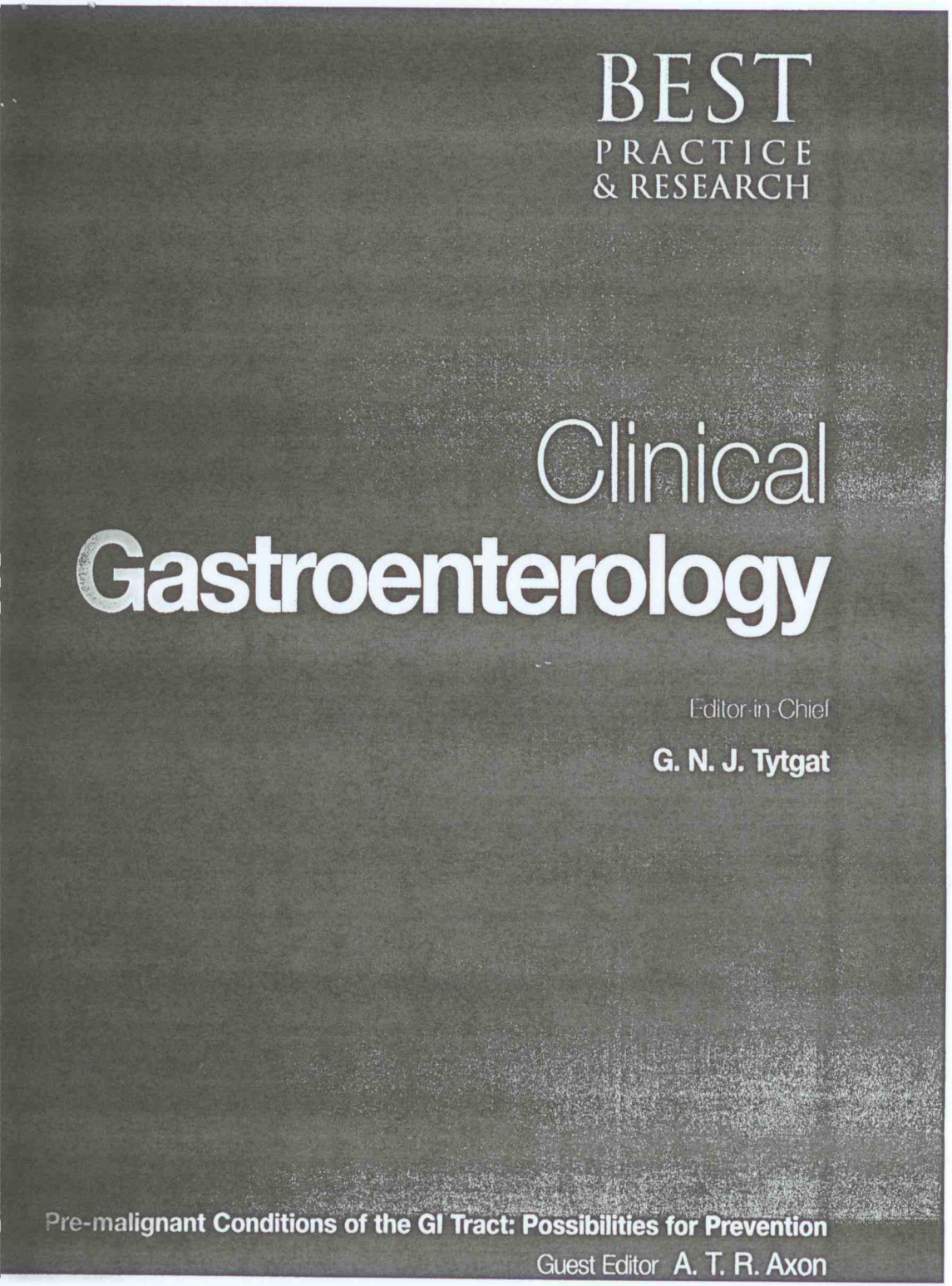

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7

Surveillance of pre-malignant disease of the pancreatico-biliary system

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Technical advancements in ultrasonography, contrast-enhanced computed tomography and magnetic resonance imaging, as well as the wider availability of these ultramodern imaging techniques, have resulted in the early detection and a better classification of various asymptomatic and symptomatic pancreatico-biliary lesions. Pre-malignant biliary and pancreatic lesions are rare disorders, and no clear data are available to define their malignant potential. Because of the lack of controlled epidemiological data, the time span for malignant transformation and its frequency cannot be defined in the majority of these lesions. Adenomyomatosis of the gallbladder and gallbladder polyps larger than 10 mm should be treated by cholecystectomy even in asymptomatic patients because of an increased risk of malignant transformation. Chronic cholangitis, primary sclerosing cholangitis and choledochal cysts are also pre-malignant conditions. The timing of surgery, once it is advised for a pre-malignant condition that is still benign, should, however, be individualized to the particular patient situation. In patients with chronic pancreatitis, surgery may be indicated for disease-related complications. In as much as chronic pancreatitis predisposes to a higher risk of pancreatic cancer, any suspicion of malignancy should warrant a surgical exploration. Intraductal papillary tumours and mucin-producing pancreatic tumours are other pre-malignant pancreatic lesions whose malignant potential cannot be precisely determined pre-operatively. They should be resected in situations where there is a high degree of suspicion even without a clear objective diagnosis. In conclusion, pre-malignant hepato-biliary and pancreatic lesions of uncertain pathology should undergo early resection in view of treatment limitations and the dismal prognosis of established cancers. While hepato-biliary and pancreatic surgery is nowadays performed in specialized centres, with a low post-operative morbidity and mortality, it is equally important to understand that observation alone with regular computed tomography or magnetic resonance imaging control can no longer be recommended in the management of these lesions.

Key words: pre-malignant lesions; biliary tract; cholangiocarcinoma; pancreas; chronic pancreatitis; cystic tumours; pancreatic cancer.

Pre-malignant lesions of the pancreatico-biliary system are uncommon entities and crucial questions about their malignant potential (frequency of occurrence, time span

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for malignant transformation, etc.) remain unanswered. This chapter will address various aspects of the diagnosis and treatment of such lesions and will attempt to provide guidelines for future clinical practice.

POTENTIALLY PRE-MALIGNANT BILIARY LESIONS

Table I summarizes the main risk factors that have been identified for biliary carcinogenesis. For some of these potentially pre-malignant lesions, the relative risk of developing cholangiocarcinoma in comparison with that of the general population has been estimated. The common denominator for biliary metaplasia, dysplastic epithelial transformation and epithelial proliferation seems to be chronic inflammation through chemical and/or mechanical irritation and cholestasis, with the activation of injurious pancreatico-biliary compounds and carcinogens.

Table I. Predisposing factors for biliary carcinogenesis and the relative risk (RR) of developing cholangiocarcinoma compared with the general population.

	Predisposing factors	RR
Anatomical anomalies	Congenital bile duct cysts	86
	Caroli's disease	NA
	Pancreatico-biliary maljunction	32
Chronic inflammatory conditions	Primary sclerosing cholangitis	30
	Typhoid carriers (gallbladder)	6
	Porcelain gallbladder	25
Parasites	Opisthorchis viverrini	5
	Clonorchis sinensis	5
Biliary calculi	Cholecystolithiasis	NA
	Hepatolithiasis	NA
Carcinogens	Nitrosamines (BOP, DEN)	NA
	Thorotrast	303
	Betel nut	NA
Autoimmune diseases	Primary sclerosing cholangitis	30
	Primary biliary cirrhosis	30
	Chronic ulcerative colitis	75

NA = not available; BOP = N-nitrosobis(2-oxopropyl)amine; DEN = diethylnitrosamine. Modified from Holzinger et al. *Annals of Oncology* 1999; **10**: 122–126.

Adenomyomatosis of the gallbladder

Adenomyomatosis of the gallbladder is characterized by hyperplasia of the mucosa and hypertrophy of the muscular layer, which may result from a functional obstruction to the outflow of bile. The resulting increased intracystic pressure results in the invagination of the mucosal epithelium through the muscularis, forming the so-called Rokitansky-Aschoff's sinuses.

According to the extent and site of the involvement, adenomyomatosis of the gallbladder is conventionally classified into three types: localized, generalized and segmental.[2] The prevalence of this condition is unknown. Autopsy studies as well as cholecystography and cholecystectomy materials reveal a variable frequency of

adenomyomatosis, ranging from 2% to 33%.[3] The type of adenomyomatosis seems to be important for the development of gallbladder cancer. Gallbladder cancer developed in 6.4% of patients with a segmental type of adenomyomatosis, whereas no clear association was found between the localized and the generalized type of adenomyomatosis and gallbladder cancer.[4] Therefore, clinicians should be aware that segmental adenomyomatosis has an elevated risk of becoming malignant and should be treated by cholecystectomy, even in asymptomatic cases.

The pre-operative diagnosis of adenomyomatosis is usually made by ultrasonography (US); however, newer investigational techniques such as endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) have been proven to provide additional important information for the differential diagnosis of adenomyomatosis.[5,6] Cholecystectomy is indicated in all patients with segmental adenomyomatosis because of the malignant potential, as well as in patients with localized or generalized adenomyomatosis presenting with symptoms, since they may be relieved by surgical removal of the gallbladder.

Polyps of the gallbladder

The prevalence of gallbladder polyps, as assessed by US in a random population, has been reported to range from 4.3% to 6.7%.[7,8] In contrast to cholecystolithiasis, the prevalence of gallbladder polyps is not associated with age, sex, weight factors, number of pregnancies or use of exogenous female hormones.[8] US has proved to be the most accurate diagnostic tool for the detection of gallbladder polyps. The sensitivity of the technique in detecting polypoid lesions of the gallbladder is 90%, with a specificity of 94%.[9] Fur a further differentiation of polypoid gallbladder lesions, EUS is recommended when US shows no signs indicative of either a cholesterol polyp or adenomyomatosis.[5]

Once gallbladder polyps have been identified, they pose a dilemma with respect to their proper long-term management, since differentiation into cholesterol polyps, adenoma, inflammatory polyps and cancer does not always follow. The available data suggest that polyps larger than 10 mm in diameter that show rapid growth, are single in number or are associated with gallstones should be considered to be suggestive of malignancy, prompting surgical treatment.[9–11] In the era of laparoscopic cholecystectomy, it is important to identify those patients with an advanced polypoid cancer, for which laparoscopic cholecystectomy is not the appropriate surgical treatment. Kubota et al[11] have shown that polypoid gallbladder lesions with a diameter less than 18 mm are potential early-stage cancer and may therefore be resected by laparoscopic cholecystectomy with full-thickness dissection. When cancer invades the subserosal layer or beyond, a second-look operation is, however, mandatory. A polypoid gallbladder lesion with a diameter greater than 18 mm may represent an advanced cancer and should be removed using open cholecystectomy with partial liver resection, or a more extended procedure with lymph node dissection.[11]

In asymptomatic subjects in whom gallbladder polyps less than 10 mm in diameter are found incidentally, the probability of malignant transformation is low, and ultrasonographic surveillance is recommended at 6-monthly intervals during the first few years after the diagnosis of a polypoid gallbladder lesion.

Sclerosing cholangitis and recurrent cholangitis

Longstanding cholangitis, especially primary sclerosing cholangitis (PSC), is associated with an increased risk of developing biliary cancer. There is pathological evidence that

cholangiocarcinoma may arise in the setting of PSC. In autopsy studies, cholangiocarcinoma is present in up to 33–42% of patients with PSC, which means that PSC is the most important risk factor for the development of cholangiocarcinoma in Western countries.[12] In this series of 30 patients, the diagnosis of PSC preceded the diagnosis of cholangiocarcinoma by a mean of 52 months.[12]

Because PSC develops mostly in patients with chronic ulcerative colitis, similar mechanisms for the carcinogenesis of colonic cancer in chronic ulcerative colitis and bile duct cancer in PSC have been assumed. Rosen et al[12] found a link between PSC and chronic ulcerative colitis in 83% of their patients. Interestingly, identical K-*ras* gene point mutations were found in both groups, which could explain the coincidental carcinogenic mechanisms in the colon as well as the biliary tract. At the same time, cholestasis with obliterative inflammation, as well as bacterial bile salt degradation with the formation of secondary bile acids, completes the multistage process of carcinogenesis in these patients.

Cholangiocarcinoma complicating PSC is mostly detected at an advanced tumour stage, which precludes potentially curative resectional therapy. Therefore, the early detection of malignant transformation of the biliary epithelium is necessary to increase the survival rate. The diagnosis of PSC is established by the radiographic features of PSC on cholangiography, an elevation of the alkaline phosphatase level to at least twice the upper limit of normal, the presence of auto-antibodies (ANA, SMA, pANCA) and a liver biopsy consistent with PSC, showing periductular fibrosis. Clinical signs that may indicate malignant transformation in PSC patients have been identified to be jaundice, weight loss, abdominal discomfort and intractable pruritus.[13] Paraneoplastic phenomena such as thrombotic events or hypercalcaemia may occasionally occur. Cholangiographic findings suggestive of cholangiocarcinoma include markedly dilated ducts, the presence of a polypoid mass larger than 1 cm in diameter and progressive stricture formation or duct dilatation.[14] Ideally, the cytological examination of brushes and biopsies will confirm malignant transformation.

There is no reliable laboratory marker that will predict the development of biliary malignancy in patients with PSC. However, a serum carcino-antigen (CA) 19-9 value greater than 100 U/ml has been shown to predict the presence of cholangiocarcinoma in PSC with a sensitivity of 89% and a specificity of 86%.[15] In a recent clinical study, an elevated index of two serum tumour markers (CA 19-9 + [carcino-embryonic antigen (CEA) × 40] > 400) had a positive predictive value for cholangiocarcinoma of 100% and a specificity of 100%, but the sensitivity of this index was only 67%.[16] More recently, positron emission tomography (PET), using a glucose analogue radiolabelled tracer, was found to detect small cholangiocarcinomas in patients with PSC with high sensitivity and specificity.[17]

The overall prognosis for patients with PSC and cholangiocarcinoma is poor. Surgical resection offers the only chance of cure, but surgery was in the past often palliative, associated with a median survival of only 13 months.[18] Liver transplantation is now the therapy of choice for patients with end-stage PSC. Cholangiocarcinoma has generally been considered to be a poor indication for liver transplantation because of the high recurrence rate of PSC and a tumour recurrence rate of 59%, even in selected patients.[19] The prevention of cholangiocarcinoma relies on the early referral of patients with PSC to specialized hepato-biliary units, where the close surveillance of patients is mandatory, and liver transplantation should be undertaken as soon as dysplasia of biliary epithelium has been detected.

Parasitic disease

The association between the occurrence of cholangiocarcinoma and the presence of the liver flukes *Clonorchis sinensis* (CS) and *Opisthorchis viverrini* (OV) is very well established. The infection is acquired by eating raw or undercooked cyprinoid fish contaminated with the encysted metacercariae of the parasites. The flukes chronically infect the intrahepatic bile ducts and the gallbladder, as well as the pancreatic duct. *Opisthorchis viverrini* is endemic in north-east Thailand (30% of the population being infected), where there is a high incidence of cholangiocarcinoma, with a relative risk of 5 for those with an antibody titre greater than 1:40 for OV.[20] This implies that at least two-thirds of cases of cholangiocarcinoma in Thailand are attributable to OV infection.[20] It has been suggested that the parasite infestation by itself is not strongly carcinogenic but exerts a marked promoting influence on cholangiocellular tumour development via chronic irritation and increased cell turnover, rendering the cells susceptible to either exogenous or endogenous carcinogens.[21] Furthermore, Haswell-Elkins et al[22] and Oshima and Bartsch[23] have shown that OV-infected subjects, as identified by the presence of OV eggs in the faeces, demonstrated an increased biosynthesis of nitrosamines and an increased nitrosation potential of macrophages compared with uninfected subjects. Their data support the hypothesis that infection with OV increases the generation of genotoxic nitric oxide, as estimated by elevated salivary nitrite and urinary nitrate levels in infected subjects.[22,23]

The primary prevention of parasite-associated pancreatico-biliary carcinogenesis can be achieved using the drug Praziquantel in high-risk populations with a high prevalence of liver fluke infestation. Administered in a single dose, this eliminates the parasites successfully from infested individuals. The successful control of liver fluke infection will require repeated medical treatment coupled with attempts to change the traditional dietary pattern, although the latter has in the past proved rather refractory to educational programmes. Furthermore, it is possible that if parasite-induced nitrosation is truly important in the aetiological process of pancreatico-biliary carcinogenesis, the administration of vitamin C may be effective in interacting with the nitric oxide synthase. The lack of clinical studies evaluating this approach means that it remains unproven. In contrast to CS and OV infection, infestation with *Fasciola hepatica* and *Schistosoma* does not appear to have a similar carcinogenic effect on the pancreatico-biliary tract of infected individuals.[24]

Choledochal cyst

Bile duct cysts of congenital origin may be intrahepatic or extrahepatic. In the latter location, they are usually solitary and called choledochal cysts. In 1977, Todani et al[25] reported 37 cases of congenital bile duct cysts and classified them into six different types. Over 80% of congenital choledochal cysts can be classified as type I according to the Todani classification.[25]

As the cause of choledochal cysts, Babbit[26] proposed an abnormal relationship between the common bile duct and the pancreatic duct, precluding a sphincteric mechanism at the junction of the common bile and pancreatic ducts, a structure present when normal development occurs. Several clinical observations have revealed that there is a high association between an anomalous arrangement of the pancreatico-biliary ducts and the development of choledochal cysts[26,27], except in patients with intrahepatic bile duct dilatation (Caroli's disease) or a choledochocele, in whom a different aetiology is proposed. The anomalous union results in a loss of normal

sphincteric mechanism at the pancreatico-biliary junction, permitting a reflux of pancreatic juice into the biliary system, as has been proved by the high amylase level found in over 20% of the fluid aspirated from choledochal cysts.[27,28] Iwai et al[27] found an abnormal choledocho-pancreatico-ductal junction in 96.2% out of 26 patients with congenital choledochal dilatation, Kimura et al[29] finding the same in 17 out of 18 of their patients, which strongly supports Babbit's theory.

The incidence of coexistent bile duct carcinoma arising in choledochal cysts is reported to vary between 2.5% and 15%, increasing with the patient's age.[30] This cancer risk is considerably greater than the frequency of extrahepatic bile duct carcinoma in patients without choledochal cysts, which has been confirmed in several autopsy studies to range between 0.012% and 0.48%.[25] It was also found that gallbladder carcinoma occurred in 24.6% of cases of anomalous ductal junction in comparison with an incidence of 1.9% among consecutive patients, confirming this lesion to be important in this subgroup of biliary tumours.[31] Although there are many possible factors responsible for the carcinogenesis of choledochal cysts, it is assumed that the longstanding inflammation of the biliary tract caused by the reflux of pancreatic juice with the activation of bile acids and the formation of mutagenic bile acids, such as lithocholic acid, might be an important factor producing pathological epithelial changes leading to biliary carcinoma as the last and fatal complication.[24,28,32]

There is general agreement that even asymptomatic bile duct cysts should be treated to prevent complications such as ascending cholangitis, gallstones and cancer.[24,33] These patients should undergo the surgical removal of their choledochal cysts rather than be placed under surveillance through frequent endoscopic retrograde cholangio-pancreatography (ERCP) with histological controls. The extent of the surgical treatment of congenital cystic dilatation of the biliary system must be based on the extent of the disease and intra-operative findings. The surgical strategy changed in the early 1970s, with a sharp trend away from the previously popular choledochocysto-duodenostomy and choledochocysto-jejunostomy with Roux-en-Y anastomosis[34,35] because of the risk of cancer development in the cystic residue several years later.[25] Primary excision of the cyst is now considered to be mandatory to prevent complications and tumourigenesis. If a cystic carcinoma is found intra-operatively, en bloc resection with partial duodeno-pancreatectomy and central liver resection should be performed if necessary to obtain an R0-resection, which appears to be the only chance for cure. This treatment, however, shows a 5 year survival rate of 10–30%, the worst prognosis being for patients with proximal bile duct cancer locations (Klatskin tumours).[36] This fact highlights the very high malignant potential of cancer arising in choledochal cysts.

POTENTIALLY PRE-MALIGNANT PANCREATIC LESIONS

Over the past few years, various pancreatic disorders have ben shown to have the potential for malignant transformation. These include chronic pancreatitis, acinar cell adenomas, intraductular papillary tumours, mucin-producing tumours and cystic pancreatic tumours. The prevalence of these pancreatic pathologies – other than chronic pancreatitis – is low, and they are nowadays more often diagnosed incidentally because of widespread and easily available imaging procedures (US, etc.). Because of the rarity of these tumours, many of these lesions are clinically not well characterized; in particular, the long-term outcome with regard to their potential to become malignant is often not clearly defined.

Chronic pancreatitis

Non-hereditary chronic pancreatitis

Chronic pancreatitis is principally a benign pancreatic disease, histomorphologically characterized by the progressive development of fibrosis and atrophy of the pancreatic parenchyma, often associated with diffuse parenchyma calcification, ductal strictures and dilatation, and non-parenchymal cystic degeneration. Clinically, these changes result in chronic relapsing pain and impaired exocrine function, and at a later stage also in endocrine insufficiency. In most cases, the disease involves the whole gland, but in about one-third of cases it is limited to a segment of the gland.[37] Chronic pancreatitis has a prevalence of less than 30 per 100 000 and a yearly incidence of less than 10 per 100 000. Alcohol consumption is the key aetiological factor in the development of chronic pancreatitis, up to 85% of cases being associated with excessive alcohol consumption.[38–40]

Although chronic pancreatitis is a benign disorder, it contains in some cases the risk of progression to pancreatic cancer.[38,41,42] Patients with sporadic chronic pancreatitis have an increased risk of developing pancreatic cancer that is approximately six times higher than that of unaffected individuals.[43,44] The results of a large historical cohort study of patients with chronic pancreatitis from seven centres located in six countries suggest that the risk of pancreatic cancer is significantly elevated in patients with chronic pancreatitis and appears to be independent of sex, country or type of pancreatitis.[38]

The initial cohort in this study consisted of 2015 patients, 463 of whom were excluded because of follow-up for less than 2 years, leaving 1552 patients who were thought to be free of pancreatic cancer for at least 2 years after the onset of the disease. Of the 1552 patients, with a mean follow-up time of 7.4 $\pm$ 5.6 years, 29 had evidence of cancer of the pancreas 2 or more years after the diagnosis of chronic pancreatitis. The standardized incidence ratio (SIR) for developing pancreatic cancer, which was used to estimate the relative risk, was 16.5 for the patients with 2 years of follow-up ($n = 1552$), 14.4 for those patients with a minimum of 5 years of follow-up ($n = 1160$) and 1.76 for an age-, sex- and centre-adjusted control population. The risk of developing pancreatic cancer was equal for patients with non-alcoholic and alcoholic pancreatitis. The other variables used to analyse the risk of developing pancreatic cancer included demographic variables (age, sex and country), clinical variables (the type of pancreatitis, diabetes mellitus, calcification and liver cirrhosis) and lifestyle variables (alcohol use and smoking status). Only increasing age was significantly related to the risk of developing pancreatic cancer.

Hereditary chronic pancreatitis

Hereditary pancreatitis is an autosomal dominant disorder with 80% phenotypic penetrance, characterized by recurrent attacks of abdominal pain beginning early in life. It affects several family members in different generations. A gene involved in this disease has been mapped to chromosome 7q35, the defect being caused by mutations in the cationic trypsinogen gene.[43,45,46] Although hereditary chronic pancreatitis is a rare disease, affected patients have an increased risk of pancreatic cancer during the long-term course of the disease, yielding an SIR of 53. The estimated cumulative risk of pancreatic cancer up to the age of 70 years in patients with hereditary chronic pancreatitis approaches approximately 40%.[44]

Because the genetic defects can nowadays be detected, a potential algorithm for screening might begin with the genetic testing of children at an age as early as 5 years. Screening for pancreatic cancer should not be unduly delayed as cancer in this group

can already occur at early age (around 30 years). The regular screening methods for pancreatic cancer include computed tomography (CT), ERCP, MRI, EUS, pancreatic juice cytology from the duodenum and serum tumour markers. At the first hint of the development of chronic pancreatitis, an evaluation of endocrine and exocrine function should be undertaken.[45] No controlled study in a larger patient cohort is, however, currently available to show whether the above-mentioned diagnostic procedures are useful for the early detection of malignant transformation.

Screening of patients with chronic pancreatitis

Independent of the aetiology of chronic pancreatitis, cellular dysfunction, chronic glandular destruction in combination with recurrent cell repair, and presumably increased cell turnover, might contribute to carcinogenesis in these patients. Because of the considerable risk of the development of pancreatic cancer in chronic pancreatitis, diagnostic measures to differentiate both conditions and to enable an early identification of the change from chronic pancreatitis to pancreatic cancer must be considered.

The clinical presentation of chronic pancreatitis resembles that of pancreatic cancer, including relapsing pain, anorexia, weight loss, obstructive jaundice, nausea, diabetes mellitus and steatorrhoea. Based on the clinical presentation, it is therefore difficult to differentiate chronic pancreatitis from pancreatic cancer. Although the frequency of these symptoms varies between the conditions, patients with chronic pancreatitis are in general younger, with a history of heavy alcohol intake.[42,47]

Most imaging techniques are useful for diagnosing chronic pancreatitis and objectively quantifying disease progression, but they have their limitations in differentiating chronic pancreatitis from early malignant pancreatic disease.[47] The first line of investigation is usually US. The typical picture of chronic pancreatitis comprises light parenchymal reflexes, fibrosis, micro- and macrocysts, gland atrophy, a dilated main pancreatic duct and intraductal calculi.[41] US is particularly effective in demonstrating dilatation of the pancreatic and the bile ductal system, as well as the level of obstruction. Dilatation of both the pancreatic duct and the bile duct is present in only about 20% of cases of chronic pancreatitis, whereas it occurs in up to 90% of malignancies.[48]

CT is currently still considered to be the gold standard for pancreatic parenchymal imaging. A useful diagnostic feature in chronic pancreatitis is the atrophy of the pancreatic parenchyma, which is not commonly seen in association with tumours.[49] The overall specificity and sensitivity in establishing the differential diagnosis between chronic pancreatitis and pancreatic cancer are about 90%.[41] However, there also remain difficulties in differentiating between inflammatory and neoplastic lesions, as well as in the ability to identify pancreatic lesions less than 2 cm in diameter.[49,50]

The abnormalities of the pancreatic duct can most reliably be shown with ERCP. In more than 70% of cases of pancreatic cancer, the main pancreatic duct shows a sharp cut-off, usually with post-stenotic dilatation, whereas in cases of chronic pancreatitis, the main pancreatic duct is usually irregularly dilated, without a sharp cut-off. The overall specificity and sensitivity of ERCP in differentially diagnosing chronic pancreatitis from pancreatic cancer is about 90%.[41] Pancreatic fluid collection or duct brushings for cytology can also be combined with ERCP. In brush cytology specimens, however, it is difficult to discriminate cells of chronic pancreatitis from those of pancreatic cancer on the basis of morphological criteria.[38,51]

Serological markers such as CA 19-9 are frequently elevated in pancreatic cancer. Although CA 19-9 antigen measurement is not accurate enough to be used as a screening tool in an asymptomatic population, and moderate elevation is sometimes

encountered in inflammatory disease, it is currently the single most useful tumour marker in differentiating benign from malignant pancreatic disease. The higher the CA 19-9 level (> 1000 U/ml), the greater its specificity and positive predictive value in diagnosing cancer of the pancreas. However, the clinical applicability of serological markers in differentiating between inflammatory lesions and small resectable tumours in the pancreas is extremely limited. While measuring several tumour markers in combination might prove helpful in enhancing the possibility of detecting mitotic lesions in certain selected cases, the overall picture is in contrast to this and appears grim.[38,52]

