
Preface

Following its publication in 1996, our book *Pankreaserkrankungen (Diseases of the Pancreas)* met with a great response. However, in the intervening seven years, the first German edition has lost its timeliness. We have summarized the vast amount of new knowledge gained in the interval in this revised edition now in its first English translation. Besides the readers, our thanks are due to the many reviewers for their praise and criticism, which are reflected in this interdisciplinary American and European revision. The new, completely revised second edition represents a summary of the evidence-based literature and the authors' own expertise in the field of diseases of the pancreas over many years. We have included up-to-date data on the diagnosis and treatment of acute pancreatitis. Besides the new necrosis markers, we have paid particular attention to techniques of imaging by means of magnetic resonance tomography and to the various randomized controlled studies on treatment.

In the chapter on chronic pancreatitis, we revised the etiology and classification and dealt in considerably greater depth with clinical aspects, pancreatic function and imaging procedures, including new clinical studies on evidence-based treatment.

With regard to pancreatic neoplasms, we focused on imaging with the use of the newer technique of spiral CT and the ultra-fast magnetic resonance tomography of the 'all-in-one' technique. The latter permits the simultaneous visualization of morphology and the state of blood vessels and ducts. