBC cases are detected in Asia, and two-thirds of the cases are detected in developing countries. Chile has the highest age-specific rate of 9.7/100,000 population followed by Bolivia and South Korea (see Figs. 15.1, 15.2, 15.3, and 15.4).

Although an incidence rate of 2.5 per 100,000 population in India appears low, as compared to these high-incidence countries, the overall disease burden is still

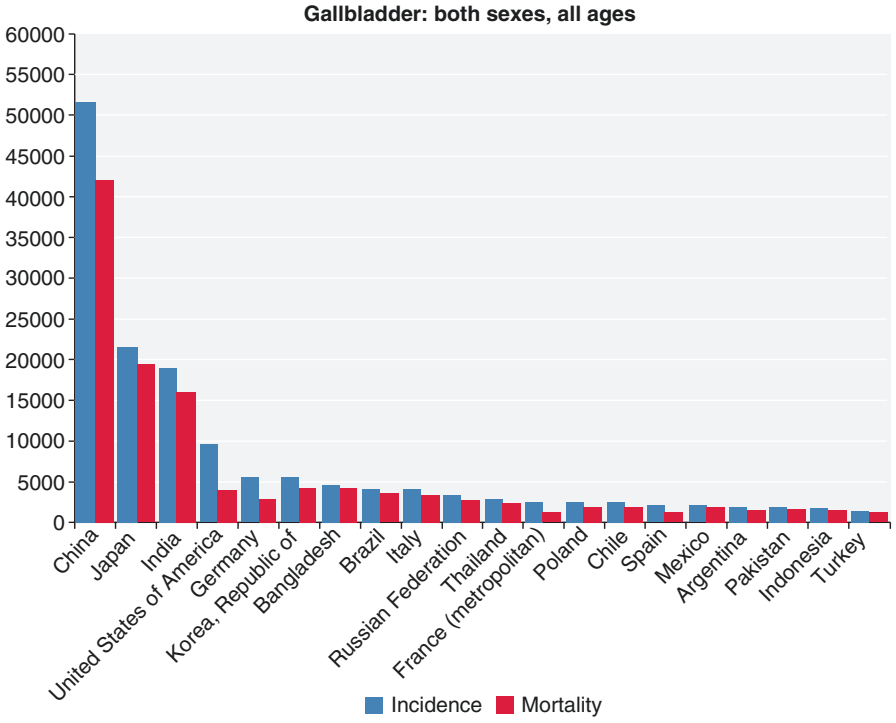

Fig. 15.1 Gallbladder cancer—annual incidence and mortality (Reproduced from—Source: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr, accessed on 21/04/2015)

high due to a very large population (Fig. 15.1) [8]. Significant regional variation in incidence of this disease has been noted in India. Population-based data reveal that the incidence of gallbladder cancer is very high in northern Indian cities (5–7 per 100,000 women) and low (0–0.7 per 100,000 women) in southern India [9]. North and Northeast Indian women along with women from Bhutan, Nepal and Pakistan have a particularly high incidence of gallbladder cancer. This is an active area of research which points to dietary habits, genetic susceptibility and poor access to healthcare as possible predisposing factors.

15.2.1 Age

Incidence gradually increases with age and is the highest above 60 years of age. Patients generally present in the sixth and seventh decades of life. However, it is not uncommon to find women in the second or third decade of life presenting with the disease [7].

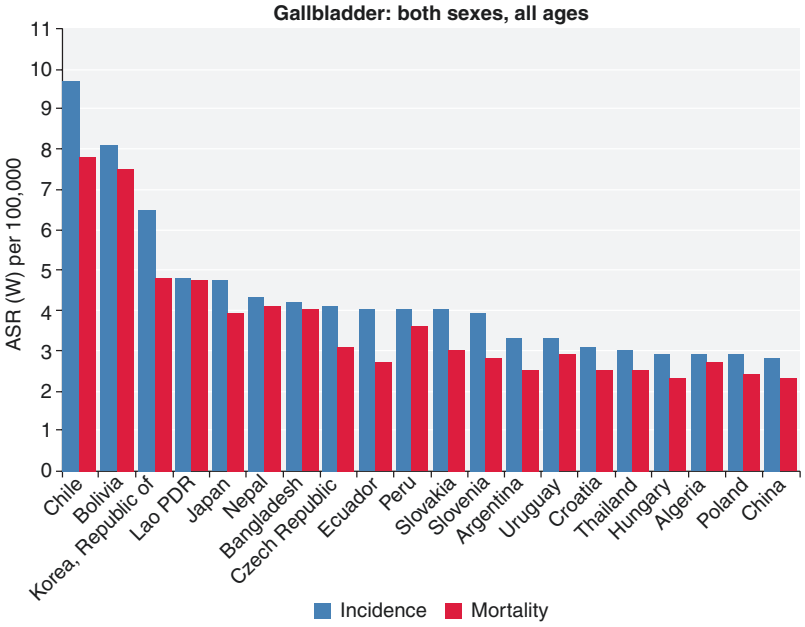

Fig. 15.2 Incidence and mortality/100,000 population (Reproduced from—Source: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr, accessed on 21/04/2015)

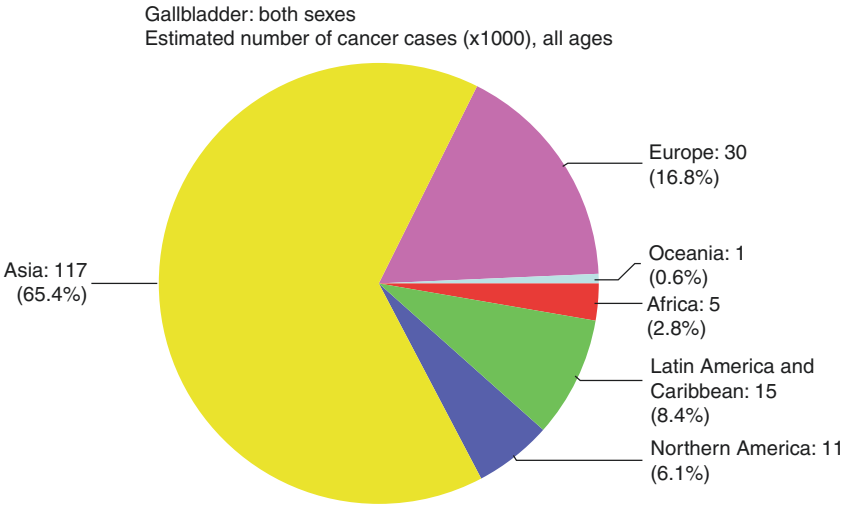

Fig. 15.3 Estimated disease distribution across continents (Reproduced from—Source: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr, accessed on 21/04/2015)

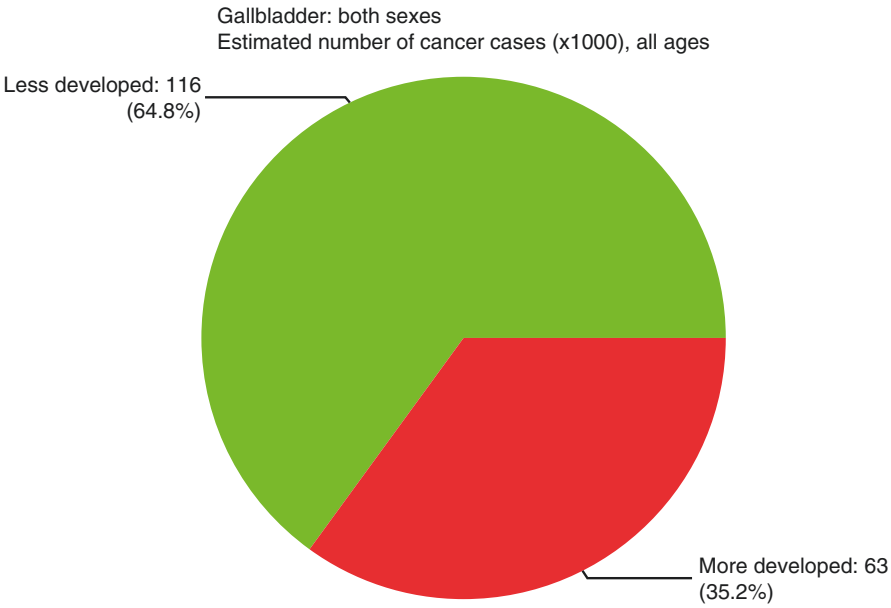

Fig. 15.4 Socio-economic distribution (Reproduced from—Source: Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr, accessed on 21/04/2015)

15.2.2 Sex

GBC is particularly common among women; they are approximately three times more likely to develop GBC than men [6]. This ratio varies geographically, and it is as high as 5:1 in countries such as Pakistan and Colombia [10].

15.2.3 Obesity

Obesity and its predisposition to various cancers is gaining importance currently due to its rising prevalence in epidemic proportions throughout the world. In a recent meta-analysis, overweight and obesity were associated with 14% and 56% excess risk of GBC, respectively. Obesity (BMI (body mass index)—>30) was found to be associated with relative risk (RR) of 1.54 for the development of GBC. Risk was found to be higher in women (RR—1.67). Overweight (BMI 25–30) was associated with GBC risk only in women [11]. Association of GBC with obesity is one of the strongest seen for any cancer sites [12].

15.3 Aetiopathogenesis

15.3.1 Pathogenesis

The development of GBC is a result of combined effects of chronic infection, inflammation, environmental exposure and genetic susceptibility. The evidence strongly supports chronic, unresolved inflammation as the main carcinogenic mechanism of GBC, regardless of the initial aetiologic trigger [13].

Multistep models of carcinogenesis similar to adenoma-carcinoma pathway in colorectal cancer have been proposed [14, 3]. More recently, the 'gallbladder carcinogenesis and dissemination model' proposed by Barreto et al. takes into consideration the pathological change occurring in the gallbladder epithelium progressing sequentially from normal epithelial mucosa to the development of cancer via the two most common pathways, namely, metaplasia/hyperplasias and dysplasia, and beyond the localized disease in the gallbladder to include the spread of the cancer to the regional and distant organs [15].

The recurrent cycles of gallbladder epithelium damage and repair result in a chronic inflammatory environment that promotes progressive morphological impairment through a metaplasia-dysplasia-carcinoma sequence and genome instability. Increased cell turnover and oxidative stress promote early alteration of TP53, cell cycle deregulation, apoptosis and replicative senescence. Inactivation of TP53 is the most common and earliest mutation noted in more than 50% of the GBCs.

Though studies have reported female hormone receptor (ER/PR) expression in GBC, results are not consistent, and their role as a direct aetiological factor in GBC is not yet established [16].

15.3.2 Aetiology

15.3.2.1 Cholelithiasis

Epidemiological evidence in many studies supports gallstones as an aetiological factor for GBC and have shown higher incidence of GBC in patients with gallstones. On the contrary, studies have also demonstrated a relatively low incidence of GBC in countries reporting a high incidence of gallstones.

Although 70–90% of GBC patients have associated gallstones, as low as 0.3% patients with gallstones are likely to develop GBC. This incidence is very low and unlikely to prove a major causative relationship. In studies where gallstones appear to have a causative role for cancer, the risk increases with increasing size, volume, weight and number of the stones. The impact of duration of the stone or its composition is not clear. A large population-based study from South Korea recently demonstrated higher mortality from hepatobiliary cancers, particularly GBC in patients with gallstones irrespective of the confounding factors [17]. Finally evidence at this time indicates that gallstones are a cofactor in the causation of gallbladder cancer. Absolute proof of their role as a cause for GBC is lacking [18].

Heavy stone load, stone >3 cm in size and even asymptomatic stones in females in high-risk areas have been proposed as indications for prophylactic cholecystectomy to reduce the risk of GBC considering the low morbidity associated with elective laparoscopic cholecystectomy [19, 20]. Considering a very low incidence of GBC in patients with gallstones, it is difficult to assess the actuarial benefit of this approach objectively. In Chile, screening and treating women under 40 years of age, with asymptomatic cholelithiasis, showed that prophylactic laparoscopic cholecystectomy can significantly benefit the population and reduce the GBC incidence at a very low incremental cost [21].

15.3.2.2 Anomalous Pancreaticobiliary Ductal Junction (APBDJ)

This congenital anomaly is known to predispose to biliary tract cancers. Patients with APBDJ develop GBC at younger age and more commonly develop a favourable papillary variant of GBC. Prophylactic cholecystectomy is recommended to obviate the risk of GBC [22].

15.3.2.3 Infection and Inflammation

Chronic infections of the gallbladder and inflammatory conditions like cholecystoenteric fistula are known to increase risk of GBC. Infections may contribute to the development of GBC either directly or through gallstone formation. The chronic carrier state of *S. typhi*, *S. paratyphi* and *Helicobacter* species is frequently implicated. Non-typhoidal salmonella species have also been recently shown to have a causative role. In cancer-endemic countries, efforts directed at treating typhoid and non-typhoidal *Salmonella* species could reduce the chronic carrier state of these species, which may be contributing to the inflammatory stimulus in carcinogenesis. This strategy may help reduce in the incidence of GBC [23]. Clonorchiasis is associated with cholangiocarcinoma. It also results in cholelithiasis and cholecystitis and may also be associated with GBC [24]. Infections and inflammatory conditions result in chronic inflammatory state and GBC through mechanism/s described earlier.

15.3.2.4 Porcelain Gallbladder

Calcification of the gallbladder wall *porcelain gallbladder* has been associated with GBC. Risk was estimated to be around 10% in the past. Towfigh et al. reviewed the records and pathology slides of 10,741 patients who underwent cholecystectomy between 1955 and 1998. Incidence of porcelain gallbladder was 15 cases (0.14%). All specimens demonstrated chronic cholecystitis and partial calcification of the gallbladder wall. No patient had gallbladder carcinoma. During this same period, 88 (0.82%) patients had gallbladder carcinoma, none of whom showed calcification of the wall. No carcinoma was identified among patients with porcelain gallbladder, and no patient with gallbladder carcinoma had calcified gallbladder. They concluded that porcelain gallbladder is not associated with GBC risk [25].

Similarly Khan et al. reviewed seven published series that included 60,665 cholecystectomies. The overall incidence of porcelain gallbladder was 0.2%, and GBC occurred in 15% of the porcelain gallbladder cases. Most of these cases were reported in old literature.

It is now understood that risk of GBC with porcelain gallbladder was overestimated in the past. Stippled and incomplete calcification may have a small risk of developing GBC, and diffuse calcification is not associated with the risk of GBC.

Though prophylactic cholecystectomy for reduction of GBC risk in this clinical scenario can be debated, it is generally accepted as an indication for cholecystectomy with or without associated symptoms or gallstones.

15.3.2.5 Miscellaneous

Smoking Tobacco smoking is associated with increased risk of GBC, and association seems to be dose dependent [26].

Alcohol consumption, oral contraceptive pills, occupational exposure to rubber, methyldopa, aflatoxins (in Chile), *rai oil* (in North India) and high mineral levels in soil and water are some other proposed risk factors with variable supportive evidence [27, 28].

15.4 Pathology and Mode of Spread

15.4.1 Pathology and Histology

GBCs have been shown to have adenomatous components. Similarly, patients with large adenomatous polyps are known to harbour in situ carcinoma or an invasive focus of adenocarcinoma, clearly establishing the existence of adenoma-carcinoma sequence in GBC. Risk associated with the polyps is known to increase with a solitary polyp, size and age.

In a study by Kozuka et al., as early as 1982, 19% of invasive GBCs had adenomatous components, and all invasive tumours occurred in polyps larger than 12 mm. The average patient age was 50.5 years for benign adenomas, 58.3 years for adenomas with malignant change and 64.8 years for invasive carcinomas [29]. It has been suggested considering the average age of the patients presenting with adenomas, carcinoma in situ and invasive carcinomas that adenoma-carcinoma progression on average takes 15 years with variable time required for intermediate stages [30]. Adenoma to carcinoma in situ progression is supposed to happen in 5 years, and carcinoma in situ to invasion happens over a decade.

Sixty percent of the tumours are located in the fundus of the gallbladder and 30% in the body, and 10% arise in the cystic duct. Tumours located in the non-peritonealized side of the gallbladder (i.e. gallbladder fossa, liver bed) infiltrate the liver early in the course. These tumours are also likely to harbour residual disease and benefit more with a re-resection in incidental GBC than those located on peritoneal side of the gallbladder [31].

Grossly tumours are greyish white in colour. Large tumours commonly replace gallbladder fossa with the formation of a liver-infiltrating large mass; sometimes gallbladder may get distended with the tumour or even constricted or deformed due to obstruction at the neck and body.

More than 95% malignant gallbladder tumours are carcinomas [32]. Most of the gallbladder cancers are adenocarcinomas. In a study by Duffy et al., histological distribution of the tumours was 88% adenocarcinoma, 4% squamous, 3% neuroendocrine and 2% sarcomas [33].

Papillary carcinomas of the gallbladder deserve a special mention for the favourable prognosis associated with them and their ability to grow to large sizes without being invasive. It can be attributed to their exophytic growth, delayed invasion into the gallbladder wall and probably early obstructive symptoms. However prognosis of invasive and lymph node-positive papillary tumours is almost similar to other invasive GBCs, and therefore distinction between invasive and non-invasive tumours among the papillary tumours is also essential [34].

15.4.2 Mode of Spread

GBC spreads by the following routes, namely:

1. Lymphatic
2. Haematogenous
3. Intraperitoneal
4. Spread via cystic duct (intraductal)
5. Direct anatomic spread involving adjacent organs

Lymphatic spread is the most common and an important mode of dissemination. Cystic, pericholedochal and periportal lymph nodes in the hepatoduodenal ligament are the primary lymph nodes draining GB. Tumours usually spread along retropancreatic, celiac and mesenteric pathways to reach superior mesenteric and celiac lymph nodes, respectively. These lymph node groups ultimately drain into interaortocaval lymph nodes below the left renal vein [35]. Lymph nodal spread to interaortocaval region and celiac and superior mesenteric arteries (N2 nodes) portends poor prognosis and has metastatic (M1) status.

Spread by venous route is via cholecystohepatic veins. They drain directly into intrahepatic branches of portal vein and subsequently into the middle and right hepatic veins. This venous spread forms the basis of excision of the middle liver segments (4b and 5) as part of radical cholecystectomy [36].

Intraperitoneal spread is common and generally involves the adjacent organs like the liver, CBD, colon, duodenum, pancreas, omentum and stomach.

Intraductal spread along the lumen and the wall of the ducts is rare and is usually seen in papillary type of GBC.

15.5 Clinical Presentation

GBC patients commonly present in old age and at an advanced stage. Presentation can be incidental, which is defined as a histopathological surprise after a simple cholecystectomy performed for apparently benign gallstone disease. It is detected incidentally after 0.3–1.87% cholecystectomies. Though the incidence varies significantly across series, it is around 1% in India [37]. Incidental detection increases the chances of curative intent treatment as more patients are likely to harbour early-stage disease [38]. This suffices for a strong recommendation for the surgeons to open a gallbladder specimen after each cholecystectomy and perform a frozen section of any suspicious lesion, at least in high-prevalence areas.

Contribution of incidental gallbladder cancers to overall series varies across institutes from 10 to 93% [39, 40]. In a retrospective review of 435 patients with GBC treated over a 10-year period at Memorial Sloan Kettering Cancer Center (MSKCC), 47% of cases were incidental GBCs [33]. More commonly though, it presents as a suspicious or obvious gallbladder mass or polyp on ultrasound. Patients commonly complain of upper gastrointestinal (UGI) symptoms like dyspepsia, persistent right upper quadrant pain, loss of appetite and weight.

Palpable abdominal mass and jaundice are signs of advanced disease. Jaundice in particular is considered an ominous sign. In a study by Hawkins et al. [41], 82 (34%) of 240 patients with GBC presented with jaundice. Jaundiced patients (96%) were more likely to have advanced-stage disease than the non-jaundiced patients (60%). Only six (7%) jaundiced patients were resected with curative intent, and only four (5%) had negative surgical margins. The median disease-specific survival in patients presenting with jaundice was 6 months and was significantly lower compared with 16 months in patients without jaundice. In the group presenting with jaundice, there were no disease-free survivors at 2 years, compared with 21% in the group without jaundice [41]. Older studies regarded the presence of jaundice as a contraindication for surgical exploration. Recent reports however have shown encouraging results especially for patients with a complete resection and surgical outcomes comparable to patients without jaundice [42–44].

Jaundice in patients with carcinoma gallbladder is an indicator of advanced disease; however, it is not a contraindication to surgery. Proper patient selection for treatment with curative intent aids in optimum treatment outcomes although morbidity may be slightly higher in patients with obstructive jaundice. Neoadjuvant treatment outcomes may also aid in better patient selection.

15.6 Investigations (Table 15.1)

15.6.1 Ultrasonography (USG)

Ultrasonography (USG) is the usual first-line investigation for any patient with right upper quadrant pain. It incites first suspicion and prompts further evaluation of the

Table 15.1 Potential use, advantages and disadvantages of various radiologic investigative modalities

Modality	Use/potential	Advantages	Disadvantages
USG	1. Primary mass 2. Lymph node involvement 3. Ascites 4. Level of block in jaundice 5. Liver metastasis 6. USG-guided FNAC/ biopsy in advanced cases and guided ascitic tapping 7. Doppler detection of vascular invasion	1. Cost 2. Availability 3. No radiation exposure 4. Detects associated gallstones	1. Operator dependent 2. No cross-sectional images—limited use in treatment planning 3. Low sensitivity—in detecting nodal disease, peritoneal disease , small metastatic lesions
CT scan	Main modality for overall staging and treatment planning	1. Better anatomic information, evaluation of regional nodes, adjacent organ involvement and liver metastases 2. Detection of extrahepatic disease	1. Radiation exposure 2. Low sensitivity in detecting small metastases and peritoneal deposits
MRI	Similar to CT scan	1. Mostly similar to CECT scan 2. No radiation exposure 3. Better evaluation of biliary tract particularly in jaundiced patients and vascular invasion	1. Low sensitivity in detecting peritoneal deposits 2. Costs
PET-CT	Detection/rule out metastatic disease	1. More sensitive in detection of occult metastatic disease in liver, nodes and peritoneum 2. Can be combined with CECT for overall better staging and treatment planning as a single modality	1. Cost 2. Difficult to differentiate between 3. Inflammation and malignancy 4. Not proven to better CT or MRI findings

disease process. Intraluminal mass, gallbladder-replacing or invasive mass and discontinuity of the mucosal echo are some important sonographic signs detected significantly more commonly in patients with GBC than non-malignant pathologies. GBC patients are also more likely to have solitary, large-sized gallstone and displaced stone [45].

Obvious metastasis and ascites can easily be detected. USG is limited in its ability to detect lymph nodal disease or peritoneal disease and fails to provide any definitive information regarding treatment planning.

15.6.2 Computed Tomography (CT) Scan

Cross-sectional imaging particularly a triple-phase contrast-enhanced CT (CECT) scan is an important part of the staging and preoperative planning of GBC.

CECT may demonstrate a hypoattenuating or isoattenuating mass in the gallbladder fossa and soft-tissue invasion of the liver. Mass may contain low-attenuation areas of the necrosis. Biliary obstruction at the level of the porta hepatis and lymph node metastasis are frequent associated findings. Metastasis to the liver and lungs can be reliably demonstrated. It also has a very good sensitivity for detection of even small quantity of free fluid in the abdominal cavity. Local extent of disease, nodal involvement, distant metastases, adjacent organ and vascular involvement can be detected with sensitivity and specificity exceeding 80%.

Helical CT provides 83–86% accuracy in the diagnosis of the local extent of GBC, showing fairly acceptable sensitivity and specificity for the T2 and more advanced lesions but poor sensitivity for the T1 lesions [46]. With nodal size greater than 1 cm and a ring-like heterogeneous enhancement, accuracy rates greater than 80% have been reported for N-stage evaluation [47]. False-negative examination results can be a problem with small-sized nodes involved by the tumour.

15.6.3 Magnetic Resonance Imaging (MRI)

Analyses of MRI for the assessment of GBC have shown sensitivities of 70–100% for hepatic invasion and 60–75% for lymph node metastases. The ‘all-in-one’ MR protocol, including MRI, MRCP (magnetic resonance cholangiopancreatography) and MRA (magnetic resonance angiography), can be an effective diagnostic method in the preoperative workup for gallbladder carcinoma. MRI with MRCP and MRA can be a single-stop complete evaluation for most patients and has an additional advantage of biliary and vascular evaluation [48]. MRI is generally equal to CT scan in its overall efficacy in the evaluation of GBC. It is mainly limited by relatively less availability as compared to CT scan, non-familiarity of the surgeons with MRI interpretation and overfamiliarity with CT scans (see Fig. 15.5).

15.6.4 Role of PET (Positron Emission Tomography) Scan

Most GBCs are FDG ([18F]-2-deoxy-D-glucose) avid. PET scan or particularly PET-CT therefore has a role in evaluation (Fig. 15.6). PET-CT has been used in the detection of metastatic disease including extra-abdominal metastases (lung, mediastinal and bone) as well as intra-abdominal metastases (peritoneal and port site) [49]. A recent meta-analysis showed FDG-PET or PET-CT to have a good sensitivity (87%) and specificity (78%) in the evaluation of primary tumours in patients with GBC. PET-CT was shown to have a better diagnostic accuracy than PET alone [50].

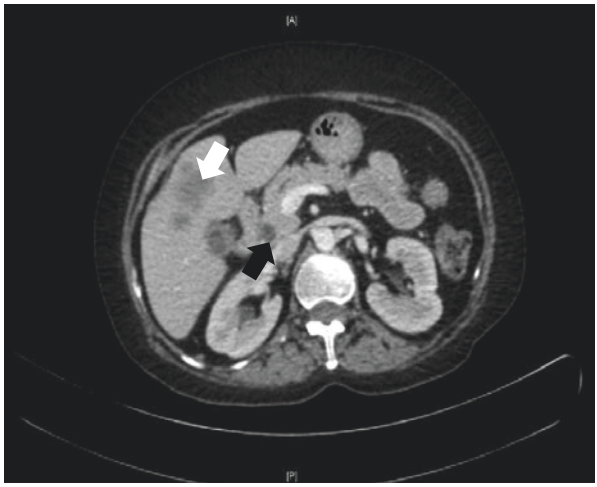

Fig. 15.5 Multidetector computed tomography axial post-contrast image demonstrating a gallbladder cancer with liver infiltration (thick arrow) and a prominent common bile duct (thin arrow)

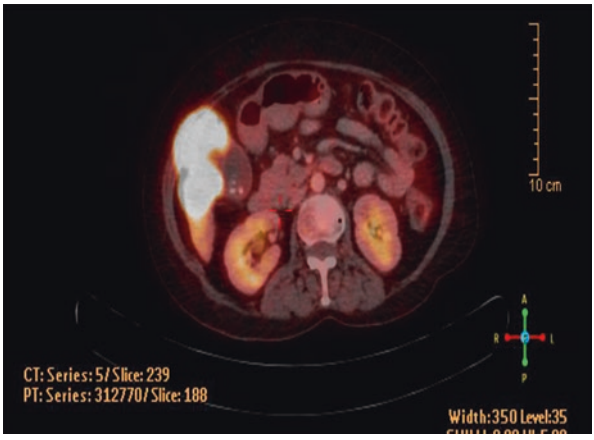

Fig. 15.6 Positron emission tomography-computed tomography (PET-CT) image of the patient in Fig. 15.5 demonstrating FDG uptake in the gallbladder mass

While using this modality, possible sources of false-positive results (such as inflammatory diseases of the gallbladder, e.g. xanthogranulomatous cholecystitis) and false-negative results (such as small-size and/or low-grade tumours) should always be considered. Risk of false positivity is high if PET is used in immediate/early postcholecystectomy period in restaging of patients with incidental GBC and while evaluating a patient with a locally advanced GBC with obstructive jaundice due to variable uptake in these patients.

The decision to perform a PET scan needs to take into consideration its additional contribution to the information already provided by the initial modalities like CECT or MRI, such as the likelihood of detecting disease at distant sites.

A study from our centre and a similar study by Butte et al. from Chile proposed the use of PET-CT in restaging of patients with incidental GBC [51, 52].

Another study from Tata Memorial Centre looked at the possible role of PET-CT in guiding treatment strategies in GBC. We showed that PET-CT-negative T1b patients do not have any residual disease in liver bed and liver wedge resection can actually be skipped in PET-negative incidental GBC T1b patients at the time of re-resection [49].

Given the inherent limitations associated with each modality, selective use is likely to increase the yield and benefit. Benefit of PET-CT is likely to be limited in a patient with a small polypoid primary lesion, a patient with no significant lymphadenopathy on CECT scan or one with incidental GBC with no evidence of residual disease on cross-sectional imaging. Similarly it is likely to detect other lesions more frequently in patients with large primary lesions with liver infiltration and patients with residual disease in incidentally detected tumours, large periportal lymph nodes, obstructive jaundice on presentation, suspicious aortocaval nodes or high CA19-9 (carbohydrate antigen 19-9) levels (see Fig. 15.6).

15.6.5 Interventional Radiology

Interventional radiology plays an important role in management of these patients. Most inoperable and metastatic patients need a histological diagnosis before initiation of any systemic chemotherapy, and many need relief of jaundice either as a palliation or as a preoperative preparation in case of perihilar blocks. USG- or CT-guided biopsies of the lesion/metastatic nodes, percutaneous biliary drainage and stenting are commonly performed. Embolization of bleeding tumours may sometimes be necessary as a palliative measure in few patients with advanced disease.

15.6.6 Tumour Markers

Serum CA19-9 and carcinoembryonic antigen (CEA) are commonly used while evaluating a suspected gallbladder mass or in GBC patients in various phases of their management. Other markers, namely, CA 125 and CA 242, are uncommonly used in clinical practice [53, 54].

CA 19-9 and CEA, as tumour markers, provide prediction regarding prognosis, overall survival and response to chemotherapy as well as postoperative recurrence. Sensitivity and specificity of these markers are around 70%, and it is well understood that they have limited diagnostic value.

Increased CEA levels are observed in alcoholics, liver dysfunction, smokers and in inflammatory disorders. CA 19-9 also rises non-specifically in several benign diseases. False negativity is observed in Lewis-negative genotype, and increased false-positive results are seen in jaundiced patients. This limits the use of these markers. They are used predominantly as a baseline supportive evaluation and in post-treatment patients on follow-up [55].

The Tata Memorial Hospital Scoring System (TMHSS), for GBC, based on radiological, clinical and biochemical features, has been proposed in 2004 and was later validated. Although not in common use, it predicts resectability and offers prognostication in GBC. The scoring system includes serum CA 19-9 level, serum bilirubin and CT scan features of disease [56].

15.7 Gallbladder Cancer Staging [57–59]

The staging for GBC is based on the depth of penetration and extent of spread. In 1976, Nevin et al. described a method which combined stage and histological grading (Table 15.2) [60]. Nevin's staging now carries only historical significance since the American Joint Committee on Cancer (AJCC) TNM (tumour, node, metastasis) staging is the most widely used and accepted today (Table 15.3). The most important prognostic factor is depth of invasion. Incidence of nodal and distant metastasis increases gradually with the increase in the depth of penetration. Fong et al. reported a progressive increase of distant and nodal metastasis from 16% to 79% and from 33% to 69%, respectively, as tumour progressed from T2 to T4 [61].

GBC staging has changed and evolved over the last few editions of the AJCC TNM staging system. In AJCC sixth edition published in 2002, T1 stage was subdivided into T1a for tumours invading up to the lamina propria and T1b for tumours reaching up to the muscular layer. This division carries significance in clinical decision-making in patients with early and incidentally detected GBC. The sixth edition also attempted to negate the nihilism associated with GBC and downstaged the node-positive (T1-3/N1) patients to stage IIb. These patients were previously placed in stage III. It also defined regional nodes (N1) as nodes found in the porta hepatis, gastrohepatic ligament and retroduodenal space. Positive nodes outside these areas were considered M1 disease.

AJCC seventh edition (2010) included cystic duct in the classification scheme, and carcinoid tumours and sarcomas were not included in this edition. This edition

Table 15.2 Nevin's staging system

Tumour extent
Stage 1—intramucosal only
Stage 2—involvement of mucosa and muscularis
Stage 3—involvement of all three layers
Stage 4—involvement of all three layers and the cystic lymph node
Stage 5—involvement of liver by direct extension or metastases or metastases to any other organ
Histologic grades
Well-differentiated (Grade I)
Moderately well-differentiated (Grade II)
Poorly differentiated (Grade III)

Table 15.3 Gallbladder cancer staging—AJCC eighth edition (2017) (Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.)

Stage	T stage	N stage	M stage
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T1, T2, T3	N1	M0
IVA	T4	N0, N1	M0
IVB	Any T Any T	Any N N2	M1 M0
Primary tumour (T):			
Tis carcinoma in situ			
T1 Tumour invades			
(a) Lamina propria			
(b) Muscular layer			
T2 Tumour invades perimuscular connective tissue on the			
(a) Peritoneal side without invasion of the serosa (visceral peritoneum)			
(b) Hepatic side without extension in to the liver			
T3 Tumour perforates serosa and/or invades the liver and/or other adjacent organs (stomach, duodenum, colon, pancreas and extrahepatic bile ducts)			
T4 Tumour invades main porta vein or hepatic artery or multiple extrahepatic organs			
Regional lymph nodes (N)			
N0 No regional lymph node metastasis			
N1 Metastases to 1–3 regional lymph nodes			
N2 Metastases to four or more regional lymph nodes			
Distant metastasis (M)			
M0 No distant metastasis			
M1 Distant metastasis			

replaced node-positive patients into stage IIIB considering the inferior prognosis associated with lymph node positivity and need to separate them from node-negative stage II patients. It also defined pericaval, periaortic, superior mesenteric artery and/or celiac artery nodes as N2 nodes. N2 category disease with its associated dismal prognosis is placed into stage IVB and has been assigned M1 status.

Stage groupings better correlate with surgical resectability and patient outcomes in current staging. The disease clearly remains operable up to stage III (T1-3/N0-1), and any preoperative assessment suggesting stage IV disease (T4/N2/M1) defines inoperability.

The recently published eighth edition of AJCC TNM staging further subdivides T2 disease into a and b stages depending upon hepatic or visceral side of GB wall involvement as these have differential prognosis. Similarly, N stage now includes number of nodes involved and redefines N2 as regional nodal involvement of four or more nodes which also correlates better with the prognosis.

15.8 Role of Preoperative Biopsy

An aggressive malignancy like GBC is prone to dissemination. GBCs seed and recur at port sites, surgical scars, cholangioscopy and needle tracts. Needle tract seeding and dissemination are a real risk [62–64]. In a clearly resectable, radiologically suspected GBC, preoperative biopsy is to be strongly discouraged and condemned. Preoperative fine-needle aspiration cytology (FNAC)/biopsy does not help/affect decision-making in a resectable lesion when clinicoradiologic suspicion is high. Negative results in this setting add to the confusion due to the possibility of false-negative results. The only possible indication for biopsy in GBC patients would be locally advanced tumours planned for systemic therapy with neoadjuvant intent. Biopsy to rule out or prove a suspected or obvious metastatic lesion would constitute another indication.

15.9 Management

15.9.1 Management of Gallbladder Polyps

A large variety of polypoid lesions can occur in the gallbladder ranging from fibromas and lipomas to haemangiomas (Table 15.4) [65]. More commonly a gallbladder polyp can be a cholesterol polyp, inflammatory polyp, hyperplastic polyp, mixed-type polyp or an adenoma in order of frequency of occurrence (Table 15.5) [66]. Adenomatous polyps have malignant potential and may harbour atypical hyperplasia and/or malignancy at the time of detection itself.

Table 15.4 Classification of gallbladder polyps

Benign tumours
Adenoma
Haemangioma
Lipoma
Leiomyoma
Polyp
Inflammatory
Cholesterol
Miscellaneous
Xanthogranulomatous inflammation
Parasitic infection
Hyperplasia
Adenomyomatosis
Ectopic rests
Gastric mucosa
Intestinal mucosa
Pancreas

Table 15.5 Types of polypoid lesions of the gallbladder in a review of 172 cases

Cholesterol polyp	62.8%
Inflammatory polyp	7%
Hyperplasia	7%
Adenoma	5.9%
Malignant	7.7%
Miscellaneous	9.6%

Adenomyomatosis is an acquired, hyperplastic lesion of the gallbladder characterized by excessive proliferation of surface epithelium with invaginations into a thickened muscularis propria. USG may reveal a thickened gallbladder wall with intramural diverticula [67]. The condition is usually not considered to be associated with malignant potential.

Most gallbladder polyps are readily detected on US incidentally while evaluating a non-specific abdominal complaint or specifically while evaluating a patient with an upper abdominal pain.

Risk of malignancy in the gallbladder polyps varies among studies. A recent large review assessing the risk of malignancy in US-detected gallbladder polyps included 12 studies and more than 5000 gallbladder polyp patients. Overall incidence of malignancy in gallbladder polyps was around 0.6%. Incidence of malignancy in adenomas is reported to be around 7%. Adenomas less than 6 mm rarely harbour an invasive cancer. Risk of malignancy in an adenoma increases with size. Established risk factors for malignant GBPs are size greater than 10 mm (risk increases with size), growth of polyp during follow-up, single polyp and Indian ethnic background. Other presumed and important risk factors are age more than 60 years, polyps with gallstones, associated primary sclerosing cholangitis, polyps in symptomatic patients and polyps with associated gallbladder wall thickening [68]. It is recommended that these patients should undergo cholecystectomy.

Any patient with a large polyp with suspicion of malignancy should undergo a cross-sectional study like CECT or MRI for proper evaluation of the lesion and surgical planning.

Patients with small polyps less than 6 mm and no associated risk factors mentioned above can be observed. Polyps larger than 6 mm are generally recommended to undergo a 6 monthly follow-up scan, and increase in size is an indication of surgery. Follow-up can be terminated if the polyp remains stable over a period of 2 years [69–72].

Another important consideration in management of GB polyps is the approach to cholecystectomy, as bile spillage during cholecystectomy in a patient with GBC can be potentially hazardous. Generally whenever preoperative assessment pointed to the possible risk of malignancy, surgeons historically adopted an open approach to perform cholecystectomy. Some surgeons selectively used open surgery when the size of the polyp was large (>10 mm) or risk of malignancy was presumed to be high on US or CECT assessment. As mentioned previously, the overall risk of malignancy in polypoidal lesions of the gallbladder is around 0.6%. Thus, the probability of coincidental bile spillage happening exactly in a patient harbouring cancer is also

very low. This should not unnecessarily prevent all patients from benefitting with the advantages of a laparoscopic approach [73]. This controversy has recently become further redundant with surgeons routinely performing laparoscopic radical cholecystectomies for gallbladder cancers.

Patients need to be counselled prior to subjecting them to cholecystectomy regarding the possibility of malignancy. Availability of frozen section is essential during the surgery. It facilitates radical resection if invasive cancer is detected.

15.9.2 Approach to Incidentally Detected GBC

Incidental GBC is detected after 1% of the elective cholecystectomies are performed for presumed benign conditions. It is recommended that all cholecystectomy specimens should be opened and sent for frozen section analysis if any suspicious lesion is identified. Intraoperatively detected GBC can also be classified as incidental GBC if it was not preoperatively suspected. Typically defined incidental GBC as a pure histopathological surprise should be a rarity. Practically in India due to the unavailability of frozen section, lack of awareness on the part of surgeons and overall low incidence of disease in the general population (except in northern India), incidental GBC as a pure histological surprise is still the most common presentation. Although incidentally detected GBCs are more likely to be early-stage tumours, patient may harbour disease belonging to any pathological T, N or M stage and may not necessarily be an early-stage disease. Majority of incidental GBC patients have pT2/pT3 primaries. In a study by Pawlik et al. on pathologic analysis of reseceted patients, T stage was T1 in 7.8%, T2 in 67.0%, and T3 in 25.2% patients. Incidence of residual disease increases with pT stage of the disease. Pathology from the re-resection specimen noted residual/additional disease in 46.4% of patients. Of those patients staged as T1, T2 and T3, 0, 10.4 and 36.4%, respectively, had residual disease within the liver ($P = 0.01$). T stage was also associated with the risk of metastasis to locoregional lymph nodes (lymph node metastasis: T1 12.5%; T2 31.3%; T3 45.5%; $P = 0.04$) [38]. Presence of residual disease correlates with T stage and has been found to be the most relevant prognostic factor for survival in patients treated with curative resection. Aggressive re-resection of incidental GBC offers the only chance for cure, but its efficacy depends on the extent of the disease found at repeat surgery. In a study by Butte et al., residual disease was predominant in the liver (29%), correlated strongly with T stage and was the most relevant prognostic factor for survival in patients treated with curative resection [74, 75].

Reassessment of histological specimen is an essential component of restaging, particularly pT stage, margins and assessment of the cystic duct stump for involvement by the tumour and cystic lymph node if available. These findings affect further clinical decision-making.

Reviewing the primary USG report, discussion with the previous operating surgeon about specific intraoperative findings, bile spillage, etc. cannot be stressed more.

Complete local and metastatic workup is desirable which will include a CECT and occasionally a PET-CT. The role of PET-CT in this clinical scenario is not defined. Though not a routine and not yet a recommendation, it is frequently used in evaluation of these patients.

In the case of intraoperatively discovered GBC, primary cholecystectomy followed by elective radical re-resection at a specialized centre has been shown to be an acceptable approach if expertise to perform radical resection at the time of cholecystectomy is not available [76].

Once staging workup is done, metastatic disease is ruled out and disease is assessed to be resectable, radical resection should be planned. It is generally agreed that simple cholecystectomy is an adequate treatment for T1a tumours. This mucosal disease reaches the lamina propria and virtually is never associated with lymph node involvement. In absence of any possibility of residual disease in this case, re-resection can neither be justified nor seems necessary.

For patients with T1b cancers discovered incidentally on cholecystectomy specimens, the utility of radical surgery remains debatable. Re-resection is currently recommended and commonly performed.

In a study by Abramson et al., a decision analytic Markov model was created to estimate and compare life expectancy associated with either simple cholecystectomy or radical resection in patients with incidentally discovered T1b gallbladder cancer. In the base case analysis, radical resection was favoured over no further surgical resection. It provided survival benefit of 3.43 years for patients undergoing radical resection. Younger patients had more benefit which gradually decreased with the increasing age of the patient. Decision analysis demonstrated that radical resection is associated with increased survival for most patients with T1b gallbladder cancer. Overall, a total of 18 studies including 157 patients and seven studies including 40 patients were used to calculate baseline probabilities for the simple and radical cholecystectomy groups, respectively. For the simple cholecystectomy alone group, they calculated a weighted mean 5-year cancer-specific survival of 61.3%. For those patients undergoing radical resection, a mean 5-year survival was 87.5% [77].

For T2 and T3, GBC radical re-resection is clearly warranted. Simple cholecystectomy cannot be an oncological operation in this scenario. Significant numbers of patients are likely to have residual disease and lymph node metastasis, and radical re-resection is the only way to achieve R0 resection and long-term survival in this group of patients.

R0 resection, lymph node dissection, well-differentiated tumours and absence of perineural and vascular invasion are important prognostic factors for overall survival [78].

For patients found to have T4 disease on reassessment, palliative approaches should be explored.

15.9.3 Principles of Surgical Treatment of Gallbladder Cancer

Surgical options in the management of GBC vary from a simple cholecystectomy to extended multivisceral resections like hepatopancreaticoduodenectomy (HPD). R0 resection is the only chance of cure and long-term survival in absence of effective adjuvant therapies.

Radical cholecystectomy, an oncologic resection for GBC usually involves:

1. A laparoscopic staging/exploratory laparotomy to rule out metastatic disease.
2. Interaortocaval lymph node sampling to rule out N2 nodal involvement which has a M1 status.
3. En bloc resection of GB mass with some form of liver resection. The extent of liver resection usually is the minimum amount required to achieve margin negative resection, and it may vary from a simple 2/3 cm wedge of liver tissue beyond the tumour to achieve negative margins (Fig. 15.7), a formal segment IVB, V resection or an extended hepatectomy.
4. Complete hepatoduodenal ligament, periportal and retroduodenal lymphadenectomy (Fig. 15.8).
5. Adjacent organ/s and/or extrahepatic biliary tract excision, if involved.

The nomenclature varies as to what may be considered as radical. The extent of resection varies from a simple cholecystectomy for an early T1a tumour to an extended hepatectomy and multivisceral resections for few advanced tumours

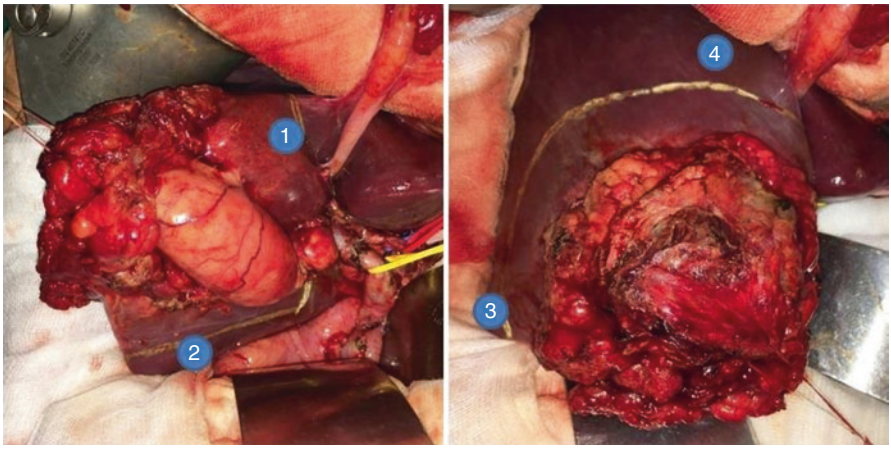

Fig. 15.7 Intra-operative photographs of the patient in Fig. 15.5 depicting the margins for wedge resection marked on the surface of the liver (numbered 1–4))

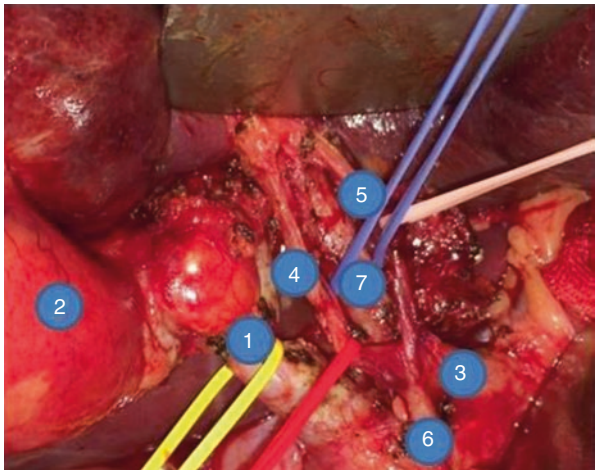

Fig. 15.8 Intraoperative photograph demonstrating a completed periportal lymphadenectomy (1, common bile duct; 2, gallbladder; 3, common hepatic artery; 4, right hepatic artery; 5, left hepatic artery; 6, gastroduodenal artery; 7, portal vein)

depending on the location and stage of the tumour. The term 'extended cholecystectomy' is used to describe an oncologic resection for GBC by some centres where the word 'extended' provides a scope for inclusion of variety of procedures. Radical re-resection for incidental GBC is termed revision cholecystectomy at our institute. Revision surgery for incidental GBC is also termed as completion extended cholecystectomy.

15.9.3.1 Role of Staging Laparoscopy

Staging laparoscopy aims to detect peritoneal and liver surface metastasis and is an important tool for evaluation of gastrointestinal malignancies. It prevents a nontherapeutic laparotomy and reduces the associated morbidity. Reduced pain, early recovery, less hospital stay and early administration of systemic therapies are associated benefits.

Significant proportions of GBC patients have advanced disease at the time of presentation. Locally advanced inoperable and metastatic gallbladder cancer patients usually don't require any palliative surgical procedure. Acceptable yield can always justify the routine use of this approach in such an aggressive malignancy.

Studies evaluating the role of staging laparoscopy in GBC have reported benefit in preventing a nontherapeutic surgical exploration in 38–62% of patients. A recent meta-analysis revealed that 27.6% of patients with GBC may avoid unnecessary laparotomy with the use of staging laparoscopy [79, 80].

In a recent large series of 409 patients from a North Indian centre, staging laparoscopy identified 94.1% of the detectable (surface) metastatic lesions and thereby obviated a nontherapeutic laparotomy in 55.9% of patients with unresectable disease; this amounted to 23.2% of overall GBC patients. It had a higher yield in locally advanced tumours. Some surgeons believe that the addition of laparoscopic ultrasound and laparoscopic interaortocaval lymph node biopsy has the potential to further increase the yield of staging laparoscopy in GBC [81].

Staging laparoscopy is recommended to be routinely performed in all GBC resections including revision surgery for incidental GBC patients.

15.9.3.2 Extent of Liver Resection

The underlying principle of surgery in GBC is R0 resection with minimum essential liver resection. The extent of liver resection is determined by the extent of liver infiltration by the primary tumour, involvement of inflow vascular structures and need of 1–2 cm negative margin. Simple 2–3 cm wedge to negative margins can be adequate in many patients with limited or no obvious liver infiltration and in patients undergoing revision surgery after incidental detection of GBC with no evidence of residual disease or minimal residual disease on evaluation or exploration. Maintaining a uniform margin may be difficult in this approach, resulting in coning and compromised margins at places. This also being a nonanatomic resection may have higher chance of bile leak and bleeding. Particular care must be taken to achieve uniform margin and prevent injury to the hilar structures while overzealously resecting a large wedge. Formal IVB/V resection is preferred and recommended by some surgeons for a disease with limited or no liver infiltration. Though this approach has the advantage of being an anatomic resection, it can be a potentially challenging resection for many surgeons.

Gallbladder cancers resulting in perihilar blocks secondary to biliary tract infiltration and jaundice, ipsilateral major inflow structure involvement and extent of liver infiltration beyond limits of segment IVB/V resection are the indications for extended hepatectomy provided R0 resection can be achieved and patient has a good performance status to undergo such a major surgery. In patients developing perihilar block, type of resection is similar to perihilar cholangiocarcinoma which includes a modified right extended hepatectomy sparing segment IVA if possible, with or without caudate lobectomy, extrahepatic biliary tract excision and complete lymphadenectomy. Major morbidity rates exceeding 50% and mortality rates as high as 25–30% have been reported with extended hepatectomies involving vascular and multivisceral resections for GBC [82, 83]. Improved results with major hepatectomy have been recently reported with improved surgical expertise and techniques of hepatic surgery and implementation of techniques such as portal vein embolization [84]. It is essential to carefully select patients for surgery with such an extensive disease as less than 10 percent of patients have operable disease and long-term survival is a reflection of stage of disease rather than the extent of resection [44, 85].

GBC patients with lateral spread of disease along the biliary tract to involve lower bile duct, duodenal infiltration, pancreatic infiltration and peripancreatic lymphadenopathy are possible indications for extensive resections like HPD [86].

Results of extended resections which include pancreaticoduodenectomy (PD) for GBC are controversial as PD particularly is associated with significant increase in morbidity. PD is not recommended to be performed for lymph node clearance in GBC. Minimal survival gain may not justify this resection in the treatment of gallbladder cancer [87].

15.9.3.3 Extent of Lymphadenectomy

Complete lymphadenectomy in radical resection of a GBC includes nodes along hepatoduodenal ligament, right and left periportal nodes, pericholedochal nodes and peripancreatic and retroduodenal nodes. These nodes form the N1 group of nodes as per AJCC seventh edition. Disease spread beyond these nodes along inter-aortocaval nodes, celiac nodes and superior mesenteric nodes, now labelled N2 as per AJCC staging, has metastatic status and is included in stage IV. Early assessment of disease spread to aortocaval nodes is recommended by frozen section analysis, and procedure can be terminated as radical resection in this setting is unlikely to provide any survival benefit. Careful systematic approach to achieve complete lymphadenectomy and adequate lymph node yield is imperative [88].

Lymph nodal metastasis is one of the strongest predictors of survival. Total lymph node count and lymph node positivity ratio have been associated with disease-free survival and overall survival. Lymphadenectomy is considered adequate if six or more lymph nodes are harvested during dissection [89].

15.9.3.4 Extrahepatic Biliary Tract Excision

Extrahepatic biliary tract excision in the management of patients with GBC is performed as part of resection of the primary disease. Instances of this would be patients having a positive cystic duct stump margin or biliary tract involvement. Some authors have recommended biliary tract excision routinely during radical cholecystectomy in the belief that it increases lymph node yield and eases the lymph node dissection. The number of lymph nodes harvested may not be different with or without bile duct excision, and bile duct excision potentially increases the morbidity associated with the surgery with requirement of an additional procedure for biliary reconstruction. Therefore routine bile duct excision is not recommended as part of radical cholecystectomy.

In an uncommon scenario, where bulky pericholedochal lymph nodes or periportal inflammation make it difficult to dissect nodes off the bile duct attempts to avoid bile duct excision may in fact result in bile duct injury, bile leak and inadequate lymphadenectomy. Achieving complete lymphadenectomy in this situation may be difficult without bile duct excision, and bile duct excision may be an acceptable decision. Barreto and Shukla have comprehensively summarized the indications for extrahepatic biliary tract excision in GBC [90].

Indications for the resection of the EHBT in all stages of disease include:

1. Tumours involving the EHBT—preoperatively indicated by the presence of obstructive jaundice.
2. Tumours/gross lymph nodal enlargement close to or involving the common hepatic duct or hilum.
3. Inflamed or a fatty hepatoduodenal ligament rendering the nodal dissection difficult.
4. Patients undergoing re-resection (since postoperative inflammation makes differentiation of tumour and scar difficult). This indication is optional as in the

authors' own experience; the extent of hepatoduodenal ligament inflammation and fibrosis need not always preclude a complete clearance.
5. Positive cystic duct margin on intraoperative frozen section.
6. Cystic duct cancers.
7. Patients with associated APBDJ/choledochal cysts of the EHBT—these patients are at an increased risk of further metachronous malignancies of the biliary tree and should hence undergo EHBT resection at the time of treatment of the GBC.
8. In case of need for associated vascular resection/reconstruction.

15.9.3.5 Port-Site Recurrences and Role of Port-Site Excision

The risk of port-site metastasis after laparoscopic removal of incidental GBC was previously estimated to be 14–30%. A systematic review recently noted a decreasing trend in incidence of port-site metastasis over the last two decades. This review analysed 27 papers for incidence of port-site metastasis in GBC and noted that incidence has decreased from 18.6% prior to 2000 to 10.3% since then. The extraction site is at significantly higher risk than nonextraction sites [91].

Palousi et al. proposed that incidences of port-site recurrence and abdominal wall recurrences after laparoscopic cholecystectomy and open cholecystectomy, respectively, in GBC are both more common than other cancers [92]. This phenomenon is related more to GBC and its aggressiveness than approach to cholecystectomy.

Presumed higher incidence of port-site recurrences after laparoscopic cholecystectomy prompted surgeons to resect port sites prophylactically during a radical re-resection of incidental GBC without proven benefit.

It has been now understood that port-site recurrences are usually associated with peritoneal recurrences and poor prognosis. Routine port-site excision fails to reduce disease recurrence, does not improve survival and results in incisional hernias in up to 8% of patients [93, 94].

Resection of isolated port-site recurrence has been reported [95]. At Tata Memorial Centre, an occasional GBC patient with disease-free interval exceeding a year presenting with a delayed isolated port-site recurrence without any evidence of systemic or peritoneal recurrence is considered a candidate for port-site excision. Even in these patients, disease stability or response to chemotherapy is a good test before embarking on port-site excision.

15.9.3.6 Current Status of Laparoscopic GBC Resections

Most GI (gastrointestinal) cancers are currently being operated by minimally invasive approach. Risk of port-site recurrences and possible ill effects of bile spillage on recurrence and survival prevented many surgeons from adopting a minimally invasive approach to GBC resection. There have been no prospective studies comparing open and laparoscopic approach to GBC. Few retrospective reports though have demonstrated feasibility in expert hands at good centres. A Korean study of 36 patients of early GBC without evidence of liver invasion on preoperative assessment, operated from 2004 to 2007, was published in as early as 2010. It demonstrated feasibility of laparoscopic approach in treating at least early GBC without

liver invasion with similar perioperative outcomes and no recurrence at median follow-up of 27 months [96]. Palanisamy et al. published results of 14 patients who underwent radical cholecystectomy for early GBC. All patients had predominantly T2 disease, and only one patient had a T3 disease, and another had a node-positive disease. Median lymph node yield was eight [97]. Another study from a high volume north Indian centre (2015) compared open and laparoscopic radical cholecystectomy and demonstrated similar perioperative outcomes, safety and feasibility of laparoscopic radical cholecystectomy [98]. Laparoscopic GBC resection is an advanced laparoscopic procedure. Performing interaortocaval LN sampling, complete and adequate periportal lymphadenectomy and margin negative liver resection demands significant surgical expertise. With current evidence, in the absence of long-term data on recurrence and survival, laparoscopic resection for GBC cannot be recommended as a routine or a standard of care [99].

15.9.4 Role of Systemic Therapy

15.9.4.1 Adjuvant Therapy

GBC is an aggressive malignancy, and postsurgical recurrences are common. Approximately 40% recurrences are systemic, presenting as liver, lung, bone or peritoneal metastasis. Retroperitoneal nodes and distant nodal stations are the sites of recurrence in another 40% of recurrences. Locoregional site recurrences, viz. resection bed in the liver, hilum, anastomotic sites and margins of resections, occur in 20% of patients [100, 101].

GBC being an uncommon disease, exact indications, combinations and regimens for adjuvant chemotherapy have not been defined.

Survival for T1a patients with simple cholecystectomy and T1b patients with re-resection approaches 100% and recurrences are uncommon in these patients. Benefit of chemotherapy cannot be justified in these patients, and it is not used in this subset of patients.

Recurrences usually happen in patients with ≥T2, node-positive disease or margin-positive resections. These are the patients who are likely to benefit with adjuvant treatment [102]. The NCCN guidelines recommend considering adjuvant treatment in patients with pT2 disease and beyond and all node-positive patients with disease beyond T1, N0 stage. Adjuvant treatment options are chemotherapy and chemoradiotherapy. ABC 02 trial demonstrated that gemcitabine in combination with cisplatin provides benefit in advanced biliary tract cancers over gemcitabine alone [103]. Single-agent gemcitabine or more commonly a combination regimen with additional platinum drug is the preferred agent in adjuvant setting (Table 15.6).

Radiation therapy reduces local recurrences although its impact on survival is not verified in a randomized trial. Adjuvant chemoradiotherapy protocols vary across institutes. It is understood that chemotherapy agents used along with radiation acts mainly to sensitize and improve the effect of radiation and is inadequate as adjuvant chemotherapy. Patients should receive at least some adjuvant full-strength

Table 15.6 Recommended treatment options as per stage

Stage	Type of surgery	Further treatment
T1a	Simple cholecystectomy	No adjuvant therapy
T1b, T2, T3, N1	Radical cholecystectomy *(see definition)* Extent of hepatic resection commensurate with extent of involvement	T2, T3, N1 adjuvant therapy
T4/N2/ M1	Inoperable/metastatic	Consider palliative therapy if performance status permits

chemotherapy cycles before starting chemoradiotherapy schedule. This facilitates early administration of proper systemic chemotherapy and prevents the use of radiation in some patients likely to recur early in the course of adjuvant treatment.

15.9.4.2 Neoadjuvant Therapy

Studies evaluating neoadjuvant chemotherapy (NACT) in GBC patients are few, and there are no RCTs (randomized controlled trials) or prospective studies. For an inherently aggressive tumour biology, NACT as an approach definitely needs to be assessed in well-selected patients using regimens with acceptable response rates. A study from Tata Memorial Centre, about our initial experience of using this approach in 37 patients which included 18 curatively resected GBC patients, demonstrated feasibility and acceptable response rates and downstaging with neoadjuvant therapy [104]. Selvakumar et al., in a similar study of 21 patients, demonstrated a resectability rate of 66.67% after NACT [105]. Kato et al. report downsizing of 36.4% of biliary tract cancers with NACT [106].

With no standard guideline on this approach, defining indications for NACT is a necessary step. We defined certain criteria (TMH criteria) based on clinicoradiologic presentations of the GBC patients where disease spread beyond GB, T3/T4 disease and node positivity, and certain poor prognostic factors were used as indication for NACT, as most of these patients would be candidates for systemic treatment after possible surgical intervention as per preoperative assessment (Table 15.7).

Our experience with this approach has now been extended to 85 curative intent resections post NACT (unpublished data). Overall response rate of 70% and pathological complete response rate of 13% were noted. Response rates with different gemcitabine-based regimens (GEMCIS /GEMOX) were similar. Median follow-up was 24 months. Median OS was 61% at 2 years and 53% at 3 years. Median OS for patients undergoing curative intent resections (R0/R1) was 77% at 2 years and 66% at 3 years. The study needs a prospective validation.

15.9.5 Palliation in GBC

Most patients with GBC present in an advanced stage, and many cases recur after curative treatment. Symptom palliation is therefore a necessity and an important aspect in the management of patients diagnosed with this disease.

Table 15.7 TMH criteria for borderline resectable/locally advanced GBC and indications for neoadjuvant chemotherapy

Patients with primary GB lesion or previous non-curative simple cholecystectomy with the following:
1. GB mass with contiguous liver involvement ≥3 cm
2. Residual mass in GB fossa/liver bed with previous non-curative simple cholecystectomy
3. Involvement of bile duct causing obstructive jaundice (type I, II, III perihilar blocks)
4. Radiologic/endoscopic suspicion/confirmation of involvement/infiltration of extrahepatic organs like antropyloric region of stomach/duodenum/hepatic flexure of the colon/intestine
5. Radiological suspicion of involvement of periportal, retropancreatic, right-sided coeliac, gastrohepatic and peripancreatic nodes (any N1 group)
6. Equivocal radiological suspicion of major inflow vascular invasion-impingement/ involvement <180° of CHA/RHA/MPV/RPV
7. Doubtful margin status/positive margins after prior resection at an outside centre with possibility of future radical re-resection
8. Isolated port-site recurrence in non-metastatic GBC, in absence of previous chemotherapy or definitive treatment for GBC

Obstructive jaundice with associated itching, cholangitis, hepatic decompensation and vomiting; pyloroduodenal obstruction secondary to tumour-infiltrating adjacent pyloroduodenal area; and pain are the three main important complaints requiring palliation.

Patients sometimes may develop intestinal obstruction secondary to colonic infiltration or adhesions to peritoneal metastatic deposits.

Large tumours infiltrating adjacent organs cause luminal or rarely intraperitoneal bleeding.

Most patients with these presentations have locally advanced non-resectable or metastatic disease, and palliative measures are at centre stage.

Patients with an acceptable performance status are candidates for active interventions/treatment for palliation to improve quality of life.

Patients with significantly deteriorated general condition and poor ECOG (Eastern Cooperative Oncology Group) performance status (ECOG >2) are candidates for best supportive care only, unless the general condition can be modified with supportive treatment.

Segment 3 bypass has been described and was being regularly used in the era prior to routine availability of endoscopic and interventional radiology expertise in drainage and stenting for relief of jaundice [107]. Endoscopic or percutaneous approaches being less invasive, equally effective and less morbid are obviously the preferred modalities in palliative setting [108].

Percutaneous approach (PTBD) is associated with a better therapeutic success rate and lower incidence of cholangitis than endoscopic approach as most blocks are perihilar, but the overall complication rate and 30-day mortality associated with the two procedures are similar [109, 110].

Quality of life improves after relief of jaundice, and if performance status improves with supportive care and nutritional rehabilitation, patients can be administered chemotherapy with palliative intent after normalization of bilirubin.

Gastroduodenal or colonic stenting is an effective measure when these organs adjacent to gallbladder are involved by the tumour. Palliative internal bypasses, diversion stomas and resections should be performed rarely in these patients with limited life expectancy and poor reserve.

The help of a specialized pain management team for management of cancer pain cannot be stressed more. Celiac plexus block is an acceptable method for relief of pain associated with the advanced UGI malignancies.

Palliative chemotherapy for locally advanced and metastatic GBC for patients with good performance status is an appropriate option. Gemcitabine remains the mainstay of the systemic treatment in biliopancreatic cancers. Gemcitabine with cisplatin or oxaliplatin is the commonly used drug in this setting sometimes replaced with 5FU or oral capecitabine [111]. An optimal regimen has not been defined, and patients should be encouraged to participate in clinical trials. Erlotinib, an epidermal growth factor receptor (EGFR) blocker, bevacizumab a vascular endothelial growth factor (VEGF) receptor blocker and lapatinib (EGFR and HER2/NEU blocker) have been used in combination with systemic chemotherapy with some benefits, but studies are carried out predominantly for cholangiocarcinoma [112].

The use of radiation in cholangiocarcinoma is a common practice, and it has been used in R+ resections and for better palliation of jaundice. Similar use with similar predicted benefits can be practised in GBC patients undergoing margin-positive resection or harbouring locally advanced non-resectable disease [113, 114]. Radiation is commonly used in combination with sensitizing chemotherapy agents. It reduces tumour growth, achieves local control, potentially reduces local tumour-related complications and even improves survival in these patients [115, 116].

15.10 Survival

Five-year survival following simple cholecystectomy for T1a GBC is excellent, ranging from 97 to 99% (Fig. 15.9). Recurrence rates for T1a tumours are low and have been reported to range from 0.6 to 3.4%, and these patients deserve no further resection. Re-resection is now routinely followed and recommended for T1b patients as it improves survival and reduces recurrence in these patients. They have a 5-year survival of 70–80% after re-resection [117, 118].

Five-year survival for T2 and T3 patients varies from 70 to 30%. Long-term survival among T4 and M1 patients is a rarity. Median survival in metastatic patients is in months.

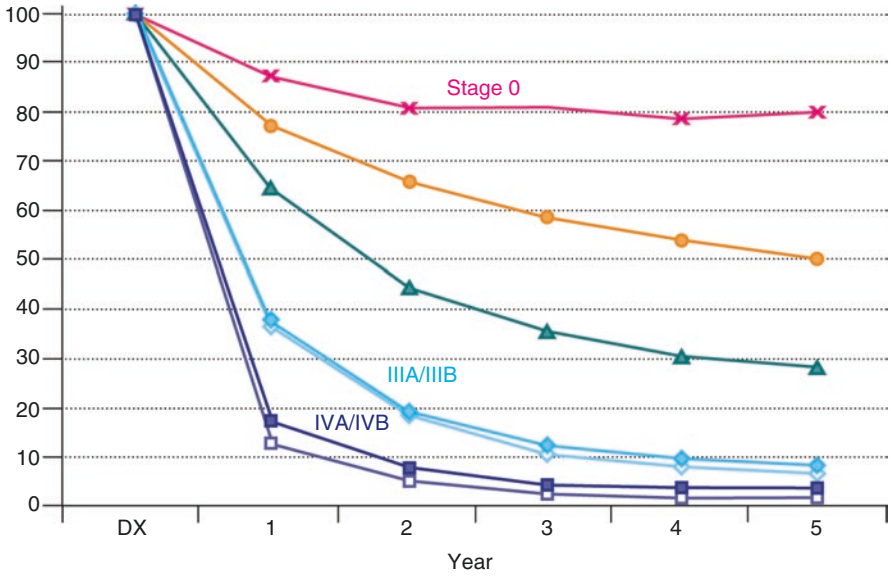

Fig. 15.9 Observed survival rates for 10,705 gallbladder cancers. Data from the National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) diagnosed in years 1989–1996. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media

15.11 Future Directions

Individual gene studies in GBC susceptibility have been insufficient to confirm association. Future research should focus on a more comprehensive approach and multistage aetiopathogenetic mechanisms as disease seems to be a result of multiple sequential events. Identifying susceptible individuals in high incidence areas, early detection of disease by screening US or biochemical markers and role of prophylactic cholecystectomy need to be defined. Randomized controlled trials focusing on perioperative therapy are lacking in GBC. Identifying candidates for perioperative (neoadjuvant) therapy and prospective studies on this approach need to be performed. GBC still remains an aggressive cancer with relatively poor prognosis, and systemic therapy as it stands today leaves a lot to be desired.

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Pancreatic Cancer

16

Savio George Barreto

16.1 Introduction

The incidence of pancreatic cancer is on the rise [1, 2]. Surgery has traditionally been considered the cornerstone in the management of resectable pancreatic cancer [3, 4]. However, we now know that improved outcomes can be achieved by combining surgery with chemotherapy under the broad umbrella of multimodality therapy [5, 6]. This multimodality approach is best suited to only 20% of patients with pancreatic cancer who present when the disease is still amenable to surgical resection. The vast majority of patients, though, present with advanced disease where the aim of therapy is disease control through efforts directed at retarding its progression [7–9].

While surgical resection rates, as well as adjuvant and palliative chemotherapy rates, have increased in the last couple of decades, there has not been a corresponding improvement in overall survival [10]. The more concerning statistic is the steadily rising mortality associated with this cancer which is unlike any other organ subsite [1, 11–14].

All this points to the fact that there yet remains much to be learnt about the biology of pancreatic cancer [15]. However, instead of the oft-adopted nihilistic view towards this cancer, we need to focus on the strategies that have provided us some success in combating the illness. This chapter provides a concise, evidence-based perspective on pancreatic cancer with an aim to highlight what is known about it and how we, as clinicians, can positively impact the outcome of these patients. Potential areas for further research are highlighted.

S. G. Barreto
Department of Gastrointestinal Surgery, Gastrointestinal Oncology, and Bariatric Surgery, Medanta Institute of Digestive and Hepatobiliary Sciences, Gurgaon, India

College of Medicine and Public Health, Flinders University, Bedford Park, SA, Australia

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16.2 Epidemiology

Pancreatic cancer accounted for 338,000 new cases in the year 2012, making it the 12th most common cancer worldwide (2.4% of all cancers excluding non-melanoma skin cancer) [16]. Keeping up to its deadly reputation, it ranks amongst the top four causes of cancer-related deaths worldwide [12, 14, 17].

The age-standardized incidence rates are varied across the world ranging from as low as 0.6/100,000 persons per year in parts of Asia to as high as 12.6/100,000 in the West [18]. However, even within regions, ethnic/racial variations do exist. In the United States, African Americans have a higher incidence of pancreatic cancer followed by Hispanics compared to other races (Caucasians and Asians). Patients of African American descent tend to present with a more advanced disease [19] and a worse overall survival [20]—a trend that has not significantly changed over the last three decades [21, 22]. There is some evidence to suggest an increased risk of pancreatic cancer amongst the Jews of North America [23].

In New Zealand, the Maoris have a higher incidence of the disease (7.3/100,000 persons per year) when compared to other ethnic groups. Interestingly, unlike the demographic profile of a male predominance that so characteristically represents pancreatic cancer [24], Maori women have an unusually high rate of the cancer (7.2/100,000) [25].

Pancreatic cancer generally presents at an older age (sixth to seventh decade of life) [24, 26]. Pancreatic cancer may occur rather uncommonly in younger patients. These individuals tend to be diagnosed at a more advanced stage, although the overall impact on survival remains unclear with one study from Japan [27] indicating a poorer survival while another European study demonstrated comparable survival to older counterparts [28]. However, there is no evidence to support a role for a genetic or hereditary causative component in these patients [27, 28].

16.2.1 Factors Implicated in the Pathogenesis of Pancreatic Cancer

16.2.1.1 Hereditary Pancreatic Cancer

At the outset it is important to appreciate the specific terminologies used in hereditary pancreatic cancer. The term hereditary pancreatic cancer encompasses two major subsets of patients with a significant family history of pancreatic cancer (≥2 relatives with pancreatic cancer if at least 1 is a first-degree relative or ≥3 total relatives with pancreatic cancer [29]). Patients with identified (known) genetic mutations are generally included under specific syndromes, while the term ‘familial pancreatic cancer’ is reserved for those families with ≥2 individuals who are first-degree relatives of one another with pancreatic cancer, in the absence of an identifiable genetic mutation [29].

Familial or genetic causes account for 10% of the overall cases of pancreatic cancer with a reliably high sensitivity of self-reporting [30]. Patients with hereditary pancreatic cancer tend to present 5 years earlier than the average median age at

diagnosis (66 vs 71 years) based on the findings of the Pancreatic Cancer Genetic Epidemiology Consortium [31].

Table 16.1 provides an overview of the various hereditary pancreatic cancer predisposition syndromes [32–41].

Patients with APC gene mutations (familial adenomatous polyposis) have an increased risk of ampullary and duodenal cancers.

Table 16.1 Hereditary pancreatic cancer predisposition syndromes

Syndrome	Phenotype	Organs at risk other than pancreas	Genetic mutations	Relative risk of pancreatic cancer compared to the general population	References
Peutz-Jeghers syndrome	Mucocutaneous pigmentation Hamartomatous polyps	Colorectal Breast Lung Uterus Testes	STK11	132	[32, 33]
Hereditary pancreatitis	Autosomal dominant inherited pancreatitis manifested as recurrent acute pancreatitis by age 10, chronic pancreatitis by age 20 and increased risk of PC after age 40	–	PRSS1	58	[34–37]
Familial atypical mole melanoma syndrome (FAMMM)	Early-onset multiple melanomas	Melanoma	CDKN2A	38	[32, 38]
Hereditary non-polyposis colorectal cancer (HNPCC)	Colorectal polyps	Colorectal Uterus Ovary Stomach Small intestine Urinary tract Biliary tree	MSH2, MLH1, MSH6, PMS2, 5′ EPCAM deletion	8.6	[32, 39]
Hereditary breast-ovarian cancer (HBOC)	Early-onset breast cancer	Breast Ovary	BRCA1 BRCA2	2.3 3.51	[40, 41]

PRSS1 protease, serine 1, *STK* serine/threonine kinase, *BRCA* breast cancer susceptibility, *CDKN2A* cyclin-dependent kinase inhibitor 2A, *MSH* MutS protein homolog, *MLH* MutL homolog, *PMS* protein homolog, *EPCAM* epithelial cellular adhesion molecule

Other mutations associated with hereditary pancreatic cancer but in whom the risk of disease development has not yet been clearly elucidated include PALB2 (additional risk of breast cancer) [42], monoallelic ATM (ataxia telangiectasia—individuals also at risk for developing breast and colon cancer) [43] and TP53 (Li-Fraumeni syndrome—individuals also at risk for developing breast, brain, sarcoma, adrenocortical and colon cancer) [44].

Patients with a strong family history of pancreatic cancer, hereditary pancreatitis or a known hereditary cancer syndrome must be advised germline genetic testing [29].

16.2.1.2 Sporadic Pancreatic Cancer

Several environmental factors have been implicated in the causation of pancreatic cancer. These factors are believed to play a significant role in the 90% of patients who do not possess a hereditary predisposition [45]. Table 16.2 provides an overview of these factors [28, 46–65].

Other risk factors include bacterial infections (*Helicobacter pylori* and a pathogen for periodontal disease, *Porphyromonas gingivalis*) [66], pancreatic cystic neoplasia (intraductal papillary mucinous neoplasia (IPMN) and mucinous cystic neoplasia (MCN); see Chap. 12) [67] and pancreatic intraepithelial neoplasia (PanIN) [68].

There is evidence to suggest that vitamin D levels are a risk factor in the development of pancreatic cancer. However, to date, the epidemiological data is inconclusive [69].

16.3 Pathology

Infiltrating ductal adenocarcinoma is the most common type of pancreatic cancer on histopathology. The less common variants include adenosquamous carcinoma, colloid carcinoma, hepatoid carcinoma, medullary carcinoma, signet ring cell carcinoma and undifferentiated carcinoma (with or without osteoclast-like giant cells) [70]. Light microscopic features consistent with invasive cancer on haematoxylin and eosin staining include haphazard glandular growth pattern with glands adjacent to vessels or touching fat, incomplete glands, perineural and intravascular invasion, nuclear variation more than 4:1 and intraluminal necrosis [71]. Useful immunohistochemical markers for pancreatic ductal adenocarcinoma include cytokeratin 7 (CK 7), CK 19, mesothelin, placental S100 (S100P), E-cadherin, insulin-like growth factor II messenger RNA-binding protein-3 (IMP3) and mammary serine protease inhibitor (MASPIN) [72]. Loss of DPC4/SMAD4 may be encountered in up to 55% of patients [70].

Recently an integrated genomic expression analysis of 456 pancreatic ductal adenocarcinomas convincingly demonstrated that pancreatic ductal adenocarcinoma represents four distinct subtypes: squamous, pancreatic progenitor, aberrantly differentiated endocrine exocrine (ADEX) and immunogenic types [73].

Periampullary cancers, on the other hand, can broadly be divided into intestinal or pancreatobiliary based on the type of differentiation [74]. The intestinal subtype

Table 16.2 Risk factors for sporadic pancreatic cancer

Risk factor	Estimated risk	Implication	References
Smoking	OR—2.2 (95% CI 1.7–2.8)	75% increased risk compared to non-smokers Reduced risk only after 10 years of cessation Active and early smoking—risk factor for early-onset pancreatic cancer (≤50 years)	[28, 46, 47]
Alcohol	OR—HR 1.62 (95% CI 1.04–2.54)	Positive association between heavy alcohol consumption (≥9 drinks per day) and risk of pancreatic cancer Dose- and age-dependent effect on the development of early (<60 years)- and very early (<45 years)-onset pancreatic cancer	[48–50]
Diabetes mellitus	OR—1.8 (95% CI 1.5–2.1)	1.5–2-fold increase in risk Risk is highest in initial 3 months (HR—3.71) and drops, although still significant (HR—1.65), at 10 years from onset Diabetes is associated with a worse survival	[51–55]
Obesity	OR—1.33 (95% CI 1.12–1.58)	Independent risk factor Centralized fat distribution may increase risk, especially in women	[56, 57]
Chronic pancreatitis	Tropical RR—100 (95% CI 37–218) Hereditary RR—54 (95% CI 35–90)	Accounts for up to 5% of cases Amongst alcoholic CP patients—eightfold increased risk after a mean of 7.4 years Higher risk amongst concurrent smokers	[58–63]
Primary sclerosing cholangitis	Pancreatic cancer OR—11.22 (95% CI 4.11–30.62) Cholangiocarcinoma OR—55.31 (95% CI 22.20–137.80)	398-fold increased risk of developing cholangiocarcinoma	[64, 65]

OR odds ratio, *CI* confidence interval, *RR* relative risk, *TCP* tropical chronic pancreatitis, *CP* chronic pancreatitis, *HR* hazard ratio

is characterized by tubular or cribriform glands and resembles colorectal adenocarcinomas with an attendant relatively better prognosis. The pancreatobiliary subtype, on the other hand, is characterized by glands associated with abundant desmoplastic stroma resembling tumours of the pancreas or extrahepatic bile ducts with an attendant worse prognosis [74–76]. Further delineation of the microscopic subtypes can be achieved by the use of immunohistochemical markers. The 'intestinal subtype' is either (1) stain positive for CK20 or CDX2 or MUC2 and negative for MUC1 or (2) stain positive for CK20, CDX2 and MUC2, irrespective of the MUC1 result, while

the 'pancreatobiliary subtype' is stain positive for MUC1 and negative for CDX2 and MUC2, irrespective of CK20 results [77].

16.3.1 Precursor Lesions

16.3.1.1 Pancreatic Intraepithelial Neoplasia (PanIN)

These premalignant microscopic (usually <5 mm) flat or papillary lesions are lined by columnar or cuboidal with varying amounts of mucin and arise in the smaller intralobular ducts of the head of pancreas more frequently than in the tail region [78–80]. They have been classified into three grades [68, 80, 81] ranging from less invasive to invasive nature. The low-grade PanIN-1A (flat) and 1B (papillary) are lined by columnar epithelial cells and possess minimal cytological or architectural atypia. Intermediate-grade PanIN-2 lesions have loss of nuclear polarity, nuclear crowding, variation in nuclear size (pleomorphism), nuclear hyperchromasia and nuclear pseudostratification with frequent papillae, while the high-grade PanIN-3, also referred to as carcinoma in situ, demonstrate high-grade dysplastic changes in cytology (enlarged, pleomorphic and poorly oriented nuclei with prominent nucleoli and abnormal mitoses) and architecture (characterized by the formation of papillae and cribriform structures sometimes having clusters of cells bud off of the epithelium into the ductal lumen) [68, 82].

These premalignant lesions have been found to possess KRAS and TP53 mutations similar to pancreatic cancer [83]. The immunohistochemical marker MUC1 is almost exclusively expressed in PanINs 2 and 3 [82].

Three characteristics of PanINs include their association with lobulocentric atrophy as well as acinar to ductal metaplasia and the tendency for being multifocal, more commonly in individuals with a strong family history [68, 84, 85].

16.3.1.2 PanINs, Carcinogenesis and Signalling Pathways

Maitra and colleagues [86] suggested that there exists a well-defined pathway in pancreatic carcinogenesis (PanINgram) leading from the precursor lesions (PanINs) to invasive adenocarcinoma as a result of the accumulation of molecular alterations seen with increasing grades of dysplasia. Yachida and colleagues [87] further elucidated the four main driver genes in pancreatic carcinogenesis, namely, KRAS, CDKN2A inactivation, TP53 and SMAD4 inactivation, the latter being associated with an increased risk for tumour dissemination and likely early failure following surgery [88]. Jones and colleagues [89], in addition to confirming that the above 4 genes were mutated at the highest frequency, identified 12 core signalling pathways in pancreatic carcinogenesis based on a global genomic analysis. These included KRAS, TGF β, Wnt/Notch, hedgehog, integrin, JNK and small GTPase signalling pathways in addition to the pathways involved in apoptosis, DNA damage control, invasion, homophilic cell adhesion and control of G1/S phase transition.

16.3.2 Pathological Assessment of the Resected Pancreatic Cancer Specimen

While not precisely defined in surgical practice, tumours of the pancreas have been anatomically subdivided, based on location, into tumours of the head of pancreas (arising to the right of the left border of the superior mesenteric vein and including the uncinate process), tumours of the body of pancreas (arising between the left border of the superior mesenteric vein and the left border of the aorta) and tumours of the tail of pancreas (arising between the left border of the aorta and the splenic hilum) [90].

A margin-negative (R0) resection is regarded as the surgeon's best contribution to pancreatic cancer patients [91]. In 2008, Esposito and colleagues [92] demonstrated that the adoption of a standardized pathology reporting of resected specimens was able to pick up previously underappreciated margin positivity. This led to a concerted effort towards the reporting of pathological specimens. Central to pathological reporting is the recognition that resected pancreatic cancer, more specifically the pancreatoduodenectomy (PD) specimen, has four relevant margins [93, 94]:

(a) The luminal margins (proximal gastric or duodenal and distal jejunal)
(b) Bile duct margin (BDM)—common bile duct or common hepatic duct margin
(c) Pancreatic transection margin (PTM)
(d) Pancreatic circumferential or radial margin (CRM)—which further includes:
    1. Pancreatic anterior margin (PAM)—anterior surface
    2. Pancreatic posterior margin (PPM)—posterior surface
    3. Pancreatic medial margin (PMM)—surface facing the superior mesenteric vessels

There exists variability in the terminology used for the CRM with European pathologists favouring the terms PPM and PMM, while the American pathologists use the terms 'deep retroperitoneal posterior surface' and 'uncinate process' margins [93]. Some of the standardized protocols currently followed are the Leeds Pathology Protocol (LEEPP) [95] and the protocols provided by the College of American Pathologists (CAP) [96], the Royal College of Pathologists [97] and the American Joint Committee on Cancer (AJCC) [90].

In general, the entire pancreatic head specimens are serially sliced in a plane perpendicular to the longitudinal axis of the duodenum thereby avoiding opening the biliary or pancreatic duct [95]. The advantage of this technique is that it permits an extensive study of the lesion and its relationship with anatomical structures and surgical margins [93]. All the above-named margins must preferentially be inked.

The final controversy in pathological specimen reporting relates to what is considered a microscopically positive margin (R1). Majority of American pathologists

regard a margin to be positive only when the tumour is directly in contact with the inked margin (0 mm clearance) [98], while European pathologists, borrowing on experience from rectal cancer assessment, label a tumour as R1 when the distance between the tumour and the resection margin is ≤1 mm [97]. The Royal College of Pathologists puts this into perspective by appreciating that for the PAM, a 0 mm clearance would be regarded as adequate clearance since it is an anatomical surface rather than a true margin, while for the other margins, the tumour is deemed incompletely excised if the margin is ≤1 mm [97].

16.4 Staging

Table 16.3 provides the seventh edition of the TNM Classification of Pancreatic Cancer as per the American Joint Committee on Cancer staging [90], while Table 16.4 details the changes proposed in the eight edition of the TNM Classification [99].

Table 16.3 Seventh edition of the American Joint Committee on Cancer staging of exocrine pancreatic cancer [90]

Primary tumour (T)			
TX	Primary tumour cannot be assessed		
T0	No e/o primary tumour		
Tis	Carcinoma in situ		
T1	Tumour limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumour limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)		
Regional lymph nodes (N)			
NX	Regional lymph node(s) cannot be assessed		
N0	No regional lymph nodal metastasis		
N1	Regional lymph node metastasis		
Distant metastases (M)			
M0	No distant metastases		
M1	Distant metastases		
Anatomic stage			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Table 16.4 Proposed eighth edition of the American Joint Committee on Cancer staging of exocrine pancreatic cancer [99]

Primary tumour (T)			
TX	Primary tumour cannot be assessed		
T0	No e/o primary tumour		
Tis	Carcinoma in situ		
T1	Maximum tumour diameter <2 cm		
T2	Maximum tumour diameter > 2 ≤ 4 cm		
T3	Maximum tumour diameter >4 cm		
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)		
Regional lymph nodes (N)			
NX	Regional lymph node(s) cannot be assessed		
N0	No regional lymph nodal metastasis		
N1	Metastasis in 1–3 regional lymph nodes		
N2	Metastasis in ≥4 regional lymph nodes		
Distant metastases (M)			
M0	No distant metastases		
M1	Distant metastases		
Anatomic stage			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	Any T	N2	M1
	T4	Any N	M0
Stage IV	Any T	Any N	M1

16.4.1 Signs and Symptoms of Pancreatic Cancer [100, 101]

The early symptoms of pancreatic head cancer are rather non-specific leading to patients presenting late with painless progressive jaundice, back pain (from retroperitoneal invasion), weight loss and asthenia and anorexia and vomiting (owing to gastroduodenal invasion). In the author's own experience of patients amenable to Whipple's resection, the most common presenting symptoms were obstructive jaundice (60%) and abdominal pain (50%).

Tumours of the body and tail are even more notorious for a delayed presentation. The reason for this is that the bile duct is away and thus by the time the patient develops symptoms of gastric outlet obstruction or back pain or a palpable lump, the tumour has already disseminated [102]. Important symptoms to be aware of in these patients are new onset diabetes mellitus, especially after the age of 60 years, and epigastric pain radiating to the back akin to an episode of acute pancreatitis [102].

Cancers of the lower bile duct and ampulla of Vater generally present early as painless jaundice (>80%; author's own data of patients with resectable tumours) with or without cholangitis as these lesions obstruct the biliary passages early in the

course of the disease. The sine qua non of 'waxing and waning' of obstructive jaundice is encountered in only one-third patients [103]. Patients with duodenal tumours (included under the definition of periampullary tumours) may present with abdominal pain and/or vomiting.

As noted above, chronic pancreatitis is a risk factor for cancer. Thus in patients with chronic pancreatitis for more than 10 years, the development of 'new symptoms' such as sudden and severe weight loss in a controlled diabetic or the development of jaundice or change in the nature of pain should alert the clinician to evaluate the patient for an underlying neoplastic process [63].

Fever may sometimes be the first symptom that brings the patient to the clinician owing to underlying cholangitis especially in periampullary tumours.

Important clinical signs in patients with cancers of the pancreas and periampullary region include icterus and other signs of obstructive jaundice such as high-coloured urine and pale stools in the absence of choledocholithiasis and scratch marks on the trunk and extremities owing to the pruritus from the cuticular deposition of bile salts. A palpable gallbladder is a sign of an underlying pancreatic head cancer (Courvoisier's law), while a palpable lump in the epigastrium or left hypochondrium may be the first sign of a tumour of the body and tail.

Clinical features in keeping with advanced cancer are the enlarged supraclavicular (Virchow) lymph node, Blumer's shelf on digital rectal examination and ascites.

16.4.2 Investigations

An abdominal ultrasound is generally the first investigation advised when a patient presents with complaints of an abdominal lump or signs and symptoms of jaundice. Findings suspicious of a pancreatic or periampullary malignancy include a dilated common bile duct (>6 mm pre-cholecystectomy or >10 mm post-cholecystectomy [104, 105]) devoid of gallstones, mass in the pancreas with or without liver metastases or ascites. In patients with a poor functional status with pancreatic mass and liver metastases and/or ascites, a fine needle aspiration or ascitic fluid cytology to confirm malignancy may be all that is required taking into consideration the wishes of the patient. However, in patients with findings suspicious of a pancreatic cancer and a good functional status, a complete work-up would include the following.

16.4.2.1 Serology

These investigations are not diagnostic of pancreatic cancer but are of value when planning therapy.

(a) Complete blood counts—anaemia, as a result of occult bleeding, may be encountered in patients with periampullary tumours as these tumours are probe to slough off. In patients with cholangitis, the white cell count is elevated and supports the decision for biliary drainage as the first intervention.

(b) Liver function tests—elevations in serum bilirubin and liver enzymes are encountered in patients with surgical obstructive jaundice. A low serum albumin level in the preoperative setting has been found to correlate with a worse disease-free and overall survival in patients with pancreatic cancer [106].
(c) Renal function tests—patients with chronic renal impairment are at increased risk of perioperative complications especially if their creatinine levels are >2 mg/dL [107].
(d) Prothrombin time and international normalized ratio (INR)—patients with surgical obstructive jaundice must be assessed for coagulopathy as this not only is important from a surgical perspective but also for the preoperative placement of the epidural catheter [108].
(e) Blood sugar levels—new onset diabetes mellitus (within the preceding 2 years) may be encountered in up to 68% of patients with pancreatic cancer [108].

16.4.2.2 Tumour Markers

(a) Serum carbohydrate antigen 19-9 (CA 19-9)

Serum CA 19-9 has a median sensitivity of 79 (70–90%) and a median specificity of 82 (68–91%) for the diagnosis of pancreatic cancer [109]. Although elevated levels of CA 19-9 are generally associated with decreased stage-specific survival (>37 U/mL) [110] and locoregional failure-free survival (>200 U/mL) [111], this is of most significance in anatomically resectable, early-stage pancreatic cancer [110]. This finding has prompted some clinicians to suggest the role for neoadjuvant therapy in this specific subgroup of patients [110]. In patients with borderline resectable or locally advanced disease, normalization of CA 19-9 levels after commencing neoadjuvant therapy may help in guiding the further course of therapy, early surgery over further therapy [112, 113]. Normalization of CA 19-9 levels post surgical resection is predictive of better disease-free survival [114] and may help in the further surveillance for disease recurrence in this patient subset.

Thus, routine analysis of serum CA 19-9 levels is advisable at diagnosis of the cancer since there is some data to support its role as a diagnostic biomarker, although its utility is more as a marker to predict tumour stage, resectability, overall survival and response to therapy [115].

Caution is advised when interpreting elevated CA 19-9 levels in patients with cholestasis [116] where false-positive elevations have been noted and those patients who are Lewis blood group antigen negative and thus unable to secrete CA 19-9 [117].

Various other markers have been tested in pancreatic cancer including carcinoembryonic antigen (CEA), CA 242, CA 125 and CA 72-4. However, they are of limited utility owing to their sensitivities being lower than CA 19-9 [118].

16.4.2.3 Radiological Investigations

(a) Pancreas protocol multi-detector computed tomography (MDCT) scan of the abdomen and pelvis with multiplanar reconstruction (Figs. 16.1, 16.2 and 16.3)—This is currently the best available modality for assessing the primary tumour, its locoregional and distant intra-abdominal spread as well as the vascular anatomy

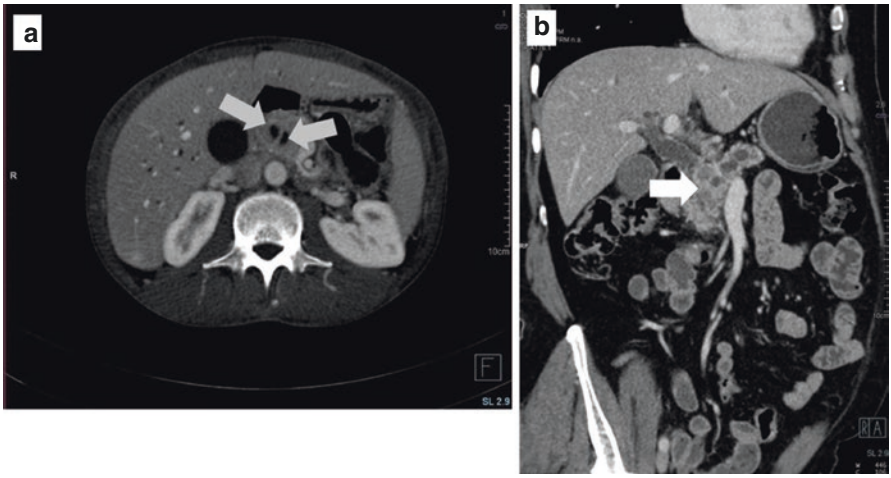

Fig. 16.1 Multi-detector computed tomography images demonstrating the 'double duct' sign—upstream dilation of the common bile duct (CBD) and main pancreatic duct (MPD) as a result of an obstructing periampullary tumour—(**a**) axial post-contrast section (CBD and MPD marked with bold grey arrows) and (**b**) coronal reformation (tumour marked with white arrow)

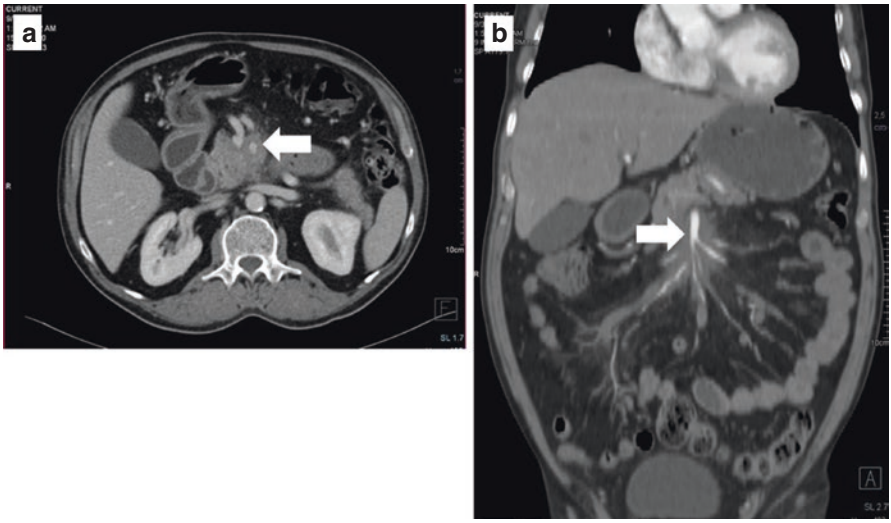

Fig. 16.2 Multi-detector computed tomography images demonstrating a locally advanced pancreatic uncinate process cancer that has infiltrated the root of mesentery resulting in a complete encasement of the superior mesenteric artery (SMA) and its jejunal branches—(**a**) axial post-contrast section (encased SMA marked with white arrow) and (**b**) coronal reformation (encased SMA marked with white arrow)

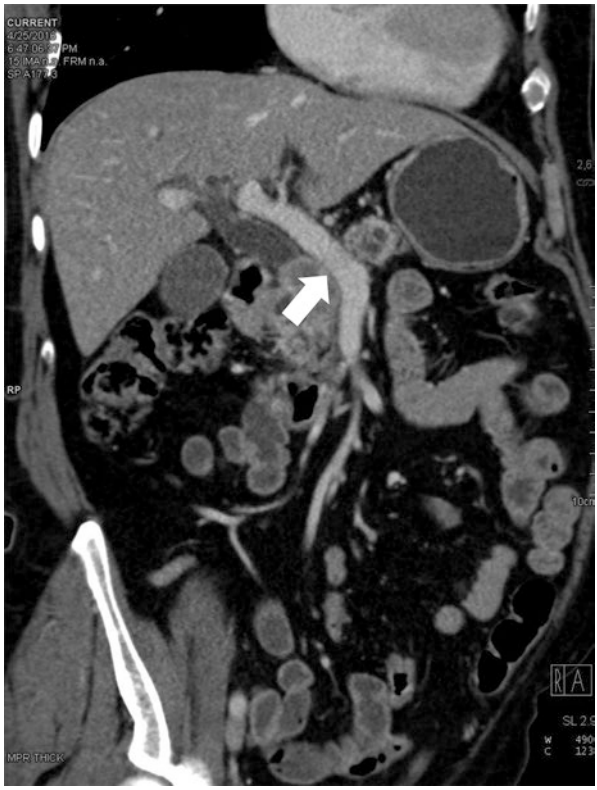

Fig. 16.3 Coronal reformation on a multi-detector computed tomography scanner image demonstrating a mass lesion in the head of pancreas abutting the distal superior mesenteric vein (SMV) marked with white arrow—borderline resectable pancreatic cancer

(an essential component of pre-surgical planning [119]). The pancreas protocol CT scan comprises a pre-contrast scan and three post-contrast phases with axial section thickness ≤5 mm [120] and water or mannitol as the negative contrast to distend the stomach and duodenum and permit delineation from the pancreas:

1. Pre-contrast scan—enables the detection evaluation of pancreatic calcifications and permits determination of the precise levels for imaging on the post-contrast phases.
2. Arterial phase—the first of the post-contrast phases obtained at 20–30 s (depending on the injection rate 5–3 mL/s [121]) permits an accurate evaluation of the pancreatic vascular anatomy without interference from venous opacification [120].
3. Pancreatic parenchymal phase—previously termed late arterial phase, is obtained at 40–50 s (depending on the injection rate 5–3 mL/s [121]). Owing to marked difference in enhancement between the maximally enhanced pancreatic parenchyma and the generally hypoenhancing pancreatic cancer, this phase allows an assessment of the tumour and its relation to the surrounding structures including vessels.
4. Portal venous phase—also termed hepatic phase, these images are obtained at 60–70 s (depending on the injection rate 5–3 mL/s [121]). This phase helps in assessing venous involvement and also hypovascular liver metastases.

(b) Magnetic resonance imaging (MRI) and MR cholangiopancreatography (MRCP)—may be an alternative to MDCT in case facilities for performing, or the expertise needed to report a CT scan, are not available.

MDCT scans are better suited as compared to MRI for the detection of pancreatic cancers as well as the assessment of nodal and distant spread and vascular involvement [122]. The only small subset of patients in whom an MRI may outperform CT scans is in the assessment of isoattenuating cancers [123]. However, it must be clearly stated that the accuracy of either investigation still falls well short of perfection especially in terms of detecting lesions <2 cm [122] as well as in the accurate characterization of venous involvement [124] and diagnosis of peritoneal and small surface liver metastases. Whether dual-energy CT scans [125] will overcome some of these shortcomings remains to be confirmed. Until then, the reliance on complementary investigative modalities such as endoscopic ultrasound (EUS), positron emission tomography-CT (PET-CT), venography and even staging laparoscopy is imperative.

(c) Chest X-ray—to rule out lung metastases.

16.4.2.4 Endoscopy

(a) Side-viewing endoscopy (Fig. 16.4)—is useful to obtain biopsies of ampullary and duodenal carcinomas. Novel technologies such as narrow band imaging (NBI) help to differentiate between ampullary adenomas and adenocarcinomas with an accuracy approaching 80% [126, 127]. Such information is vital when deciding on local endoscopic excisions versus directly offering surgery to these patients.

(b) Endoscopic retrograde cholangiopancreatography/ERCP—to obtain biliary cytology for diagnosis. Given the declining diagnostic role for ERCP, the main indication is the relief of biliary obstruction and placement of stents (Fig. 16.5) in patients with cholangitis. Such a strategy is valuable preoperatively in patients with cholangitis with or without renal impairment or in those unfit for surgery in

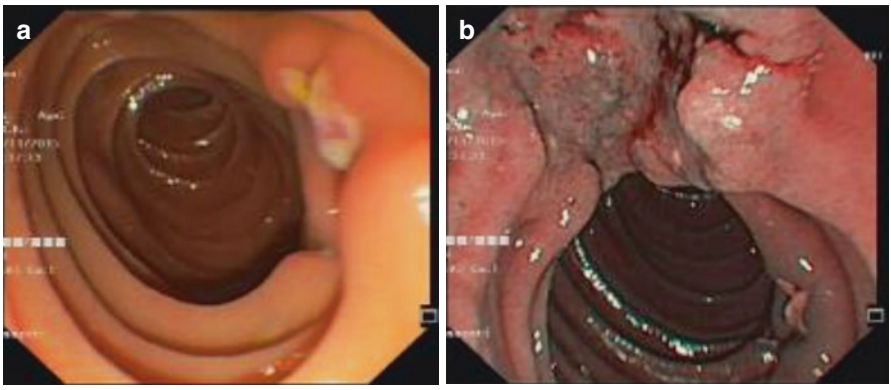

Fig. 16.4 Ampullary mass images on endoscopy—(**a**) side-viewing image showing an ulcerated mass at the ampulla of Vater and (**b**) the same lesion on narrow band imaging

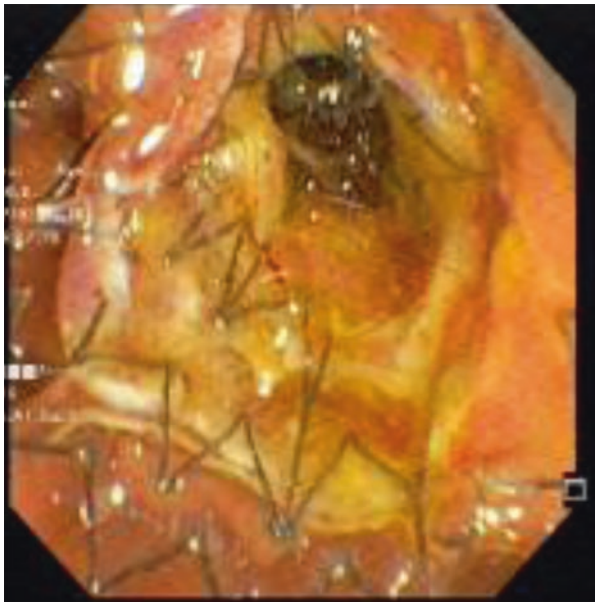

Fig. 16.5 Side-viewing endoscopic image of a successfully deployed SEMS placed across a malignant lower CBD stricture

whom optimization prior to surgery is essential or as a definitive procedure for biliary obstruction in patients with an unresectable lesion [128–130]. Endobiliary drainage results in biliary colonization with rates reported to be around 64% [131]. Thus, it should be preferably performed only in the above situations and not in every patient who presents with surgical obstructive jaundice since it is associated with an increased risk of surgical site infections [132], increased hospital stay and increased costs [133]. While there is no standard time frame for performing surgery following endobiliary drainage, the period of 4–6 weeks to permit the attendant inflammation to settle is generally accepted [128].

In terms of the choice of stent, short-length self-expandable metal biliary stents (SEMS) are preferred to plastic stents if extended delays (>6 weeks) are anticipated between the stenting and PD [134, 135]. In terms of long-term palliation of biliary obstruction, too, SEMS are preferred [136] as the durability of the stent offsets the initially perceived increased costs [137].

(c) Endoscopic ultrasonography/EUS (Figs. 16.6 and 16.7)—EUS has steadily emerged as one of the most useful complementary tools to standard imaging. It is not only of value in delineating lesions <2 cm [138]; EUS is the best available modality for the accurate T-staging of pancreatic cancer with sensitivities approaching 72% for T1-2 lesions and 90% for T3-4 lesions [139]. It is useful in obtaining cytology (EUS—fine needle aspiration) for histopathological as well as molecular analysis to aid in confirming the diagnosis of malignancy which is of prime importance to patients who have unresectable/borderline resectable or metastatic disease and also to assess suspected vascular involvement in CT or MRI. EUS has a superior sensitivity as compared to CT scan (69% versus 48%) for the detection of vascular involvement by the tumour [140].

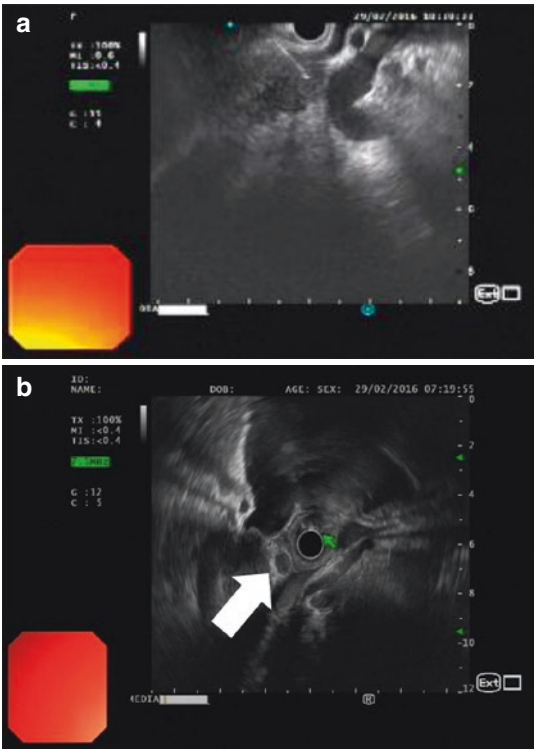

Fig. 16.6 (**a**) Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) with a 22-gauge needle of a pancreatic head mass. (**b**) A peripancreatic lymph node (marked with a white arrow) oval in shape with irregular borders depicted on EUS—such lymph nodes can also be subjected to FNA

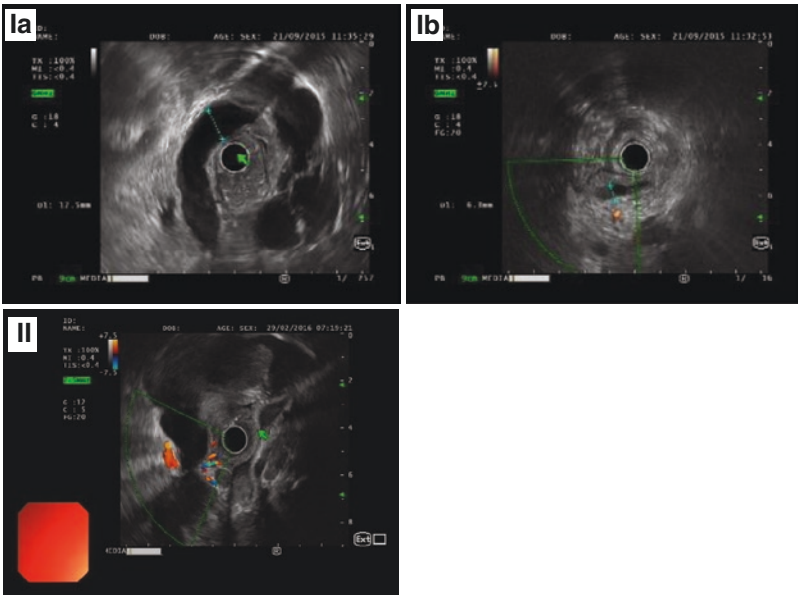

Fig. 16.7 Endoscopic ultrasound (EUS) images obtained with a radial endoscope using 7.5 MHz frequency depicting (I) a resectable ampullary tumour causing upstream dilation of (**a**) the CBD and (**b**) the MPD. (II) Portal vein invasion

16.4.2.5 Complementary Investigations

(a) Positron emission tomography in combination with CT (PET-CT) or MRI (PET-MRI)—was initially regarded as a useful adjunct to MDCT or MRI in patients with locally advanced or borderline resectable tumours to detect or rule out metastases outside the abdominal cavity [141]. However, there is steadily emerging evidence that PET imaging parameters such as standardized uptake values (SUV max) on CT [142] or the minimal apparent diffusion coefficient (ADC_{min}) [143] correlate with survival in patients with resectable and metastatic disease [144]. PET-CT is also useful in conjunction with MDCT to detect tumour recurrences on follow-up [145]. PET-CT is now recommended for routine staging of resectable pancreatic cancer.

(b) Staging laparoscopy (SL) and laparoscopic ultrasonography—the best indication for staging laparoscopy in pancreatic cancer is in the assessment of patients with non-metastatic, unresectable or borderline resectable disease on conventional imaging. In this subset of patients, SL will help detect occult liver and/or peritoneal metastases (sensitivities of 88% and 93%, respectively) [146] or confirm their non-metastatic nature and hence help direct patients towards neoadjuvant treatment protocols [147]. When used in all patients with pancreatic cancer, SL with ultrasound correctly predicted resectability in 79% compared to 55% by standard imaging, thereby avoiding non-curative laparotomies in 33% of patients [148].

(c) Venography [149]—this modality consists of images obtained either by CT scan, superior mesenteric arteriography or intraoperative portal venography following cannulation of a superior mesenteric venous tributary. Venous involvement has been classified as type A (no narrowing), B (unilateral narrowing), C (bilateral narrowing) and D (stenosis or obstruction with collaterals). The correlation with histology was noted in 100% of patients with type A (no invasion), while invasion was present in 51%, 74% and 93% of patients with types B, C and D, respectively.

16.4.3 Surgical Management

Surgery offers the only chance of cure in patients with pancreatic and periampullary cancer. However, it should only be attempted in patients in whom a complete (R0) resection is deemed feasible. The available evidence does not support the role for gross margin-positive (R2) resections. Endoscopic ampullary excisions may be considered only in benign lesions. For lesions harbouring a malignancy, a pancreatoduodenectomy (PD) must be performed as nearly 30% of patients with T1 lesions harbour lymph node metastasis [150].

From a surgical perspective, pancreatic cancers can be classified as resectable, borderline resectable, locally advanced and metastatic depending on the tumour extent and contact with or involvement of adjacent blood vessels (superior mesenteric artery or vein/SMV or SMA, hepatic artery/HA, celiac axis, portal vein/PV). The term ‘resectable’ pancreatic cancer has been loosely used to include all tumours amenable to a resection irrespective of whether this resection would entail a synchronous vascular resection. The advent of the anatomical term *borderline resectable* pancreatic tumour or cancer (BRT) to include tumours with limited involvement

of the mesenteric vessels (abut SMA, abut or encase common HA over a short segment or occlude SMV-PV confluence), in which a resection with venous reconstruction is technically possible but which carry a high risk of margin-positive resection unless neoadjuvant therapy is employed before surgery [151, 152], has certainly been useful. It has enabled a clearer delineation of locally advanced but non-metastatic (unresectable) cancers from those tumours in whom a resection can be contemplated with hope of providing a survival benefit.

The surgery for pancreatic head and neck cancers is a PD, while a distal or subtotal pancreatectomy (with splenectomy) is performed for cancers of the distal neck, body and tail.

Perioperative antibiotic prophylaxis must be considered in all patients undergoing pancreatoduodenectomy owing to the risk of bactibilia (12–18%) [131, 153] even in those who have not undergone prior biliary intervention.

16.4.3.1 Pancreatoduodenectomy (PD)

The Resection

PD (Fig. 16.8) involves removal of the stomach and duodenum, the pancreatic head, uncinate process and neck along with the distal common bile duct (and gallbladder)

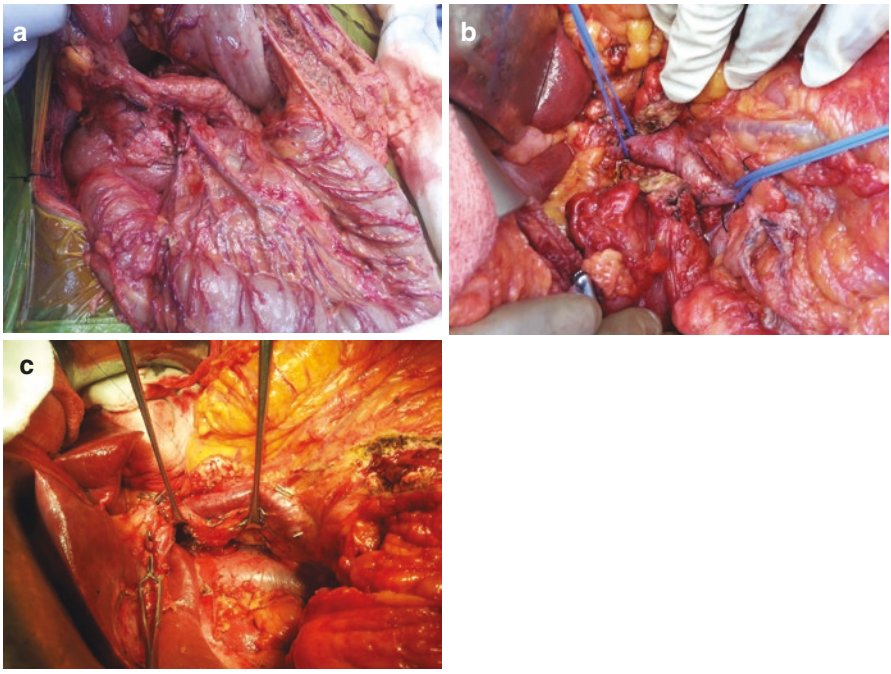

Fig. 16.8 Intraoperative photographs depicting (**a**) completed dissection of the pancreatic neck tunnel, (**b**) transected pancreatic neck with the portal vein (cranial) and SMV (caudal) with blue vessel loops and (**c**) completed Whipple's resection with the SMA being retracted by a vein loop

and the first few inches of the jejunum. Based on the location of the proximal margin of transection (stomach or pyloro-duodenum), there are two named procedures, viz. the classical Whipple's procedure (proximal transection at the junction of distal body and antrum of the stomach) and the pylorus-preserving PD (PPPD). Distally, up to 15 cm of the jejunum (from the duodeno-jejunal flexure) may be resected. It is important for every surgeon to identify the portal vascular anatomy to avoid inadvertent injury to aberrant vessels [119]. It is preferred that the mesopancreatic tissue in the region of the uncinate process be divided between ligatures/LIGACLIPS®. In a broad uncinate process, surgeons have successfully employed the use of endovascular staplers after ensuring adequate clearance from the cancer without compromising the radicality of the procedure [154]. In such a scenario, the author would advise that the operating surgeon thoroughly inspect the staple line prior to commencing the pancreaticoenteric anastomosis as there is a tendency for small vessels to bleed. These can be secured with 4-0 polypropylene sutures. Alternatively, the Ligasure® or harmonic scalpel may be used to divide the mesopancreatic tissue.

The Reconstruction

At the end of the resection, the surgeon is faced with a transected pancreas, transected bile or hepatic duct and remnant stomach. The reconstruction following PD progresses in an anti-clockwise manner commencing with the pancreaticoenteric anastomosis followed by the hepatico-enteric and finally the gastro-enterostomy. While the common hepatic duct and stomach are anastomosed to the jejunum (hepaticojejunostomy/HJ and gastrojejunostomy/GJ), the choice of anastomosis of the pancreatic remnant is between the stomach (pancreaticogastrostomy/PG) and the loop of jejunum (pancreaticojejunostomy/PJ). The PG/PJ and HJ are always behind (retrocolic) the transverse colon, while the GJ may be performed antecolic (in front of) or retrocolic.

The existing literature, including the most updated Cochrane review, indicates that there is no difference in terms of oncological benefit, overall morbidity and mortality when PPPD was compared to a classical Whipple's procedure [155]. However, on closer inspection of the data, while the review indicated that delayed gastric emptying (DGE) was higher in PPPD, pylorus preservation was associated with shorter operating times, lower intraoperative blood loss and hence a reduced need for blood transfusion [155]. The studies included in this analysis were heterogenous with no uniform information provided regarding intention-to-treat, use of adjuvant and neoadjuvant therapy, etc. Thus, this remains an area that warrants future well-designed trials [156]. Despite this, it must be borne in mind that in specific situations such as duodenal cancers or large pancreatic head tumours invading the gastric antrum and/or the first part of the duodenum, a classical PD should be performed.

The most recent meta-analysis has concluded that there exists no difference in the rate of overall and clinically significant post-operative pancreatic fistula (POPF), morbidity, mortality, reoperation and intra-abdominal sepsis between PG and PJ [157]. Similarly, while the duct-to-mucosa PJ has been shown to reduce duration of hospital stay, it did not significantly reduce rates of pancreatic fistula and other adverse events as compared to invagination PJ [158]. Thus, the focus of a

pancreaticoenteric anastomosis must be on the performance of a standardized, meticulous anastomosis [159] based on sound surgical principles.

Performance of an antecolic gastro- or duodeno-jejunostomy after PD is associated with a reduction in the rate of DGE as well as post-operative days to start a diet and length of hospital stay as compared to a retrocolic reconstruction [160].

Lymphadenectomy is central to the oncological completeness (staging and survival) of PD for pancreatic cancer as in the case of other solid organ cancers. A standard lymphadenectomy involves removal of stations 5, 6 and 8a along with lymph nodes of the right side of the hepatoduodenal ligament (12b1, 12b2, 12c), posterior pancreaticoduodenal nodes (13a, 13b), nodes to the right side of the superior mesenteric artery from the origin of the superior mesenteric artery at the aorta to the inferior pancreaticoduodenal artery (14a, 14b) and anterior pancreaticoduodenal nodes (17a, 17b) [161]. The existing literature suggests that a standard lymphadenectomy is not only associated with a lower morbidity (increased risk of intractable diarrhoea in the early post-operative phase seen with extended lymphadenectomy) but also comparable survival compared to an extended lymphadenectomy [162].

16.4.3.2 Distal/Subtotal Pancreatectomy

While surgeries such as spleen-preserving distal pancreatectomy as well as middle or central pancreatectomy may be considered in benign or borderline malignant lesions of the neck, body and tail of the pancreas, depending on the location of the tumour, the standard procedure for a pancreatic cancer involving the distal neck, body and/or tail is a distal/subtotal pancreatectomy with splenectomy [163, 164].

Cancers of the body and tail of pancreas are notorious for presenting at an advanced stage. If not yet metastatic at presentation, in up to one-third of patients, the tumours at surgery have evidence of involvement of surrounding organs either as a result of direct tumour infiltration or inflammatory adhesions [165]. In such patients, an en bloc resection (including multivisceral resections) in these patients should be attempted so long as a complete (R0) resection can be achieved. There is evidence to suggest that in patients undergoing an R0 resection, the long-term survival rates are similar to patients undergoing standard resection for resectable tumours [166–168] and markedly improved as compared to patients with unresectable locally advanced disease [167]. Given the high morbidity and risk of mortality associated with these resections, they should preferably be undertaken in high-volume centres [169].

Owing to the high frequency of POPF following distal pancreatic resections, there has been a focus on whether the method of transection (staplers or suture, use of ultrasonic dissection devices) or the re-enforcement of the pancreatic stump with mesh or glue improves outcomes. The results of Cochrane systematic review, largely influenced by a single multicentre randomized controlled trial (DISPACT) [170], concluded that the outcomes following hand-sewn closure of the pancreatic remnant after stapled or scalpel resection are comparable in terms of POPF, overall mortality and surgical time [171]. While the available evidence does support practices such as the use of ultrasonic dissection devices or re-enforcement of the pancreatic remnant with glue or mesh [172], it must be appreciated that the data is sparse and fraught with heterogeneity that precludes the generation of firm conclusions. Irrespective of

the technique used to transect/close the pancreatic stump, meticulous attention needs to be paid to transfixing the pancreatic duct.

Removal of lymph node stations 10, 11 and 18 is considered part of a standard lymphadenectomy for lesions in the pancreatic body and tail [161].

16.4.3.3 Borderline Resectable Tumours (BRT)

Maurer and colleagues [173] were the first to appreciate that some cancers of the pancreas may not be completely resectable at the outset but may be so after neoadjuvant therapy. This entity was christened BRT by the group from the MD Anderson Cancer Center [151]. The definition of BRT has evolved over the years (Table 16.5) [151, 174–177]. The outstanding issues with managing BRT are whether to offer upfront surgery or neoadjuvant therapy; if neoadjuvant therapy is to be used, then should it include chemotherapy only or chemotherapy with radiotherapy; what is the ideal regimen of chemotherapy to be used; and finally what is the true benefit of embarking on such resections in terms of survival improvement. The rationale behind recommending neoadjuvant therapy in BRT was to increase the rate of R0 resections [152]. However, the neoadjuvant chemotherapy protocols such as FOLFIRINOX (5-fluorouracil + oxaliplatin + irinotecan + leucovorin) are quite toxic, and the preliminary results from the ongoing ALLIANCE trial [178] suggest that the improvement in resection rates may not be significantly increased. The issues regarding vascular resections are discussed below. Besides, restaging of BRT post-neoadjuvant therapy is fraught with difficulties in interpretation owing to desmoplastic/inflammatory changes in and around the tumour and pancreas which could either be from the tumour or therapy induced [179]. Thus, the consensus regarding the optimum management strategy for BRT remains ‘a work in progress’. However, if a patient presents with features clearly indicative of BRT as per radiological features, then such patients must be considered for a staging laparoscopy followed by neoadjuvant chemotherapy (if non-metastatic) followed by a trial of resection (if the disease remains non-progressive) with the need for synchronous venous resection and reconstruction. The role of studying genetic markers such as SMAD4 (to help in decision-making) needs to be addressed in this subset of patients [88, 180].

Vascular Resections

Arterial and venous resections have been performed as part of pancreatic resections for a few decades [181] with the rationale that they are beneficial so long as an R0 resection could be achieved [182]. In the case of distal pancreatic resections, there have been reports of 28 highly selected patients undergoing synchronous celiac artery resections with (bypass from the aorta to the common hepatic artery) or without relying on the presence of collateral arterial circulation via an intact pancreaticoduodenal arcade and the gastroduodenal artery to maintain prograde hepatic arterial perfusion reconstruction (modified Appleby procedure) [183].

However, recent analyses made surgeons rethink the true benefit of such resections. Synchronous arterial resections are associated with higher R2 margin rates [184], an increased risk of perioperative morbidity and mortality [185] and survival rates comparable to non-resected patients with locally advanced and non-metastatic disease [184, 186]. The most recent meta-analysis has demonstrated the same results with synchronous venous resections [187]. The reasons for the findings of

Table 16.5 Variations in the definition of borderline resectable pancreatic cancer (Reproduced with permission from Barreto SG, Windsor J. Justifying vein resection with Pancreatoduodenectomy. Lancet Oncol 2016; 17: e118–24)

Organization(s)	MD Anderson Cancer Center	Americas Hepato-Pancreato-Biliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology	National Comprehensive Cancer Network	Intergroup trial (Alliance A021101)	American Pancreatic Association[a]
Year	2006	2009	2012	2013	2014
Author (ref)	Varadhachary et al. [151]	Callery et al. [174]	Tempero et al. [175]	Katz et al. [176]	Al-Hawary et al. [177]
SMV-PV	Short-segment occlusion of SMV, PV or SM-PV confluence with suitable option for vascular reconstruction available because of a normal SMV below and normal PV above area of tumour involvement	Tumour abutment with or without impingement and narrowing of lumen or encasement of SMV-PV or short-segment venous occlusion resulting from either tumour thrombus or encasement but with suitable vessel proximal and distal to vessel involvement, allowing for safe resection and reconstruction	Abutment with impingement or narrowing	Interface between primary tumour and ≥180° of the circumference of SMV-PV and/or short-segment occlusion of SMV-PV with normal vein above and below the level of obstruction amenable to resection and venous reconstruction	Tumour contact of >180° with SMV or PV Tumour contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to site of involvement allowing for safe and complete resection and reconstruction
SMA	Tumour abutment involving ≤180° of circumference	Tumour abutment not to exceed >180°of circumference	Abutment	Interface between tumour and <180° of the circumference of wall	Tumour contact of ≤180°
GDA	–	Encasement	–	–	–

CHA/HA	Short-segment encasement amenable to resection and reconstruction	Either short-segment encasement or direct abutment	Abutment or short-segment encasement	Short-segment interface (of any degree) between tumour and HA with normal artery proximal and distal to the interface amenable to resection and arterial reconstruction	Contact with CHA or HA bifurcation allowing for safe and complete resection and reconstruction
Celiac trunk/axis	No extension	No extension	No abutment or encasement	Interface between tumour and <180° of the circumference	No extension
IVC	–	–	–	–	Tumour contact
Vascular anomalies	–	–	–	–	Tumour contact with variant arterial anatomy (e.g. accessory or replaced RHA or replaced CHA)

[a]Adopted by National Comprehensive Cancer Network in 2015 [40]

SMV superior mesenteric vein, *SMA* superior mesenteric artery, *PV* portal vein, *RHA* right hepatic artery, *IVC* inferior vena cava, *CHA/HA* common hepatic artery/hepatic artery, *GDA* gastroduodenal artery

this meta-analysis as compared to previous studies suggesting a role for venous resections [188] are likely due to the fact that venous resections do not alter outcomes so long as the vein is truly involved, especially the tunica media and intima [189], and if the length of involvement is more than 3 cm [182].

The role of synchronous vascular resections thus needs to be more carefully studied, and such resections performed in highly selected individuals preferably within the confines of clinical trials [185] should be limited to high-volume centres with experienced surgical and multidisciplinary teams [188].

A useful technique in determining whether the vessels are involved early in the course of the surgery is the superior mesenteric 'artery first' approach [190].

16.4.4 Surgery for Metastatic (M1) Disease

There is evidence in literature that pancreatic resections along with, or followed by, removal of oligometastatic disease (interaortocaval lymph nodes, liver and peritoneal metastasis) are feasible [191, 192]. However, the number of patients in the individual reported series is small. Thus, the true impact of such resections in terms of prolonging overall survival remains unclear [193]. More recently, Paiella and colleagues analysed the data on para-aortic lymph node metastases and found that involvement of this group of lymph nodes is associated with a poor prognosis and significantly reduced survival [194]. De Jong and colleagues when analysing their data of 40 patients who underwent resections and/or radiofrequency ablation of periampullary liver metastases inferred that there may be a modest benefit in the intestinal subtype but none in the pancreatobiliary subtype [195].

Thus, such resections must not be performed unless further evidence from well-conducted trials emerges to support such practices.

16.4.5 Laparoscopy and Robotic Surgery for Pancreatic and Periampullary Carcinoma

Minimally invasive surgery (laparoscopy and robotic surgery) has been demonstrated to be feasible in pancreatic surgery. Based on a national observational study, Sulpice and colleagues of the French Pancreatectomy Study Group [196] deduced that distal pancreatectomy has acceptable short- and long-term outcomes although it has not been widely accepted. This has been better elucidated in a well-conducted study of accelerated recovery after laparoscopic distal pancreatectomy that indicated a high readmission rate [197]. Even for PD, the combined experience of the world is barely a thousand cases, and these are performed only in well-selected cases [198]. To date, there exists no level 1 evidence to suggest that minimally invasive pancreatic surgery is equal to, or superior to, open surgery in terms of overall survival for pancreatic and periampullary cancer [199]. Possible reasons for the slow adoption of minimally invasive surgery into pancreatic surgery could be the costs associated, the time taken for individual procedures and the realization that the morbidity associated with pancreatic surgery (POPF, DGE, post-pancreatectomy

haemorrhage/PPH) is unrelated to the length of the abdominal incision but rather to the anastomoses [200].

16.4.5.1 Complications of Pancreatic Surgery

The three most important complications specific to pancreatic surgery are POPF [201], DGE [202] and PPH [203]. Complications following pancreatic surgery are a significant contributor not only to costs but also overall survival [204]. Many of the factors contributing to the occurrence of complications such as a soft pancreas, small duct diameter and comorbidities are beyond the control of the surgeon. Thus, central to reducing complications from a surgeon's perspective is the improvement in the quality of surgery and perioperative care [204]. This would include standardization of technique [159], attention to detail and focus on training [205], regionalization of pancreatic surgeries [206, 207] and implementation of clinical pathways [208, 209]. The role of intraoperatively placed drains in the development of complications has been addressed [210]. While drains certainly do not prevent complications, they aid in the early detection of complications, especially POPF and PPH [211].

16.4.6 Irreversible Electroporation (IRE)

The technique of IRE involves the delivery of high voltage (maximum 3000 V) at small microsecond pulse lengths (70–90 μs) to the tissue. This results in permanent cell death through cell membrane perforation and a further protracted cell death by apoptosis as a result of cellular electrolyte instability [212]. This technique is still in the phase of evolution, and while it has been found to be safe and feasible, the complete benefit is yet to be appreciated. At the present time, the two indications for which IRE has been selectively employed include locally advanced pancreatic cancer (Stage III) of the head or body/neck after induction chemotherapy (with or without chemoradiotherapy) either by itself or as an intraoperative adjunct to pancreatic resectional surgery [213] and in resections for borderline resectable cancers [214] where it may offer the benefit of margin accentuation. This benefit though is yet to be completely appreciated. It has been shown to offer a superior advantage in terms of survival in locally advanced pancreatic cancer when the data was compared to published data of patients treated with only chemotherapy and/or radiotherapy [213].

16.4.7 Fast-Track Protocols/Enhanced Recovery

Spurred on by the success of evidence-based clinical pathways in other surgical specialties such as colorectal and vascular surgery in enhancing perioperative patient experience and outcomes, ERAS® has found its way into pancreatic surgery, too. The initial experience suggests that it has contributed to significantly reduced morbidity, in general, as well as no increase in readmission rates [208]. In the author's experience [209], clinical pathways help to significantly reduce the duration of hospital stay. However, uniform application of clinical pathways may not be feasible with the need to tailor them to specific groups of patients such as obese

patients and those with respiratory comorbidities [209]. The aspect of ERAS® will be covered in detail in the chapter on perioperative patient care.

16.4.8 Palliation in Advanced Pancreatic Cancer

Palliation as defined by O'Neill and Fallon [215] and later reaffirmed by Miner and colleagues [216] includes treatments in advanced cancer that help relieve symptoms and improve quality of life. In pancreatic and periampullary cancers, the symptoms that would need to be palliated include obstructive jaundice, uncontrolled vomiting from gastroduodenal obstruction and pain. Traditionally, the surgery performed in the case of a patient undergoing a laparotomy and found to have an inoperable tumour is the triple bypass surgery that includes a side-to-side or end-to-side choledochojejunostomy with a retrocolic, side-to-side gastrojejunostomy and a side-to-side jejuno-jejunostomy.

A recent multicentre study demonstrated that palliative surgeries are associated not only with increased morbidity but no difference in survival compared to aborted laparotomies [217]. The concern in this subset of patients is that mortality rates in actual practice may be as high as 2.4-fold compared to reported literature [218]. Further, complications following palliative surgeries have been shown to significantly impact long-term survival [219].

The alternatives to surgery are SEMS for biliary and gastroduodenal obstruction. SEMS have been shown to have a low morbidity and mortality (procedure-related as well as 30 days) as compared to surgery [220]. Lyons and colleagues [221] have demonstrated that neither were bypass surgeries associated with fewer invasive procedures or reduced number of inpatient hospital days prior to death when compared to SEMS.

Optimization of cancer staging by effective use of staging laparoscopy especially in patients with borderline resectable or locally advanced cancers, as well as reducing the time interval between imaging and the planned surgery (shown to be associated with an increased ability to pick up metastases) thereby avoiding non-beneficial laparotomies in pancreatic cancer [222], should be the aim of clinicians dealing with likely unresectable pancreatic and periampullary cancers.

In patients with metastatic disease, non-surgical modalities for palliation should preferentially be resorted to. In patients with locally advanced cancers with a good performance status (European Co-operative Oncology Group score of 0–2) in whom non-surgical methods of palliation have been attempted and have been unsuccessful, and/or in those who have received neoadjuvant therapy and on surgical exploration (with an aim for trial of resection) were found to harbour non-metastatic, but unresectable, disease, the available evidence supports the creation of a prophylactic gastrojejunostomy in the setting of an inoperable pancreatic or periampullary cancer irrespective of the presence of features of gastric outlet obstruction [223, 224]. The author would also advise the creation of a feeding jejunostomy in patients who undergo a triple bypass and who had features of gastroduodenal obstruction preoperatively. Such patients tend to have a persistence of these symptoms in the early post-operative course, and a feeding jejunostomy helps maintain an enteral portal of nutrition.

Deep boring pain radiating to the back is a sign of advanced pancreatic cancer and may be encountered in up to 70% of patients. The cause of pain is multifactorial and has been hypothesized to be due to pancreatic ductal obstruction and resultant hypertension, neural (celiac plexus) invasion and the invasion of surrounding structures [225]. While treatment with non-steroidal anti-inflammatory drugs and opioids (working up the World Health Organization ladder) is useful in the initial management of pain, celiac plexus block performed either through image guidance, through endoscopic ultrasonography or at the time of palliative surgical exploration affords the best relief of pain. Although these patients may experience local pain, diarrhoea and hypotension on account of the celiac plexus block, these symptoms are transient. On the flipside, these patients required significantly less narcotic analgesics with a consequent reduction in the attendant side effects (constipation) [226].

16.4.9 Chemotherapy and Chemoradiotherapy for Pancreatic Cancer

16.4.9.1 Adjuvant Therapy

There have been eight randomized controlled trials that have examined the role of adjuvant chemotherapy and/or chemoradiotherapy in patients with resectable pancreatic cancer [227–236]. Table 16.6 provides an overview of these trials. The evidence clearly supports a survival advantage with adjuvant therapy. While three trials demonstrated a benefit of adjuvant chemotherapy (5-fluorouracil or gemcitabine) in terms of overall survival [227, 229, 230], two trials indicated a benefit of chemoradiotherapy [228, 233]. The ESPAC-1 trial, however, determined that only adjuvant chemotherapy and not chemoradiotherapy is associated with a significant survival benefit [230]. While single-agent gemcitabine has been the preferred drug in the adjuvant setting [237], the most recent trial from Japan [235] has demonstrated a significant survival advantage for S-1 (tegafur) over gemcitabine. These results need to be validated outside of Japan. The results from the 30.5 month median follow up of the PRODIGE24 trial (238) were recently presented. For patients aged 18–79 years, 21–84 days after R0 or R1 resection, WHO Performance status ≤1, adequate hematologic and renal function, and no cardiac ischaemia, mFOLFIRINOX has not only been shown to be safe, but associated with a significantly better disease-free and overall survival compared to Gemcitabine.

16.4.9.2 Neoadjuvant Therapy

Neoadjuvant therapy, chemotherapy with or without radiotherapy, is being considered in pancreatic cancer in two specific scenarios, namely, locally advanced or borderline resectable cancers with the aim of tumour downstaging [238] and tumour downsizing so as to increase the proportion of margin-negative resections [152], and in resectable cancers on the premise that pancreatic cancer is a systemic disease at the time of diagnosis [239, 240] and thus neoadjuvant therapy will help the tumour to declare its biology enabling surgical resections to be reserved for patients who would truly benefit from them [180, 241].

Table 16.6 Overview of the major randomized controlled trials exploring the role of adjuvant therapy in pancreatic cancer (updated from Shrikhande and Barreto [236]) [227–235] (Reproduced with permission from Elsevier)

Author	Trial name (year)	Comparative groups (*n*)	Median survival (months)	Conclusions
Kaiser and Ellenberg	GITSG (1985)	Surgery alone (22)	11	Adjuvant therapy may prolong
		Sx + 5-FU + RT (21)	20	Survival
Klinkenbijl et al.	EORTC (1999)	Sx alone (103)	19	Adjuvant chemo-RT is safe and well tolerated with no significant benefit
		Sx + 5-FU + RT (104)	24.5	
Neoptolemos et al.	ESPAC-1 (2004)	Surgery alone (69)	16.9	Adjuvant chemotherapy, but not chemo-RT, has a significant survival benefit
		Sx + 5-FU + RT (73)	13.9	
		Sx + 5-FU/leucovorin (75)	21.6	
		Sx + Chemo + RT + chemotherapy (72)	19.9	
Oettle et al.	CONKO-001 (2007) (2013)	Sx alone (175)	20.2	Following macroscopic complete removal of pancreatic cancer, adjuvant Gem (6 months) resulted in increased DFS and OS
		Sx + Gem (179)	22.8	
Regine et al.	RTOG 9704 (2008)	Sx + Gem + 5-FU/ EBRT + Gem (221)	20.5	Addition of gemcitabine to adjuvant fluorouracil-based chemo-RT is associated with a significant survival benefit
		Sx + 5-FU + 5-FU/ EBRT +5-FU (230)	16.9	
Ueno et al.	JSAP 02 (2009)	Sx alone (60)	22.3	Adjuvant Gem affords a significant improvement in DFS but does not influence OS
		Sx + Gem (58)	18.4	
Neoptolemos et al.	ESPAC-3 (2010)	Sx + 5-FU/leucovorin (551)	23	Adjuvant Gem offers no significant benefit as compared to 5-FU
		Sx + Gem (537)	23.6	
Uesaka et al.	JASPAC 01 (2016)	Sx + Gem (190)	25.5	Adjuvant S-1 offers a significant benefit as compared to Gem
		Sx + S-1 (187)	46.5	

Sx surgery, *S-1* tegafur (oral prodrug of 5-FU), *5-FU* 5-fluorouracil, *Gem* gemcitabine, *NCICCTG* National Cancer Institute of Canada Clinical Trials Group, *DFS* disease-free survival, *OS* overall survival, *QoL* quality of life, *FOLFIRINOX* 5-FU + oxaliplatin + irinotecan + leucovorin

While radiotherapy has been suggested to improve resection rates in locally advanced pancreatic cancer when combined with chemotherapy, the most encouraging results have been obtained with FOLFIRINOX-based therapy [238]. A recent study has reported a 60% resectability rate with FOLFIRINOX that was better than gemcitabine in combination with radiation therapy (46%) [242]. Downstaging with radiotherapy

occurs in less than one-third of patients [243]. Radiation (hypofractionated or conventional) has been shown to actually improve local control without impacting survival [244]. Neoadjuvant therapy does not appear to alter tumour biology [178]. Moreover, radiological restaging of tumours post-neoadjuvant therapy is still a challenge [179]. Whether neoadjuvant therapy actually increases margin-negative resections remains yet to be determined [245]. The PREOPANC trial [246] comparing preoperative chemoradiotherapy versus upfront surgery for resectable and borderline resectable tumours will certainly provide a clearer insight into whether neoadjuvant chemoradiotherapy alters survival, R0 resection rates, disease-free survival, etc.

In retrospective cohort series, survival rates following neoadjuvant therapy are best in patients who undergo a complete (R0) resection [247], who complete the therapy [152] and in those who have an increased histopathologic response [248]. Additionally, neoadjuvant therapy does not appear to influence post-surgical outcomes (morbidity and mortality) [249] and thus presents itself as a promising strategy in pancreatic cancer.

16.4.10 Metastatic Pancreatic Cancer

For decades, metastatic pancreatic cancer was regarded as chemotherapy-resistant. The first trial that heralded the role of gemcitabine as a single-agent monotherapy for palliation was conducted by Burris and colleagues [250]. Table 16.7 provides an

Table 16.7 Overview of the major randomized controlled trials exploring the role of chemotherapy in the palliation of metastatic pancreatic cancer [8, 9, 250–252]

Author	Trial name (year)	Comparative groups (*n*)	Median survival (months)	Conclusions
Burris et al.	– (1997)	Pain stabilization followed by:		Significantly better: (a) Clinical benefit response (b) Median survival (c) Survival at 12 months
		Gem (63)	5.65	
		5-FU (63)	4.41	
Moore et al.	NCICCTG (2007)	Gem + erlotinib (285)	6.24	First RCT to demonstrate a survival advantage by adding an agent to Gem
		Gem + placebo (284)	5.91	
Conroy et al. Gourgou-Bougade et al.	PRODIGE 4/ ACCORD 11 (2011)	FOLFIRINOX (171)	11.1	Significant survival advantage and reduced QoL impairment with increased toxicity
		Gem (171)	6.8	
Von Hoff et al.	MPACT (2013)	Nab-paclitaxel+		Significant improvement in OS, PFS and response rate with the addition of nab-paclitaxel
		Gem (431)	8.5	
		Gem (430)	6.7	

5-FU 5-fluorouracil, *Gem* gemcitabine, *NCICCTG* National Cancer Institute of Canada Clinical Trials Group, *PFS* progression-free survival, *OS* overall survival, *QoL* quality of life, *FOLFIRINOX* 5-FU + oxaliplatin + irinotecan + leucovorin

overview of the sentinel randomized (phase III) trials in metastatic pancreatic cancer [8, 9, 250–252]. The PRODIGE 4/ACCORD 11 trial [8] was not only the first trial to demonstrate an advantage of FOLFIRINOX over gemcitabine; the regimen was also found to be more cost-effective [253]. Ultimately, the choice of chemotherapy in this subset of patients would be between FOLFIRINOX (with its attendant better survival profile) and gemcitabine with nab-paclitaxel (with its better toxicity profile).

16.5 Future Research

There is a need for randomized trials to truly determine if M1 resections confer a survival benefit in pancreatic or periampullary cancers. Within the current realms of evidence, such studies must be undertaken preferably in high-volume centres and with all patients receiving chemotherapy first followed by randomization to either surgery and further therapy or chemotherapy alone.

There is a need for high-quality level 1 evidence to ascertain whether patients with borderline resectable cancers should undergo upfront surgery or surgery following neoadjuvant therapy. The impact of either therapy on overall survival needs to be determined within the context of a trial strictly adhering to the current definition of borderline resectable disease.