MRI with gadolinium enhancement may marginally improve the accuracy of assessing pancreatic tumours, but its ability to differentiate inflammatory lesions from cancer remains unevaluated and needs to be investigated.[53]

PET is another relatively new, non-invasive diagnostic imaging technique, in which the increased uptake of 2(^{18}F)-fluoro-2-deoxy-D-glucose (FDG-PET) observed in malignant tumours has been used for the differential diagnosis of pancreatic cancer and chronic pancreatitis.[54–56] The standard uptake in patients with pancreatic carcinoma is higher than that in patients with chronic pancreatitis. However, the clinical value of FDG-PET scanning requires further evaluation because the technique's specificity seems to be limited (a) in patients with chronic pancreatitis who have previously had upper gastrointestinal surgery, (b) if pancreatitis-related complications leading to unspecific FDG accumulation (intracystic haemorrhage) have occurred, or (c) if interventional techniques (stent and probe placement) have been used.[54,55]

Percutaneous or endoscopic biopsies achieve histological confirmation of the diagnosis with a high specificity. It is, however, difficult to exclude malignancy with this technique because of a relatively low sensitivity. A high proportion of connective tissue causes difficulty in acquiring enough pancreatic material for adequate histological examination.[38] Another objection to percutaneous biopsy is the increased prevalence of positive peritoneal cytology in pancreatic cancer patients who have had a percutaneous needle aspiration for cytological diagnosis.[41,57]

EUS allows high-resolution imaging of the pancreas and the adjacent organs and represents the most promising technique for establishing a correct differential diagnosis for chronic pancreatitis and pancreatic cancer.[50,58] The experience of the endosonographist is, however, crucial. In a comparative study with dynamic CT scanning and MRI, EUS was shown to be the most sensitive, specific and accurate method for diagnosing a pancreatic tumour. The sensitivity was 94% for EUS, 69% for CT and 83% for MRI. The specificity was 100% with EUS, 64% with CT and 100% with MRI, and the accuracy was 96%, 67% and 84%, respectively. The sensitivity of the detection of tumours less than 3 cm in diameter was 93% for EUS, 53% for CT and 67% for MRI.[41,59]

With full delineation of the pancreatic and the common bile ducts, EUS may help to differentiate focal pancreatitis (a more irregularly dilated pancreatic duct with side branches throughout the mass, and small intraductal calcifications) from pancreatic carcinoma.[59] Moreover, EUS-guided fine needle aspiration (EUS-FNA) biopsy of suspicious tumour lesions has been shown to be an effective procedure in establishing a tissue diagnosis, enhancing the diagnostic accuracy, specificity and sensitivity of EUS in the differentiation of benign and malignant pancreatic masses, even when tumour size is small. In addition, the danger of spreading tumour cells may be lower than by the percutaneous approach. The overall accuracy, specificity and sensitivity of EUS-FNA for differentiating benign from malignant masses of the pancreas are 85–96%, 85–100% and 82–96%, respectively. The technique's positive and negative predictive values are 98–100% and 51%, respectively.[50,60,61] The morbidity associated with EUS-FNA is less than 2% for solid lesions, bleeding, infection and pancreatitis being the

main complications. The complication of malignant seeding along the needle biopsy tract has not yet been reported with the use of EUS-FNA.[50]

Recent developments in molecular biology have also provided the potential to improve the differentiation of chronic pancreatitis from pancreatic cancer. Mutations in codon 12 of the K-*ras* proto-oncogene have been identified in 70–95% of pancreatic cancers and can be identified from cytological brushings or pancreatic juice taken at ERCP.[62] K-*ras* mutations have, however, also been detected in chronic pancreatitis, limiting the usefulness of this so far best-evaluated molecular marker for diagnostic purposes.[63,64]

If the differential diagnosis of chronic pancreatic inflammation and pancreatic cancer cannot be safely established, which is the case in approximately 5–10% of patients, surgical exploration is needed. In cases of suspected early pancreatic cancer, observation might ruin any possible chance of a long-term cure. For hereditary pancreatitis, with the high lifetime risk of pancreatic cancer, a prophylactic pancreatectomy should be kept in mind, but no evidence-based data are currently available on this topic. However, inasmuch as the prognosis of pancreatic cancer is poor, any chance of a possible cure should not be missed by the clinician.

Acinar cell adenomas

The acinar cell adenoma is a rare pancreatic tumour entity. It is a focal, well-demarcated nodule in which acinar cells are converted into cells with pleomorphic or small, dense nuclei. They possess a diminished complement of cytoplasmic zymogen granules and therefore appear paler. The features of a neoplastic process are generally lacking.[65] Some researchers have, however, referred to these lesions as 'focal acinar cell dysplasia' and have suggested a progression to carcinoma in a minority of cases. An abnormal nuclear DNA content has been found in lesions of this type in humans and rats. Considering the relative frequency of this change and the rarity of acinar cell carcinomas, an association between the two needs further examination.[65,66]

Intraductal papillary tumours

The term 'pancreatic intraductal papillary tumour' includes lesions such as intraductal papilloma, which may be solitary, multiple or diffuse, diffuse intraductal papillary adenocarcinoma and in situ carcinomas of the pancreas. In contrast to invasive ductal adenocarcinoma, these tumours show a slow overgrowth of neoplastic epithelium, forming minute mural nodules with a more favourable prognosis. Only the affected branch duct is dilated, by the hypersecretion of mucin. In the majority of reported cases, the tumour arises in the main pancreatic duct in the head region.[65,67,68] Intraductal papillary neoplasms are soft and friable, distending and obstructing the ductal lumen. There is marked dilatation of the duct system distal to the tumour, causing chronic obstructive pancreatitis with marked fibrosis. There may be a spectrum of cellular atypia up to a degree indistinguishable from carcinoma in situ. Atypical epithelial proliferation, extending into the smaller side branches, may be extremely difficult to distinguish from invasive carcinoma.[67,69] Because of the risk of developing invasive cancer, intraductular papillary tumours should undergo resection.

Mucin-producing tumours of the pancreas

Mucin-producing tumours of the pancreas are characterized by a dilatation of the pancreatic duct system. Tumours develop in the main duct as well as in side branch ducts and can be malignant or benign.[70,71] The presenting symptoms are usually similar to those of chronic pancreatitis, with upper epigastric pain and weight loss, associated with a raised amylase level. On ERCP, a wide open orifice of the ampulla of Vater and a swollen papilla with the excretion of mucin are highly suggestive of a mucin-producing tumour. Characteristically, these duct ectasias lack strictures but possess filling defects, although the defects are sometimes difficult to visualize using ERCP.[72] The epithelium is in most cases well differentiated or only focally atypical, but it may in some cases show carcinoma in situ and infiltrative cancer.[73] The DNA content is higher in the cells of mucin-producing tumours than in normal cells, its level ranging between that of normal and carcinomatous growth.[65,70]

Morphologically speaking, mucin-producing tumours appear similar to mucinous cystic tumours of the pancreas. However, mucinous cystic tumours predominantly occur in a younger age group of female patients and more frequently involve the distal pancreas. Moreover, mucinous cystic tumours usually form multilocular or unilocular cystic spaces with densely fibrous walls, often associated with calcification, which can be detected by CT scanning.[70,74] Inasmuch as little is known about the long-term risk of mucin-producing cystic pancreatic tumours progressing to malignancy, these lesions should be removed, especially in young patients.

Cystic pancreatic lesions

Cystic tumours of the pancreas are rare, accounting for only 10–15% of all pancreatic cysts and approximately 1% of pancreatic malignancies. Between 70% and 90% of all cystic lesions of the pancreas are pseudocysts.[75,76] Out of all pancreatic cystic neoplasms, serous cystadenomas account for about 30%, mucinous cystic neoplasms – including mucinous cystadenoma and cystadenocarcinoma – account for about 50%, and others represent about 20%. Serous cystadenomas are uniformly benign with no malignant potential[75], whereas mucinous cystadenomas carry a latent or overt malignant potential. Thus, the appropriate and crucial classification of cystic tumours of the pancreas must be made microscopically rather than macroscopically.[75,77]

The cell of origin of serous cystadenomas is the centroacinar cell, that of mucinous cystadenomas being the pancreatic mucin-producing ductal cell. Serous cystadenomas tend to be composed of a honeycomb-like collection of small-diameter cysts, sometimes only microscopic in size, that are lined by a low cuboidal, bland-appearing epithelium lacking cellular atypia or dysplasia. A fairly vascular, fibrous stroma separates the microcystic areas. The lack of surrounding inflammation differentiates these lesions from harmless pancreatic pseudocysts. Serous cystadenomas tend to occur slightly more frequently in the proximal pancreas, while mucinous cystadenomas are often found in the body/tail region of the pancreas.

In contrast to serous cystadenomas, mucinous cystic lesions of the pancreas are classified as mucinous cystadenomas, non-invasive proliferative mucinous cystic neoplasms or invasive cystadenocarcinomas.[78] Histologically, they range from benign cystadenomas with a latent risk of malignant transformation to overt cystadenocarcinomas with frank tissue invasion and metastatic potential. Mucinous cystic neoplasms are lined by a tall, columnar epithelium secreting mucin, whose origin is probably ductal cells or stem cells as immunostaining for CEA and somatostatin have been shown to be positive. Cystic neoplasms may contain areas of atypia, dysplasia, carcinoma in situ and/or overt invasive carcinoma, often within the same tumour. Most pathologists consider all mucinous cystic neoplasms of the pancreas to have a latent malignant potential, some even believing all these lesions to be at least a grade I

cystadenocarcinoma.[75,78,79] The intracystic fluid, which contains mucus, is thicker and more viscous than that of serous cystadenomas.[80,81]

One of the most prominent clinical features of pancreatic cystic neoplasms is their marked propensity to appear in females, with a ratio of 4:1. The mean age of diagnosis with mucinous cystic neoplasms occurs in the fifth decade of life, the mean age of affected females being almost 20 years less than that of males.[75]

Unlike many other pancreatic disorders, there are no specific symptoms or pathognomonic signs for cystic neoplasms. Twenty per cent of mucinous cystic neoplasms and 50% of serous cystadenomas will be asymptomatic and discovered incidentally. The most common clinical presentation is some degree of abdominal pain or discomfort. Other symptoms include weight loss, a palpable mass, postprandial fullness, nausea and vomiting.[75,77] The history of recent, concurrent or past acute or chronic pancreatitis is notably absent in patients with cystic neoplasms. When present, symptoms are usually related to effects of the pancreatic mass. Pain is unusual, but a vague feeling of epigastric or left upper abdominal fullness is often present. Unlike pancreatic ductal carcinoma, mucinous cystic neoplasms do not invade the retroperitoneal nerves (which is thought to cause back pain) or involve the duodenum (causing duodenal obstruction). Also, jaundice is unusual despite their often large size.[77]

The diagnosis and differential diagnosis of cystic neoplasms of the pancreas relies on CT and/or US. In conjunction with the clinical history, especially when a solid eccentric component exists within the wall of the cyst, the differential diagnosis of a serous cyst from a mucinous cystic neoplasm or from pancreatic pseudocysts can be made.[75] Most mucinous neoplasms of the pancreas are composed of fewer than six cysts, and many are large (generally >2 cm) in size. In contrast, serous cystadenomas are generally multicystic masses, consisting of cysts less than 2 cm in diameter. When the calcification takes on an eggshell-type distribution, the probability of a malignant cystadenocarcinoma increases significantly.[82] Calcification is present in approximately 30% of serous cystadenomas and takes the appearance of a 'sunburst'-type central distribution within the fibrous stroma. Imaging tests can usually discriminate serous cysts from mucinous neoplasms, but differentiating cystadenomas from invasive cystadenocarcinomas is less reliable. Other imaging techniques besides CT and US, such as angiography, MRI and ERCP, offer little additional benefit in the diagnosis of cystic neoplasms of the pancreas.

