15.26.3 Tumours of the pancreas 3227

15.26.3 Tumours of the pancreas 3227

15.26.3 Tumours of the pancreas 3227 plastic stents. Several studies have shown higher efficiency, prob- ably due to the larger diameter (equivalent to seven 10 Fr plastic stents). They are also associated with a reduced number of endo- scopic procedures and a lower incidence of stent obstructions, but large comparative prospective studies are needed to prove their safety, removability, and efficacy before they can be recommended as a first-line treatment. Pseudocysts Indications for pseudocyst drainage are persistent symptoms and cyst-related complications, including gastrointestinal or biliary obstruction, infection, rupturing, or bleeding from a pseudoaneurysm. The risk of developing these complications is low (<10%), but so is the chance of spontaneous cyst resolution. Available data suggest that for cysts smaller than 6 cm, a wait-and-see policy is defendable. Rapid growth is still considered an indi- cation for drainage. Endoscopic drainage by placement of multiple side-by-side pig- tail stents, either transpapillary or transmurally, under EUS guid- ance is highly effective (>90–95%), and should be the treatment of first choice (Fig. 15.26.2.5). In the case of a concurrent pancre- atic duct disruption or obstruction, treatment not only entails cyst drainage, but also addressing pancreatic ductal abnormalities to prevent recurrence once the cystogastrostomy stents are removed, 6 to 8 weeks after cyst resolution. Percutaneous drainage or surgery should be reserved for patients in whom endoscopic drainage is not possible or has failed. Future developments Many patients with chronic pancreatitis suffer from refractory pain and have a reduced quality of life. Physicians struggle to effectively manage this disease and patients with chronic pan- creatitis consume a disproportionate volume of healthcare re- sources. Evidence-based treatment algorithms are urgently needed. Early interventions, endoscopic or surgical, may improve quality of life, preserve pancreatic function, and reduce associated healthcare costs. FURTHER READING Cahen DL, et al. (2007). Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med, 356, 676–84. Conwell D, et al. (2014). American Pancreatic Association practice guidelines in chronic pancreatitis. Evidence-based report on diag- nostic guidelines. Pancreas, 43, 1143–62. Dite P, et al. (2003). A prospective, randomized trial comparing endo- scopic and surgical therapy for chronic pancreatitis. Endoscopy, 35, 553–8. Dumonceau JM, et al. (2012). ESGE guideline for endoscopic treat- ment of chronic pancreatitis. Endoscopy, 44, 784–96. Etemad B, Whitcomb DC (2001). Chronic pancreatitis:

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section 15 Gastroenterological disorders 3228 for the diagnosis and staging of pancreatic cancer are contrast- phased CT scan and occasionally MRI. The only curative treatment for pancreatic cancer is surgical exci- sion. This is technically feasible in up to 20% patients at presentation, but even after careful selection almost 40% of these will have positive microscopic resection margins, and overall postoperative survival is only around 10% at 5 years, the remainder experiencing metastatic disease in the peritoneum, liver, or lungs. Adjuvant chemotherapy with gemcitabine can double the 5-year survival rate. Palliative management may require biliary stenting for jaundice, duodenal stenting (or surgical bypass) for gastric outlet obstruction, pain control, and palliative chemotherapy. Introduction A plethora of tumours can develop within the pancreas, but pan- creatic ductal adenocarcinoma is by far the commonest, comprising 85 to 90% of pancreatic tumours. Other pancreatic tumours can be solid or cystic and are usually derived from the

endocrine or exo- crine pancreas itself, although metastatic tumours derived from other primary sources can rarely be diagnosed. This chapter will focus principally on pancreatic ductal adenocarcinoma, although there is some discussion of other tumour types. Pancreatic ductal adenocarcinoma is the 10th most common cancer in the United Kingdom but the fourth commonest cause of cancer death, predominantly because over 80% of patients have lo- cally advanced or metastatic disease at presentation and are there- fore not able to undergo surgical resection, the only potentially curative treatment modality. Overall survival following a diagnosis of pancreatic ductal adenocarcinoma therefore remains extremely poor, with most patients able to be offered palliative management strategies only. Aetiology The underlying cause of pancreatic ductal adenocarcinoma re- mains largely unknown, with the vast majority of cases occurring sporadically, although certain risk factors have been identified (Table 15.26.3.1). Those with chronic pancreatitis from any aeti- ology have a 15 times increased risk of developing pancreatic ductal adenocarcinoma, and those with PRSS1 (cationic tryp- sinogen) gene mutations leading to hereditary pancreatitis carry a lifetime risk of up to 55%. However, overall, less than 10% of pancreatic ductal adenocarcinoma diagnoses have been shown to have a hereditary or genetic element, and although a specific gene defect cannot usually be identified, those with two or more first-degree relatives carry an elevated risk, and in some families there may be an autosomal dominant transmission with impaired penetrance. There is also an elevated risk in certain specific fa- milial cancer syndromes, such as Li–Fraumeni syndrome (TP53 mutation), Lynch syndrome (microsatellite instability), Peutz– Jeghers syndrome (microsatellite instability), familial atypical multiple mole melanoma, hereditary nonpolyposis colorectal car- cinoma, familial breast–ovarian cancer (associated with BRCA1/ BRCA2 mutations), and familial adenomatous polyposis (APC gene mutation). All such individuals are eligible for screen ing as part of the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer study (EUROPAC; http//:www. europac-org.eu). Other known risk factors for sporadic pancreatic ductal adeno- carcinoma include smoking, obesity, and a new diagnosis (within the last 2 years) of diabetes mellitus in those over the age of 50 years. Meta-analyses demonstrate that type 2 diabetes increases an individual’s risk of pancreatic cancer by at least 40%, but it remains unclear whether diabetes is related to the cause of pancreatic ductal adenocarcinoma, or simply an early sign of its presence. Obesity has been linked to the development of many cancers and meta-analyses demonstrate that as body mass index, waist circum- ference, or waist-to-hip ratio increases, the risk of pancreatic cancer increases. Tobacco smoking potentially accounts for 29% of pancreatic cancer diagnoses in the United Kingdom and the risk increases with the number of pack-years smoked and the number of cigar- ettes smoked per day, with an associated odds ratio of 3.4 in those who smoke over 35 cigarettes per day and an odds ratio of 2.4 in those with 40 pack-years. This risk decreases following smoking ces- sation, becoming equivalent to the rest of the population at approxi- mately 20 years after stopping. Similarly, the risk of pancreatic ductal adenocarcinoma increases with the number of alcoholic drinks con- sumed per day, being 60% higher in those consuming five or more alcoholic drinks per day. There are no confirmed protective factors against the devel- opment of pancreatic ductal adenocarcinoma, but both physical Table 15.26.3.1 Risk factors for pancreatic ductal adenocarcinoma Increased risk Possible increased risk Possible decreased risk Familial/genetic Alcohol consumption Folate Chronic pancreatitis Occupational exposure to chemicals, e.g.: • Thorium-232 and its decay products (contrast medium in early X-ray diagnostics) • Benzidine • β-Naphthylamine Fruit Smoking X-rays Physical activity Obesity Gamma radiation Aspirin Diabetes mellitus type 2 Red meat