The benefit of procedures such as IRE in accentuating surgical resection margins in borderline and locally advanced pancreatic cancer needs to be tested within the confines of a clinical trial.

Whether genetic markers such as SMAD4 inactivation (predictive of early metastases [88]) will help in further selecting patients for such resections needs to be determined.

16.6 Summary

The overbearing nihilism in our perception of pancreatic cancer is preventing us from appreciating the small, but certain, advances in the management of this cancer. Periampullary cancer, on the other hand, remains a less investigated entity possibly due to its early presentation and hence relatively better outcomes as compared to pancreatic cancer. Scientifically tempered surgical aggression aimed at complete surgical resection coupled with the use of adjuvant chemo- or chemoradiotherapy (when indicated) offers the best possible outcome in patients with resectable or locally advanced but resectable disease. Data on the role of neoadjuvant chemotherapy in borderline resectable is encouraging, and this deserves further attention. Palliative surgery may yet possess a valuable role in pancreatic cancer in terms of improving quality of life coupled with gemcitabine-based mono- or combination therapies.

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17

Perioperative Patient Care in Pancreatobiliary Surgery: From Preoperative Assessment to ERAS

Kristoffer Lassen and Olle Ljungqvist

Following on the seminal studies on early food after hysterectomies by Ib Hessov [1], the Danish surgeon Henrik Kehlet pioneered the modern emphasis on attenuating surgical trauma and the physiological stress response [2]. The ensuing collaboration with a group of surgeons focussing on nutrition, early recovery and myth busting led to the first Enhanced Recovery After Surgery (ERAS) consensus guidelines for colonic surgery in 2005 [3], updated and expanded in 2009 [4]. The first experiences with a protocol for liver surgery were published in 2008 [5]. Hip surgery, cardiac surgery, gynaecology, urology and other areas followed suit.

Until quite recently, pancreatobiliary and gastroesophageal surgery was the Dark Continent as far as ERAS regimens went. From the birth of enhanced recovery thinking in the 1990s, a main obstacle to implementing modern, evidence-based, stress-reducing treatment protocols was the scepticism to do away with the nasogastric decompression tube and allow patients to eat ordinary food at will. No other field of surgery could muster a similar conservatism and reluctance to change old (often dogmatic) routines. The reason was easy to understand: complication rates in pancreatic and gastroesophageal surgery were traditionally staggering, and anastomotic leaks were frequently fatal [6]. In addition, loss of gastric function following pancreatoduodenectomies (PD, Whipple resections) was common, and evidence for the safety of the modern routines was initially scarce and of poor quality [6].

K. Lassen (✉)
Department of Gastrointestinal Surgery/Hepato-Pancreato-Biliary (HPB) Section, Oslo University Hospital at Rikshospitalet, Oslo, Norway

Institute of Clinical Medicine, Arctic University of Norway, Tromsø, Norway

O. Ljungqvist
Department of Surgery, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
e-mail: Olle.Ljungqvist@ki.se

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This has changed. The latest decade has seen PD become a routine operation with mortality below 3% in high-volume centres [7], re-laparotomy rates below 15% and contained leaks mainly managed by percutaneous drainage. Laparoscopic and robotic surgery is now becoming more common for pancreatic resections. The ERAS Society (www.erassociety.org) published the first comprehensive consensus guidelines for pancreatoduodenectomies as a brokered simultaneous publication in 2012 [8, 9].

It became evident that dedicated ERAS protocols reduce the length of stay also in upper GI and HPB surgery [10]. Prospective cohort data [11, 12] and a recent meta-analysis of data in pancreatic surgery suggest that they also reduce complication rates [13]. Methodologically, however, this is hard to evaluate. The problem of poor or contaminated control groups makes complex protocols unsuited for randomized design [14] and it has been argued that an overall protocol is more important than its constituents [15]. Nevertheless, both in single- and multiple-site investigations, higher adherence to the ERAS colorectal guideline protocol is consistently associated with better outcomes [16, 17]. While a hysterectomy in a fit 50-year-old woman may work well without adhering to a score of protocol items, largely due to the wide safety margins, undertaking a pancreatoduodenectomy (PD) in a frail and co-morbid octogenarian will call for utmost care in optimizing every possible detail of the perioperative journey.

This chapter will discuss some of the ERAS items of particular importance in pancreatobiliary surgery. Some items are more generic to all major abdominal surgery and are not included here. For advice about patient counselling, prevention of thromboembolic events, antibiotic prophylaxis, preoperative fasting, prevention of postoperative nausea and vomiting, prevention of intraoperative hypothermia, access and incision, glycaemic control and early and scheduled mobilization, the reader is kindly asked to consult the most recent ERAS Society guidelines and consensus papers [8, 18–22], in addition to national and/or in-house guidelines.

17.1 Preoperative Nutrition

The sinister implications of weight loss prior to major surgery have been recognized since the 1930s [23]. Modern data indicate that even 5% weight loss, estimated by the difference in patient-reported premorbid weight and simple scaling before surgery, is significantly associated with increased risk of complications [24]. The natural response is to treat preoperative malnutrition with artificial nutrition to restore nutritional status before high-risk surgery. Nutrition support (parenterally, enterally or orally by sip feeds) has generally been advocated when weight loss is significant prior to major surgery [25], but high-quality, blinded trials with satisfactory control groups showing improved clinical outcome are uncommon, and the vast majority are old publications. The control groups vary and the outcomes are inconsistent. As this is an issue that lends itself well to double-blinded RCTs (stable intervention, not skill-dependent and no learning curve [14]), this is the type of evidence that is required. It is to date not proven that preoperative nutritional support reduces

complication rates or enhances recovery. It appears sound to offer nutrition support to those who are severely malnourished, and it may increase their well-being. For patients who are mildly malnourished, nutrition support preoperatively remains advocated by the ESPEN guidelines from 2006, but this is based mainly on uncontrolled or open-labelled trials or addressing surrogate endpoints [25]. The ESPEN guidelines [25] also advocate including immune-enhancing components (e.g. glutamine and arginine) in attempts to reduce especially infectious morbidity. But of the many trials that claim to show a benefit, there are very few that are double-blinded with isonitrogenous control groups and addressing clinically relevant outcomes. Recent high-quality trials in high-risk patients do not show any benefit [26–28]. There are no high-quality trials that only address pancreatobiliary patients.

17.2 Obstructive Jaundice and Preoperative Drainage

Jaundice due to an obstructed extrahepatic bile duct will frequently need to be relieved by stenting when neoadjuvant chemotherapy is planned as several drugs need biliary clearance. The issue is somewhat different when the patient is scheduled for surgery first. The risk of complications following endoscopic retrograde (ERC) or percutaneous transhepatic (PTC) stenting is not negligible. While not very frequent, they are potentially devastating. Acute pancreatitis, duodenal or bile duct perforations or liver abscesses resulting from instrumentation may delay cancer surgery for months or even preclude surgery completely. This must be taken into consideration when viewing the very modest physiological impact of even severe jaundice. A major RCT showed that routine preoperative stenting increased the overall rate of complications of patients with bilirubin levels up to 250 μmol/L [29]. For those with higher levels of bilirubin, randomized data is not available, and the number of patients means we will probably not see such a trial. In the meantime it appears rational to extrapolate the conclusions from the Dutch RCT and avoid routine preoperative drainage [29, 30]. The exceptions will be patients with ascending cholangitis or intractable itching where surgery for some reason cannot be performed without delay.

17.3 Cessation of Smoking

Smoking reduces delivery of oxygen to peripheral tissues. A freshly fashioned pancreatic, biliary or gut anastomosis is indeed in the periphery, and rapid safe healing is dependent on oxygen supply. An increasing body of evidence shows that improvements in pulmonary function and oxygen delivery can be achieved by quitting smoking for just 3–4 weeks [31, 32]. It is probably prudent in high-risk surgery, even in patients with malignant tumours, to allow for 4 weeks of complete abstention from smoking. As a measure to prevent complications, smoking cessation is easy to grasp and comes with some financial benefit, and it places some of the responsibility for risk attenuation with the patients.

17.4 Prehabilitation

Reduced cardiopulmonary capacity is a significant risk factor for patients undergoing major surgery and frequently bars frail patients from undergoing any surgery at all [33]. As resections for malignant tumours are generally performed as soon as possible, only a few weeks are available to improve on the patients' cardiopulmonary capacity. To be worthwhile, an intervention would need to improve elderly patients to an extent that would reduce risk for major complications and to achieve this within a time frame of less than 4 weeks. A recent trial demonstrated that a hospital-based 4-week prehabilitation programme did increase cardiopulmonary capacity for high-risk patients [34]. Compliance was a problem in this trial (daily commuting to hospital), and it might be more feasible to investigate home-based exercise programmes supervised by local physiotherapists or collaborating with local fitness centres. Most available data are from patients with colorectal cancer [35, 36], but extrapolation appears reasonably rational for this kind of intervention. While waiting for dedicated trials in pancreatic surgery patients, it appears logical to instruct patients to perform physical exercises at home daily, e.g. by repeatedly climbing staircases or a graduated exercise programme.

17.5 Preoperative Carbohydrate Loading

This involves breaking the traditional preoperative fasting before major surgery by having the patient drink a carbohydrate-rich broth. The safety of this has been documented [37], and as a physiological concept, it is appealing in an attempt to avoid a glycogen-depleted state during surgery [38]. Insulin resistance after surgery is also attenuated, as is thirst and anxiety [37]. As the drinks are safe and reasonably cheap, they are frequently recommended. While there may be a reduction in hospital stay and recovery time, a reduction in the complication rate after surgery has yet to be demonstrated [39].

17.6 Postoperative Analgesia

Optimal pain relief is a universally agreed target to help prevent atelectasis and pneumonia from poor inspiration and to help achieve early mobilization and early oral intake of a normal diet. A patient who feels secure and cared for and aware of the steps of recovery will experience less anxiety and less pain.

17.6.1 Thoracic Epidural Analgesia (EDA) and Patient-Controlled Analgesia (PCA)

A thoracic epidural is a neuroaxial block that provides excellent analgesia and attenuates the stress response [40]. As such it has been widely used and adopted

in ERAS programmes [3, 8]. Positive effects on morbidity and mortality have been proposed [41], but this has been challenged by others because control groups were not ideal and because modern comprehensive care protocols were not adhered to [42, 43]. The fall-back option for the significant proportion of epidurals that do not function adequately has been opiate-based patient-controlled analgesia (PCA). Traditionally frowned upon in the opioid-sparing environment of early ERAS protocols, it now appears that opioids are better tolerated than previously assumed as long as other modern enhanced recovery principles are adhered to [42].

The role of epidural analgesia as the backbone of analgesia after pancreatoduodenectomy has also recently been questioned [43, 44]. Non-function rates are significant and failure may influence morbidity [45]. Epidural-induced hypotension has been a specific concern as it may lead to insufficient oxygen supply to the anastomoses [44, 46]. Because of this, thoracic epidurals were recommended by the latest ERAS consensus for PD patients [8], provided hypotension can be avoided. In a single-centre cohort from a dedicated HPB service, intrathecal morphine was associated with improved clinical recovery outcomes when compared to epidural analgesia [47]. A recent meta-analysis found that epidurals provided excellent analgesia but that recovery or morbidity was not favourably altered compared to alternative analgesic techniques when performed within an ERAS setting [48]. The concern for increased morbidity in PD patients having epidural analgesia has spurred the ongoing PAKMAN trial to compare this with PCA for their effect on postoperative complication rates [49].

Other modalities for pain control have emerged in the latest decade, but their impact has been moderate in major, open surgery compared with laparoscopic colorectal surgery. So while data for PD patients are lacking, interesting results have been presented for the use of wound catheters, transverse abdominal plane (TAP) blocks and intravenous lidocaine [8]. Especially the role of lidocaine as an adjunct to PCAs constitutes an interesting perspective as an alternative to EDA [50–52] but has yet to be evaluated in patients undergoing PD.

17.6.2 Per Oral, Non-opioid Analgesics

The cornerstone of oral analgesia is the use of multiple agents to reduce the risks for side effects while maintaining good-quality pain relief and at the same time avoiding excessive use of opioids. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol/acetaminophen have been useful per oral analgesic adjuncts and important components of ERAS recommendations [8]. There have been some series suggesting an association between NSAID use and increased risk of anastomotic failure, but the data are conflicting and not of high quality, and sufficiently powered RCTs are not available [53–56]. This has prompted some to avoid its use in patients with high-risk anastomoses, as in PD.

17.7 Intravenous Fluids

The principal aim for perioperative care is to optimize oxygen delivery to vital organs and critical tissues, especially tissues that constitute an anastomosis. Further, the avoidance of tissue oedema to facilitate tissue perfusion is important. Direct measurement of anastomotic tissue oxygenation is not readily available. Central venous pressure, systemic blood pressure, oxygen saturation in the capillaries of the fingers as well as urine output may all reflect perfusion of the anastomosed gut segments, but all have limitations.

Several options are available to ensure optimal intravenous fluid therapy during and after surgery. They are all variations of the same principle, which is to determine whether giving more intravenous fluids, often as a bolus, will increase stroke volume. While this will provide an indication of whether increased preload will improve cardiac output, it does not actually determine whether this intervention will be beneficial to the patient overall.

After surgery, intravenous fluids are generally used to correct hypotension and low urine output, and this often results in significant volumes being infused [57]. Bearing in mind that epidurals frequently cause hypotension, intravenous fluid boluses may not be appropriate in the postoperative setting with epidural analgesia and may increase splanchnic oedema.

There is a tendency to compare modern balanced fluid protocols to obsolete regimens and to include only the fittest patients [8, 18, 58, 59] or to focus on surrogate endpoints. This significantly reduces the value of these studies as low-risk patients would be assumed to have wider safety margins and most will probably do fine without fluid optimization at all [60]. There is a need for more data for the frailest patients and for trials performed in an enhanced recovery setting. In the ERAS consensus document, it is advocated that fluid optimization should be performed by an experienced anaesthetist in ASA III/IV patients [8, 18, 61]. Obvious hypotension will indicate inadequate tissue oxygenation and must be treated. Provided there is no hypovolaemia, fluid boluses exceeding maintenance are not called for and careful use of vasopressors is a more physiological intervention [46], although these can increase splanchnic vasoconstriction. Stopping epidural analgesia and switching to intravenous analgesia (PCA) should be considered in the presence of persistent hypotension and before excess intravenous fluids are given. It is easier to do this than reverse the effects of excess water, sodium and chloride.

The available data does not allow for easy conclusions regarding IV fluid administration in PD patients. One RCT measured gastric emptying in 48 PD patients randomized to 10 mg/kg/h of intravenous fluids or half this rate but could not demonstrate a 30-min reduction in gastric emptying at POD 7 [62].

Low urine output may be a normal physiological response to trauma, and treating it with IV fluid may induce unnecessary salt and water load and is probably misconceived [63, 64]. It is important to bear in mind that “normal saline” is indeed not physiological, containing about three times the daily sodium requirements per litre. Excreting excess sodium puts additional strain on kidney function.

17.8 Nasogastric Drainage

The delayed return of normal gastric emptying (DGE) is reasonably common after PD, and this has probably contributed to the preference for prophylactic NG decompression by many surgeons. This problem might be caused by loss of motility-enhancing factors released from the duodenum. It has also been shown that this occurs in association with a subjacent anastomotic leak. Other factors include hypoalbuminaemia and splanchnic oedema. The prevailing international classification denotes a grade A DGE to patients with indwelling NG tubes for more than 3 days in the absence of gastric retention [65]. Over the last decade, there has been an increasing recognition that a NG is not routinely required. While there is a lack of high-powered trials, modern meta-analyses and systematic reviews conclude that PD patients do not routinely require a postoperative NG tube and that a selective approach is safe [8, 66, 67].

17.9 Surgical Drains

The role of surgical drains after PD is a contentious issue, and three RCTs have yielded conflicting results. The single-centre trial by Conlon concluded that routine use of drains is not required [68]. A nine-centre US trial was prematurely halted due to an excess mortality in the no-drained group, and the authors advised against omitting drains routinely [69]. Recently, the two-centre German PANDRA trial showed no inferiority for omitting drains [70], which is in accordance with the Cochrane meta-analysis [71]. While the German trial, being the most recent and the largest, will probably exercise some sway in the years to come, it should be noted that it only recruited 13% of the eligible patients and hence will have reduced external validity [70]. There were also a worrisome number of crossovers due to surgeons violating the protocol. A very interesting recent trial compares two prospective and consecutive cohorts from high-volume centres, showing that a risk factor analysis can predict which patients will need no drain and hence avoiding this in a quarter of the patients [7]. The factors associated with increased risk for clinically relevant postoperative pancreatic fistula (CR-POPF, equalling POPF grades B and C) are soft gland texture, small duct diameter, pathology other than ductal carcinoma or pancreatitis and intraoperative blood loss [7]. Patients at low risk could safely be treated without routine use of drains. In situations where a drain is used, the amylase content in drain effluent on postoperative day 1 is closely associated with risk of CR-POPF [72]. A large Italian trial has shown that prolonged use in low-risk cases is again associated with inferior outcomes when compared to early removal [73], and this was again evaluated in the recent trial by McMillan and co-workers using 5000 U/L on POD1 as a cut-off for POD3 removal [7]. Extrapolating these findings to other centres relies on a similar pretest probability for a fistula. The shift away from routine drainage in recent decades is aided by the increasing expertise and availability of interventional radiologists and interventional endoscopists to provide drainage of confirmed collections.

17.10 Stimulation of Bowel Movement

All abdominal operations will cause some degree of gut paralysis, due to drugs and handling amongst other factors. One of the aims of ERAS programmes is to reduce the duration of gut paralysis and restore motility. While difficult to measure (as it is both an intervention and an outcome), the resumption of a normal diet stimulates gut motility. A multimodal approach includes the avoidance of excessive opiates, early mobilization, oral intake and avoiding excessive IV fluids and consequent intestinal oedema [8]. Chewing gum has been proposed as a way to trigger the vagal reflexes and enhance gut motility. Mostly investigated for colonic surgery (where the data are conflicting), a small, underpowered trial in PD patients has been undertaken without showing any benefit [74]. Chewing gum remains, however, cheap and safe, and a benefit cannot be excluded without larger trials. The wider use of minimally invasive surgery, which reduces intestinal handling, may also have a positive impact on the return of bowel activity.

17.11 Postoperative Nutrition

Traditionally, and in some areas even today, PD patients were to exercise nil-by-mouth for days and even weeks postoperatively [75]. One must exercise a clear distinction between terms that have been somewhat blurred in earlier trials [76]: Enteral nutrition is an artificial feeding modality through tube or catheter placed in the stomach or further distal in the GI tract. It bypasses some physiological reflexes, as is also the case with parenteral nutrition. Both have their roles in complicated cases but are not needed as routine treatment in modern protocols. The alternative is to eat and drink, a volitional and physiological process integrating all the physiological reflexes that enhances digestion and well-being. The abolishment of routine use of the NG tube (see above) opened the stage for allowing patients to drink and eat a normal diet from the first postoperative day. This is now supported by meta-analysed data and cohort series [66, 67] and reflected in modern recommendations [8]. Importantly, one must keep in mind that gut function is somewhat impaired in the first days following a PD. We should offer our PD patients normal food at will from POD1 while informing them to begin carefully and to increase according to tolerance. The calorie count may appear dismal during the first 3–4 days, but this must be weighed against the known risks of tube feeding. The addition of oral nutritional supplements will increase energy and protein intake in the postoperative period, but the benefit on outcome is not documented. Postoperative, artificial nutrition by enteral or parenteral tube feeding should be reserved for the few patients who suffer major complications and are unable to eat and the (even fewer) patients who have long-standing gastric retention in spite of repeated attempts at oral intake and temporary drainage. Whenever possible, the enteral route is preferable to parenteral nutrition in these situations.

Conclusion

Enhanced recovery depends on a modern multimodal approach based on best available evidence. For several treatment items, high-quality evidence is still lacking. Multicentre collaboration will frequently be needed to evaluate single items. Importantly, several issues are not well suited for randomized design [14], among them laparoscopic approach and complex treatment protocols. Well-conducted prospective cohort studies are easier to conduct and will, for many issues, yield high-quality evidence. There is still a great need for good trials to elucidate the optimal way to treat our pancreatobiliary surgery patients before, during and after surgery.

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