The clinical features of serous and mucinous tumours often overlap, making it difficult to establish a differential diagnosis. Cytology, chemical analysis (viscosity and amylase level) and the measurement of tumour markers (CEA, CA 15-3 and CA 72-4) in cyst fluid have been suggested to be helpful.[75,77,80,83] CEA is probably the simplest, most readily available marker for differentiating mucinous neoplasms from serous tumours and pseudocysts. Other tumour markers, such as CA 72-4 and CA 15-3, can distinguish overtly malignant mucinous cystic neoplasms from benign or pre-malignant mucinous neoplasms.[75] Management decisions based on aspiration cytology alone[75,80] cannot, however, be recommended, and if the benign character of a cystic pancreatic lesion cannot be properly verified, surgical exploration and removal are recommended.

SUMMARY

Hepato-biliary and pancreatic resection can nowadays be performed safely with a low post-operative morbidity and mortality, and minimal long-term sequelae.[84] Therefore, all biliary or pancreatic lesions that cannot be surely classified as a benign lesion and in which long-term malignant transformation cannot be ruled out should be removed, especially in younger patients. In cases of an unclear pancreatic lesion, most pancreatologists believe that surgical resection is the best treatment, be it a Whipple procedure for tumours in the head of the pancreas, a distal pancreatectomy for those located in the body or tail, or a total pancreatectomy in those whose tumorous lesions are located within the whole organ. Only a few cases, however, still require a total pancreatectomy.[75,77] In benign lesions, organ-preserving operations such as a duodenum-preserving pancreatic head resection or a segmental pancreatic resection should be performed. All mucinous cystic neoplasms should be considered to be malignant and should be treated as such since extensive histological sampling (and thus certainty of benignity) cannot be achieved until the tumour has been completely excised. If metastases are present and resectable, they should also be resected, along with the primary tumour, especially in the absence of co-existing risk factors.[75]

Practice points

Pre-malignant lesions of the biliary tract
- pre-malignant lesions are rare
- there is a lack of clear data to define their malignant potential
- the frequency of, and time span required for, malignant transformation cannot be defined
- gallbladder lesions (adenomyomatosis and gallbladder polyps) should be treated early by surgery; cholecystectomy is simple and safe
- lesions of the biliary ductal system resulting from cholangitis, primary sclerosing cholangitis and choledochal cysts should be carefully monitored and the timing of surgery individualized
- any suspicion of malignancy warrants surgical exploration without delay

Pre-malignant lesions of the pancreas
- pre-malignant lesions are rare and often cannot be precisely defined
- alcoholic chronic pancreatitis is associated with a higher risk of pancreatic cancer
- the cumulative risk of pancreatic cancer in hereditary chronic pancreatitis is much higher than in alcoholic chronic pancreatitis, approaching nearly 40%
- intraductal papillary tumours should be resected
- mucin-producing tumours of the pancreas should be resected, especially in young patients
- serous cystadenomas are benign whereas mucinous cystadenomas have an overt malignant potential – if a clear diagnosis cannot be established, surgical exploration should be considered
- any suspicious pancreatic lesion warrants surgical exploration

Research agenda

For pre-malignant lesions of both the biliary tract and pancreas
- to define the molecular profile and the genes that are altered
- to define molecular markers that could predict the risk of carcinogenesis

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BEST PRACTICE & RESEARCH

8

Colonic screening and surveillance

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Screening for colorectal cancer has not obtained worldwide acceptance in spite of its proven survival benefit for average-risk persons and some high-risk groups. The incidence of and mortality from colorectal cancer are worrying in Europe as well as in the USA, Australia and Japan. The best evidence-based studies are those published on screening using faecal occult blood tests, endoscopic methods and different tumour markers having been evaluated to a lesser degree. Feasibility studies are necessary before massive screening can be undertaken because the results obtained from randomized studies may not be reproduced to a satisfactory degree in average- as well as high-risk populations. Primary prevention by dietary intervention and drugs has been studied in great detail, so far without any major breakthrough. This chapter will address different screening methods in populations with a varying risk of colorectal cancer, together with providing a short review of prevention and intervention strategies.

Key words: adenoma; colonoscopy; colorectal; colorectal cancer; faecal occult blood test; hereditary cancers; inflammatory bowel disease; polyps; prevention; screening; sigmoidoscopy.

The symptoms of colorectal carcinoma (CRC) are often non-specific and occur late in the course of the disease by which time the outlook is unfavourable. Therefore, much effort has been put into the detection of asymptomatic CRC and even possible precursors to CRC (adenomas). High-risk as well as average-risk groups have been targeted, the latter possessing an increased risk of CRC over the age of 50 years and representing at least 80% of all CRCs. The screening techniques used are legion, but only a few have been evaluated in a scientific way.

Eliminating the risk of CRC is possible by surgical removal of the colon and rectum. It may also be possible to influence the risk by pharmacological and dietary intervention (so far to a minor degree), but the scientific evidence for this is not strong.

FAMILY HISTORY

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is followed by CRC in nearly 100% of the patients unless the colon is removed. Today, however, FAP seldom results in CRC in countries with a polyposis register. Such registers organize biennial sigmoidoscopy from the age of 12–14 years in both first degree relatives who are confirmed gene carriers and first-degree relatives in whom no genetic diagnosis has been reached. When adenomas have

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