15.26.3 Tumours of the pancreas 3229 activity and aspirin have been shown to reduce the risk of many cancers, probably including pancreatic ductal adenocarcinoma. Due to the overall low incidence of pancreatic ductal adenocar- cinoma and a lack of specific associated risk factors, development of an accurate screening tool has proved problematic and, at pre- sent, there are no general population screening programmes for pancreatic ductal adenocarcinoma. There may be some benefit in screening selected, high-risk individuals (e.g. family history of pan- creatic ductal adenocarcinoma (two first-degree relatives or three diagnoses within the immediate family), and hereditary pancreatitis predisposing genetic syndromes), but the most suitable screening modality remains unclear. Epidemiology The incidence of pancreatic ductal adenocarcinoma is higher in Western and industrialized nations, with rates in Europe and North America remaining among the highest in the world, possibly due to the prevalence of smoking, obesity, and diabetes. In the United Kingdom, approximately 8800 people were diagnosed with pancre- atic cancer in 2014, while approximately 8300 people died from the disease (Cancer Research UK figures). Pancreatic ductal adenocar- cinoma is slightly more common in men, and in North America the incidence is 1.5 times higher in African Americans than Caucasians, although the overall incidence in African nations remains low. In the United Kingdom, the number of diagnoses of pancreatic cancer has continued to rise over the last 30 to 40 years, although the age-standardized mortality rates remain stable, potentially due to the increasing overall age of the population in Western coun- tries. The incidence of pancreatic ductal adenocarcinoma in the United Kingdom is approximately 12 per 100 000 and increases with age: only 25% of diagnoses are made in patients under 65 years (and it is extremely uncommon in those under 40 years), and ap- proximately 80% of all cases are diagnosed in those between 60 and 80 years of age (Cancer Research UK). Approximately half of all pa- tients present as medical/surgical emergencies, usually with abdom- inal pain or obstructive jaundice, whereas those presenting from the community have seen their general practitioner an average of three times before a diagnosis is made. Pathogenesis/pathology The pathogenesis of pancreatic ductal adenocarcinoma remains poorly understood despite major advances in molecular biology. Three histological precursors have now been identified: pancreatic intraepithelial neoplasia, mucinous cystic neoplasm, and intraductal papillary neoplasm (see ‘Other pancreatic tumours’), and each are associated with specific molecular and genetic abnormalities. There are multiple combinations of both inherited and acquired al- terations in specific core-signalling pathways and cancer-associated genes leading to activation of oncogenes (e.g. KRAS), inactivation of tumour suppressor genes (e.g. TP53 and SMAD4), and inactiva- tion of genome maintenance and DNA repair genes (e.g. MSH2 and hMLH1). Recent comprehensive genome-wide analysis has served to emphasize the high degree of complexity and heterogeneity in the genomics of pancreatic ductal adenocarcinoma. Such genetic and molecular complexity is rendered more difficult by an intrinsic chemotherapeutic resistance attributable to the presence of a dense stromal reaction that appears to significantly impair the local pan- creatic delivery of chemotherapy and other drugs. There are multiple pancreatic ductal adenocarcinoma mouse models, but—although progress continues to be made—findings from these models have thus far proved poorly applicable to clinical practice for either diag- nosis or risk stratification. Clinical features Patients with pancreatic ductal adenocarcinoma can present with a multitude of symptoms (Table 15.26.3.2), largely dependent upon the specific intrapancreatic location of the lesion and whether the tumour remains localized or has metastasized. The early diagnosis of pancreatic ductal adenocarcinoma is therefore reliant upon an understanding of such anatomically dependant symptoms. Approximately 50% of patients will develop a tumour in the head of the pancreas, most of whom will present with painless jaun- dice (classical presenting symptom of pancreatic ductal adenocar- cinoma)

secondary to obstruction of the intrapancreatic common bile duct (although occasionally this can be due to the presence of liver metastases or nodal infiltration at the liver hilum), whereas others will present with, or go on to develop, pain in the epigastrium or back. Those with masses in the pancreatic body or tail away from the common bile duct will generally present with pain or pancrea- titis without jaundice, and because of this will often present with more advanced disease. Nonspecific early symptoms are common and include abdom- inal or back discomfort, and dyspepsia and reflux symptoms re- sistant to simple therapies (both often postprandial due to common bile duct obstruction), both of which may be misinterpreted by patients and general practitioners leading to diagnostic delay; and swift or unintentional weight loss, which is an independent pre- dictor of poor outcome. Further early symptoms include nausea and vomiting, change in bowel habit (often due to pancreatic hor- monal imbalance but can be due to extensive obstruction leading to exocrine dysfunction and malabsorption), weight loss and loss of appetite, and new-onset diabetes not associated with the meta- bolic syndrome. Later symptoms include rapid and unintentional weight loss, and ascites. Table 15.26.3.2 Important clinical features of pancreatic cancer Early Late Nonspecific epigastric or back discomfort (70%) Obstructive jaundice (50%) Dyspepsia/reflux resistant to simple therapies Epigastric or back pain Nausea and vomiting Unintentional, rapid weight loss Loss of appetite/anorexia Change in bowel habit New diabetes without risk factors for metabolic condition

section 15 Gastroenterological disorders 3230 Clinical evaluation includes a full history, including the patient’s current performance status, nutritional status and significant comorbidities, and a thorough clinical examination assessing for the presence of jaundice, lymphadenopathy, and anaemia, as well as abdominal tenderness or masses. This then leads on to investiga- tion and tissue diagnosis (Fig. 15.26.3.1). Differential diagnosis The differential diagnosis of pancreatic ductal adenocarcinoma depends largely upon the mode of presentation but remains wide (Table 15.26.3.3). Diagnosis is usually reached following radio- logical assessment and confirmed with tissue biopsy. Following radiological confirmation of a pancreatic mass, usually with CT, the differential diagnoses are much narrower and include other pancreatic tumours or inflammatory masses/pseudocysts associated with chronic pancreatitis or autoimmune (IgG4- related) pancreatitis. Investigation Blood tests Blood analysis is a routine part of assessment and should include the following: Full blood count: to assess for the presence of chol- angitis in those with biliary obstruction or anaemia as a result of chronic disease or gastrointestinal bleeding. Renal function: to as- sess for the presence of electrolyte imbalance and as a baseline as- sessment prior to treatment. Liver function: the presence of raised bilirubin, alkaline phosphatase and γ-glutamyl transferase with normal or only slightly elevated transaminases may indicate bil- iary obstruction, but cannot distinguish between benign or malig- nant causes, or the site of obstruction (e.g. pancreas, liver hilum, Fig. 15.26.3.1 Investigation and tissue diagnosis for pancreatic ductal adenocarcinoma. Table 15.26.3.3 Differential diagnoses of pancreatic ductal adenocarcinoma Presenting complaint Differential diagnosis Obstructive jaundice Other pancreatic tumours; gallstone or gallbladder disease; periampullary tumours, e.g. ampullary cancer, cholangiocarcinoma, duodenal cancer; benign biliary strictures; acute, chronic or autoimmune pancreatitis with or without mass or pseudocyst; primary sclerosing cholangitis Epigastric or back discomfort, dyspepsia Other pancreatic tumours; acute, chronic, or autoimmune pancreatitis with or without mass or pseudocyst; gallstone or gallbladder disease; gastro-oesophageal reflux disease; aortic aneurysm; mesenteric ischaemia; small-bowel obstruction Change in bowel habit Colorectal carcinoma; inflammatory bowel disease; irritable bowel disease; gastroenteritis

15.26.3 Tumours of the pancreas 3231 or intrahepatic). Clotting studies: patients with jaundice and hep- atic impairment may have impaired coagulation. Further, most patients will require intervention in the form of endoscopy, per- cutaneous drainage, or surgery and a baseline assessment of co- agulation function is therefore required. A raised serum amylase suggests pancreatic inflammation: this may occur in the presence of a tumour but is more common in acute pancreatitis and less so in chronic pancreatitis. Carbohydrate antigen (CA)-19-9 may be elevated in pancreatic cancer but also in biliary tract cancers, such as cholangiocarcinoma, and is often raised in the presence of jaundice of any cause, both benign and malignant, and in some in- stances of pancreatitis or cirrhosis. However, it can also be normal in the presence of pancreatic cancer and has a sensitivity and speci- ficity of approximately 80%. Testing of hepatitis serology is appro- priate as part of the assessment of jaundice. Radiological assessment Radiological imaging remains the diagnostic method of choice for the diagnosis of pancreatic adenocarcinoma. Potential modalities include the following: Ultrasonography This can demonstrate the presence of dilated intra- and extrahepatic biliary ducts but is often unable to further delineate the cause (e.g. bile duct stones or a mass in the head of the pancreas). Its use can lead to delays in diagnosis if employed inappropriately in pa- tients where there is a high suspicion of malignancy. CT Multislice, high-resolution, contrast-enhanced CT of the chest, ab- domen, and pelvis provides detailed information on the presence and exact location of the primary tumour, as well as the presence of any locally advanced or distant disease. In particular, the precise relationship of the tumour with local vascular structures such as the superior mesenteric vein and artery, and portal vein is crucial in the assessment of resectability. Current CT scanners are capable of ac- curately predicting resectability in up to 90% of patients. MRI The superior soft tissue delineation of MRI can be helpful in the characterization of noncontour-deforming pancreatic masses, as well as the presence of hepatic and peritoneal involvement, but CT remains the radiological modality of choice. Tissue diagnosis Prior to consideration of surgery or chemoradiotherapy, a tissue diagnosis is usually required, although this should not delay po- tentially curative resection. This can, on occasion, be crucial as a diagnosis of neuroendocrine tumour or lymphoma (for example) may radically alter treatment strategies. Inflammatory lesions due to acute or chronic pancreatitis can also mimic malignant lesions. Methods of achieving a tissue diagnosis include the following: Endoscopic ultrasonography-guided fine needle aspiration Cytology from a pancreatic mass or aspiration of cyst material at the time of endoscopic ultrasonography (EUS) can help in the confirm- ation of diagnosis. Endoscopic retrograde cholangiopancreatography Biliary brushings at the time of stenting in those with obstruc tive jaundice can confirm the diagnosis of pancreatic ductal adenocarcinoma. Percutaneous biopsy This can be used if the other methods are inconclusive or par- ticularly if there is locally advanced or metastatic disease which is amenable to radiologically guided biopsy. Preoperative assessment Prior to surgery, further potential investigation modalities may include positron emission tomography (PET)-CT. The United Kingdom PET PANC study, a multicentre, prospective diagnostic accuracy and clinical value study of PET-CT in suspected pancre- atic malignancy, showed that PET-CT improved diagnostic ac- curacy and reduced the rate of unnecessary resections. EUS can be used to assess for the presence of locally advanced disease and for tissue diagnosis. Staging laparoscopy is used to assess for the presence of hepatic, peritoneal, or distant disease and can be per- formed immediately before planned resection to avoid the neces- sity for two general anaesthetics. Staging Pancreatic ductal adenocarcinoma typically metastasizes to re- gional lymph nodes and then to hepatic, pulmonary, and peri- toneal sites. Bone metastases are less common but can also occur. Tumours may also extend locally to surrounding struc- tures such as the duodenum, stomach, and colon. The standard staging system

for pancreatic ductal adenocarcinoma is via the American Joint Committee on Cancer TNM classification (Table 15.26.3.4). Table 15.26.3.4 American Joint Committee on Cancer TNM classification of pancreatic ductal adenocarcinoma Primary tumour (T) TX: primary tumour cannot be assessed T0: no evidence of primary tumour Tis: carcinoma in situ T1: tumour limited to the pancreas, <2 cm in greatest dimension T2: tumour limited to the pancreas, >2 cm in greatest dimension T3: tumour extends beyond the pancreas, but without involvement of the coeliac axis or superior mesenteric artery T4: tumour involves the coeliac axis or the superior mesenteric artery (unresectable primary tumour) Regional lymph nodes (N) NX: regional lymph nodes cannot be assessed N0: no regional lymph node metastasis N1: regional lymph node metastasis Distant metastases (M) M0: no distant metastases M1: distant metastases

section 15 Gastroenterological disorders 3232 Management General principles All patients should be managed at a regional tertiary centre and in a multidisciplinary setting, with input from surgeons, gastro- enterologists, radiologists, palliative care physicians, and allied health professionals (e.g. dieticians/nutritionists and physiother- apists) and with close collaboration between hospital and primary care practitioners. Treatment strategies should be discussed in a multidisciplinary meeting and conclusions finalized regarding disease suitability for resection (curative intent, with or without neoadjuvant or adjuvant treatment), downstaging, or palliation (see Fig. 15.26.3.2). The general principles of management include optimization of pancreatic endocrine (management of diabetes or impaired glu- cose tolerance) and exocrine function (with pancreatic replacement therapy as necessary), together with enhancement of nutrition and caloric intake to counteract the effects of cachexia and optimize pa- tients for further treatment (surgery or chemoradiotherapy), and control of pain, nausea, or other symptoms. Healthy patients should be optimized for surgery as soon as possible, but those with lesions in the head of the pancreas will often require relief of malignant biliary obstruction via endoscopic stenting or external biliary drainage, as well as management of sepsis/chol- angitis where appropriate. Severe, intractable epigastric or back pain requires progression along the World Health Organization analgesic ladder, with long-acting opiates often necessary, assessment by pain and palliative care teams, and occasional input from radiological and endoscopic specialists for administration of percutaneous, CT-guided or EUS-guided coeliac plexus blocks for those with advanced disease. Depression is common and both patients and their families may re- quire psychological, psychiatric, or bereavement support services. Biliary drainage Wherever possible, patients should proceed directly to exped- ited surgery without biliary drainage, as several studies have dem- onstrated a significantly lower number of complications with this strategy (39% early surgery vs 74% biliary drainage followed by sur- gery in a Dutch study of 196 patients). Biliary drainage is therefore usually required only if the serum bilirubin is extremely high (>200 µmol/litre), the patient has biliary sepsis, there is diagnostic uncer- tainty, or there is likely to be a delay until surgery. In patients with locally advanced or metastatic disease, endo- scopic biliary stenting may be required to relieve jaundice and pre- vent sepsis, and is associated with lower complication rates than percutaneous biliary drainage or surgical biliary bypass. Endoscopic stent insertion can be performed as soon as a treat- ment strategy is decided. Preoperatively (depending upon local availability and expertise), fully covered self-expanding metal stents, rather than plastic stents, are preferred in patients who are deeply jaundiced or cholangitic, or in whom there is another reason for delaying surgery more than 1 to 2 weeks. Uncovered self-expanding metal stents are generally reserved for patients with cytologically/ histologically confirmed unresectable disease. Endoscopic stents carry a risk of endoscopic retrograde cholangiopancreatography- induced acute pancreatitis,

stent migration, or later stent occlusion, but overall are associated with a low complication profile. If patients are found to have unresectable disease at operation, a surgical biliary bypass is often the management method of choice and can be combined with gastrojejunostomy for those patients in whom gastric outlet obstruction is suspected or imminent. Gastric outlet ob- struction occurs in 10 to 20% of patients with locally advanced disease and those with successful endoscopic or percutaneous biliary drainage can be managed either by surgical bypass (open or laparoscopic) in pa- tients with good performance status or via endoscopic stent insertion. Fig. 15.26.3.2 Treatment algorithm for patients with pancreatic ductal adenocarcinoma.

15.26.3 Tumours of the pancreas 3233 Surgical resection Most patients with pancreatic ductal adenocarcinoma present with distant metastases or locally advanced disease (involvement of nearby structures that would prevent a clear resection margin), hence only 10–15% of patients are able to undergo surgical resection. Specific operative strategies depend upon the site and extent of disease: tu- mours in the head of the pancreas require pancreaticoduodenectomy, either via a classical Whipple's procedure or via pylorus-preserving pancreaticoduodenectomy (usually open but occasionally laparo- scopic), whereas tumours in the body or tail can be resected via distal pancreatectomy with or without concurrent splenectomy (laparo- scopic where possible; involvement of the spleen or splenic vessels is not a contraindication to surgery). All pancreatic surgery carries a potential risk of significant com- plications and patient selection is therefore crucial. Since the intro- duction of the National Cancer Plan in 2001 in the United Kingdom, all such resectional pancreatic surgery is now undertaken in re- gional specialized centres as there is good evidence that central- ization of such services results in improved rates of morbidity and mortality (now 1–2% in high-volume centres), as well as oncological outcomes. There has been much recent discussion regarding the defin- itions of operable and locally advanced disease (inoperable but no progression to distant metastases), and the concept of borderline operable disease has recently been introduced (Table 15.26.3.5). The ESPAC-5 trial (European Study group for Pancreatic Cancer— Trial 5F), a multicentre, prospective, randomized, feasibility phase II trial comparing neoadjuvant therapy to immediate surgical ex- ploration in patients with borderline resectable pancreatic cancer, is currently recruiting. Chemotherapy Advanced disease In patients with advanced disease, chemotherapy improves both survival and quality of life as compared to best supportive care alone. Overall, gemcitabine (a nucleoside analogue) is the most commonly used chemotherapeutic agent. The phase III, multicentre GemCap study randomized patients to receive gemcitabine alone or in com- bination with capecitabine (an oral prodrug enzymatically degraded to 5-fluorouracil, a pyrimidine analogue) in 533 patients with ad- vanced pancreatic ductal adenocarcinoma to demonstrate a trend to- wards improved survival in patients receiving combination therapy (7.1 vs 6.2 months overall survival; 1-year survival 24.3% vs 22%; $p = 0.077$). The phase III randomized MPACT study demonstrated a significantly improved overall survival in patients administered weekly nab-paclitaxel (a mitotic inhibitor) with gemcitabine, as compared to gemcitabine alone (8.5 vs 6.7 months; $p = 0.0001$). Gemcitabine-based therapy is therefore a common combination regimen and has been shown to significantly improve progression- free and overall survival, as well as overall objective response rates, although this can be offset by the greater toxicity profile associated with combination therapy. Trials of biological agents have largely yielded disappointing re- sults, although a Canadian phase III trial did demonstrate a small improvement in overall survival with the addition of erlotinib (an epidermal growth factor receptor inhibitor) to gemcitabine, as com- pared to gemcitabine alone (6.2 vs 5.9 months; $p = 0.038$). Other agents are under investigation. In a French multicentre study of FOLFIRINOX (oxaliplatin

(platinum-based chemotherapeutic agent), irinotecan (topoisomerase I inhibitor), fluorouracil, and leucovorin (folic acid derivative)) or gemcitabine, there was im- proved survival in the FOLFIRINOX group (11.1 vs 6.8 months; p <0.001). Similarly, a recent meta-analysis demonstrated that cetuximab-based therapy (monoclonal antibody) led to improve- ments in progression-free survival, overall survival, and overall re- sponse rate as compared to noncetuximab therapy. Neoadjuvant therapy Neoadjuvant therapy can be utilized in attempts to downstage the primary pancreatic tumour and enhance the probability of a disease- free margin at subsequent surgical resection (e.g. ESPAC-5 trial), or in efforts to select patients with stable or treatment-responsive disease prior to surgery. A meta-analysis of 38 studies incorporating 3484 pa- tients, 49.9% of which underwent neoadjuvant treatment, suggests a significant increase in overall survival with the use of neoadjuvant treatment on an intention to treat basis alone, but particularly in those patients that actually underwent resection (26.1 months neoadjuvant and surgery vs. 15.0 months surgery alone). More recent data suggest even more promising results with the use of FOLFIRINOX rather than standard gemcitabine-based regimens. However, the efficacy of neoadjuvant treatment remains uncertain and further trial data are required. All patients require restaging following neoadjuvant treat- ment and before ultimate decisions regarding surgery. Adjuvant therapy The use of adjuvant chemotherapy improves survival in patients with resectable pancreatic cancer that have adequately recovered from surgery. Younger patients with good life expectancy and per- formance status should be considered for adjuvant therapies (4–8 weeks following resection) such as systemic gemcitabine regimens Table 15.26.3.5 Definitions of operable, borderline operable, and locally advanced disease in the presence of no distant metastases Operable Borderline operable Locally advanced

1. Tumour confined to pancreas with no evidence of involvement of venous or arterial structures, or other organs, e.g. abutment, distortion, encasement, or tumour thrombus
   On radiological assessment, clear fat planes should be visible between the tumour and all nearby structures,
   e.g. superior mesenteric vein (SMV), portal vein (PV), inferior vena cava (IVC), superior mesenteric artery (SMA), common hepatic artery (CHA), coeliac axis, aorta
2. Involvement of loco-regional venous structures (SMV or PV),
   e.g. abutment, impingement, or distortion
3. Short segment (<2 cm) encasement of, or tumour thrombus within, SMV or PV but with suitable vessel proximally and distally to allow resection and reconstruction
4. Gastroduodenal artery (GDA) involvement (e.g. abutment, impingement, or encasement) up to the level of the common hepatic artery
5. Abutment of SMA or CHA of <180° of the circumference of the vessel wall
6. Long segment (>2 cm) venous encasement of SMV or PV
7.

> “180° abutment of SMA or CHA National Comprehensive Cancer Network. NCCN Guidelines Version 2.2015. Pancreatic Adenocarcinoma. (http://www.nccn.org).

section 15 Gastroenterological disorders 3234 in combination with capecitabine or oxaliplatin, which have been associated with improved overall survival and response rates, as compared to

gemcitabine monotherapy. Chemoradiotherapy regi- mens may also benefit those patients with positive resection margins (R1 or R2), but further clinical trial data are needed. Ablative therapies Relatively few patients present at a stage suitable for surgical resec- tion and most have only a limited response to surgery, hence the development of novel therapeutic strategies are necessary for both those with inoperable disease and those with resectable disease that are unfit to proceed with surgery. Recent technological improve- ments in the delivery of ablative therapies, which have become standard in other solid tumour types, have reduced complications and renewed interest in their potential applications. Radiofrequency ablation Radiofrequency ablation can be applied endoscopically and some trials have demonstrated an improvement in tumour-related symp- toms, particularly reductions in back pain and analgesic require- ments, as well as reductions in CA19-9 levels following ablation, with one single-centre study of 25 patients reporting increased survival as compared to those receiving standard therapy (33 vs 13 months; $p = 0.0048$). However, studies have generally involved small cohorts with limited follow-up. Current guidance from the National Institute for Health and Care Excellence recommends that radiofrequency ablation should only be utilized in the context of clinical trials. Experience with microwave ablation, which can be applied per- cutaneously or intraoperatively, is even more limited. Cryoablation can be used to freeze pancreatic lesions either percutaneously or at the same time as palliative bypass surgery or endoscopic biliary/ duodenal stenting, and can be used in association with other mo- dality therapies. The largest experience of cryoablation derives from centres in Asia, which have reported improvements in pain control, CA19-9 levels, performance status, and survival after treatment. Photodynamic therapy Photodynamic therapy can be delivered under endoscopic guidance and has been used in small numbers of patients, and preliminary experience of high-intensity focused ultrasonography has also been reported. NanoKnife or irreversible electroporation is a nonthermal ablative therapy that involves the use of electrodes placed within the tumour to deliver currents of up to 3 kV, thus irreversibly damaging the cell membrane and resulting in apoptosis. Unlike thermal tech- niques, it can be utilized in tumours close to important vessels and structures without significant risk of damage. Studies remain limited, but its performance under general anaesthetic has thus far been promising in a few patients. Other applications and considerations Ablative techniques can also be utilized to treat malignant biliary strictures including tumour ingrowth into uncovered self-expanding metal stents, although studies again remain limited. Further poten- tial applications include use in patients with premalignant condi- tions such as mucinous cystic neoplasms of the pancreas, but further evidence is required. Overall, long-term data remains lacking and large, prospective randomized studies will be required before con- sidering their use as part of standard care algorithms. Prognosis Overall, the prognosis following a diagnosis of pancreatic ductal adenocarcinoma remains poor and has not improved significantly over the last 20 years despite improvements in imaging techniques, operative strategies, and chemotherapy. The annual mortality rate from pancreatic cancer is approximately 11 per 100 000 popula- tion, and currently both 1- and 5-year survival rates for pancreatic cancer are lower in the United Kingdom than most other parts of Europe. The 1-year survival rates remain at 10 to 20% and patients presenting with locally advanced or metastatic disease have a me- dian survival of only 6 to 10 months or 3 to 6 months, respectively. The few patients suitable for surgical resection have an improved median survival of 10 to 20 months, yet only 5 to 20% survive 5 years. Other pancreatic tumours Ductal adenocarcinomas comprise 95% of pancreatic cancers but a number of benign and malignant, solid and cystic tumours can be diagnosed within the pancreas, most of which are managed by sur- gical resection with overall good outcomes. All patients with pan- creatic tumours should be assessed in the aforementioned way and managed in a tertiary,

multidisciplinary setting. Neoplasms of the exocrine pancreas Acinar cell carcinomas The second commonest type of pancreatic malignancy, comprising approximately 5% of all exocrine pancreatic tumours. It generally has a similar presentation and demographic profile to pancreatic ductal adenocarcinoma, but up to 20% can produce functional di- gestive enzymes, resulting in classical symptoms of subcutaneous fat necrosis (presenting as skin rashes and nodules), polyarthritis, and eosinophilia (Schmid's triad). They are often associated with a raised serum lipase and can grow to a considerable size. Histologically, tu- mour cells resemble pancreatic acinar cells but have a characteristic cytoplasmic appearance, which contains granules enclosing enzyme precursors. When localized, acinar cell carcinomas should be surgi- cally excised. Adenosquamous carcinoma There is limited information on the rare adenosquamous carcinoma, which is also known as adenoacanthoma, mixed carcinoma, and mucoepidermoid carcinoma. Histologically, it contains at least 30% malignant squamous cell carcinoma, although both glandular and squamous differentiation must be present. Presentation, assessment, and treatment are similar to pancreatic ductal adenocarcinoma, al- though tumours are more likely to be large and located within the tail of the pancreas. Following resection, which is a positive pre- dictor of survival, histology often demonstrates poor differenti- ation with lymph node and vascular invasion. Overall prognosis is particularly poor.

15.26.3 Tumours of the pancreas 3235 Colloid (mucinous, noncystic) carcinomas These are rare and often mistakenly categorized as pancreatic ductal adenocarcinoma or mucinous cystadenocarcinoma. Histologically, nodular extracellular mucin lakes can be found with scanty ma- lignant epithelial cells floating within them in various patterns of distribution, which often represents the invasive component of intraductal papillary neoplasm or mucinous cystic neoplasm. Patients tend to present with larger but lower grade tumours than patients with pancreatic ductal adenocarcinoma and hence there is a comparatively better prognosis. Intraductal papillary neoplasms A premalignant, precursor condition to pancreatic ductal adeno- carcinoma that can arise within the main pancreatic duct or side branches of the duct (or both, known as mixed type). Comparatively slow growth often enables early diagnosis and potentially curative surgical resection. They produce mucin, are usually unifocal (but can be multifocal), and microscopically have differentiated papil- lary features. Intraductal papillary neoplasms above a certain size may be assessed via EUS-fine needle aspiration of cyst contents for assessment of viscosity and amylase, and carcinoembryonic antigen levels. Immunohistochemical staining with mucin antibodies al- lows differentiation into gastric, intestinal, pancreaticobiliary and oncocytic subtypes, all of which carry a slightly different prog- nosis. Intraductal papillary neoplasms affecting the main duct have higher malignant potential and should always be excised, whereas current guidelines recommend that side-branch intraductal papil- lary neoplasms should be resected if over 3 cm in size and/or rap- idly enlarging, with ongoing surveillance by noninvasive imaging for smaller lesions. Secondary tumours Metastatic pancreatic tumours are rare and may be derived from a breast, renal, or sarcomatous primary tumour. These can be excised for both diagnosis and treatment. Mucinous cystic neoplasms These are rare cystic neoplasms that contain thick mucin and are often located in the tail and body of the pancreas. Mucinous cystic neoplasms are usually diagnosed in females between the fourth and sixth decades of life and can be differentiated from intraductal pap- illary neoplasms by a lack of connection to the pancreatic ductal system and an ovarian-type stromal component. Mucinous cystic neoplasms should be excised to prevent malignant transformation. Pancreatic intraepithelial neoplasia A precursor lesion of pancreatic ductal adenocarcinoma, which is usually too small to be detected with current imaging techniques

and which tends to involve ducts of less than 5 mm in diam- eter. The presence of noninvasive pancreatic intraepithelial neo- plasia describes a microscopic proliferative epithelial lesion of the pancreas and affected ducts are found to be lined by columnar to cuboidal mucinous cells, although mucin may be depleted in high- grade lesions. It can be divided into three grades (1–3) according to cytological and architectural atypia, and higher-grade pancreatic intraepithelial neoplasia lesions have been demonstrated to be asso- ciated with higher frequencies of genetic alterations, which become more similar to pancreatic ductal adenocarcinoma as the pancreatic intraepithelial neoplasia grade increases to grade 3. Pancreatoblastomas Rare malignant tumours that occur mainly in boys in their fourth or fifth year of age. They are the commonest pancreatic neoplasm in children and are often associated with a raised α-fetoprotein. Radiologically they appear as solid tumours, which can be large, and microscopically as flat nests of cells that can exhibit acinar, squa- mous, or endocrine differentiation. Presentation is often with ab- dominal pain, jaundice, and vomiting in the presence of advanced or metastatic disease. Lesions should be resected where possible, with subsequent adjuvant chemotherapy even in low-grade disease. Patients presenting with advanced disease should undergo chemo- therapy as a first-line treatment. Serous cyst neoplasms Previously referred to as serous cystadenomas, these are the com- monest cystic pancreatic tumours and are benign and usually asymptomatic. They characteristically have a honeycomb structure with a microcystic (or more rarely macrocystic) internal arrange- ment. They only very rarely undergo malignant transformation, but they can grow to a significant size, requiring excision for the treat- ment of local symptoms or progressive/rapid growth. Solid pseudopapillary neoplasms Solid pseudopapillary neoplasms are usually diagnosed in younger women and are benign in over 90% of cases. Rarely, they can undergo transformation to low-grade malignant tumours (which rarely me- tastasize) containing a mixture of solid and papillary elements, which often have a necrotic core. Radiologically they can be diffi- cult to distinguish from pancreatic ductal adenocarcinoma, hence surgical resection is generally recommended. Prognosis is excellent, with 95% 5-year survival. Neuroendocrine tumours Tumours arising from the endocrine pancreas are significantly less common than exocrine tumours, accounting for up to 5% of all pan- creatic tumours. Clinically, they can be associated with various fa- milial syndromes, particularly multiple endocrine neoplasia type 1, but are more often sporadically diagnosed. Macroscopically they are often small, yellow, or tan masses, which can be firm due to an accompanying desmoplastic reaction. Microscopically, they tend to have minimal pleomorphism with bland cytopathology and cyto- plasm containing secretory granules. They can be benign or malig- nant and although approximately 60% are nonsecretory, and most are morphologically small, some can produce high levels of func- tioning peptides and hormones, producing a spectrum of symp- toms depending upon the hormone produced. Similarly, some neuroendocrine tumours will possess specific receptors capable of hormonal uptake, which can be exploited via targeting for both radiological diagnosis and treatment. CT remains the diagnostic method of choice where possible, but smaller functional tumours can be difficult to demonstrate with conventional imaging techniques. These can be localized fol- lowing intravenous administration of somatostatin analogues such as octreotide (a synthetic analogue of somatostatin with a longer

 half-life), which can be combined with PET to offer whole-body tumour localization. Treatments can be aimed at disease cure or symptom alleviation, depending upon tumour site and disease extent. Low-grade or benign neuroendocrine tumours can be often be watched and followed with sequential imaging, whereas small and localized tumours

can be re- sected to prevent spread or hormone-related symptoms. Metastatic tumours can be surgically debulked for palliation and symptom control, improved quality of life, and occasionally prolonged length of life. Systemic somatostatin analogues (e.g. lanreotide) adminis- tered subcutaneously or intramuscularly can block hormonal re- lease and help in the control of symptoms, as well as occasionally reducing tumour size. Further systemic chemotherapeutic agents include everolimus (inhibitor of mammalian target of rapamycin) and sunitinib (receptor tyrosine kinase inhibitor), which can be used independently or combined with 5-fluorouracil, doxorubicin (anthracycline, antitumour antibiotic), or cisplatin (platinum based) in combination regimens. Locally directed treatment can be given in the form of peptide receptor radionuclide therapy, which can be tar- geted to the tumour via previously established hormone receptors. Hepatic metastases can often be the source of significant symptoms in patients with functional tumours. Treatments include transarterial chemoembolization, where spheres lined with chemotherapy agents are directly embolized into tumour vessels, thus obstructing tumour blood flow and directly delivering chemotherapy. This can lead to a significant (up to 80%) reduction in tumour size. Selective internal ra- diation therapy (yttrium-labelled radioactive microspheres delivered directly to the tumour) can also be used in some cases. Functional tumours are routinely classified according to the hor- mone that is most strongly secreted, as follows: Insulinomas These result in hypoglycaemic episodes that can be sudden, severe, and extremely troublesome, and can be diagnosed in those with a biochemical profile of low serum glucose associated with elevated insulin, proinsulin, and C-peptide levels. Insulinomas can be local- ized by conventional radiology modalities supplemented by angiog- raphy and should be treated via surgical resection wherever possible. Glucagonomas Patients exhibit increased serum glucagon levels, activating gluconeogenesis and lipolysis, and resulting in hyperglucagonaemia, decreased amino acid levels, anaemia, diarrhoea, and weight loss. Necrolytic migratory erythema is the presenting problem in up to three-quarters of patients and is characterized by the presence of erythematous blisters and swelling in the lower abdomen, groins, axillae, and buttocks. Diabetes is often present. An elevated blood serum glucagon (in the absence of liver disease) is usually diagnostic but can be supplemented by assessment of blood amino acids and skin biopsies to confirm necrolytic migratory erythema. Tumours should be localized via radiological imaging and resected. Vasoactive intestinal peptide-omas These are rare neuroendocrine tumours originating from non-β-islet cells of the pancreas and which may be associated with mul- tiple endocrine neoplasia type 1 syndrome. Excess production of vasoactive intestinal peptide leads to the development of profuse watery diarrhoea, hypokalaemia, achlorhydria, hypercalcaemia, and hyperglycaemia, as well as flushing and hypotension due to excess vasodilation. Treatment is via surgical resection, which is possible in a third of patients, with the rest requiring somatostatin analogue radionuclide therapy. Somatostatinomas These are tumours of pancreatic delta cells that produce somato- statin, clinically manifesting as diabetes (inhibition of insulin), steatorrhoea (inhibition of pancreatic exocrine hormones), gall- stones (inhibition of cholecystokinin), and achlorhydria (inhibition of gastrin), as well as a reduction in rates of gastric emptying and in- testinal peristalsis, and are also associated with psammoma bodies, microscopic collections of calcium. Treatment is via surgical resec- tion supplemented with chemotherapy as necessary. FURTHER READING Aune D, et al. (2012). Body mass index, abdominal fatness and pancre- atic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol, 23, 843–52. Bosetti C, et al. (2012). Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol, 23, 1880–8. Callery MP, et al. (2009). Pretreatment assessment of resectable and borderline resectable pancreatic cancer:

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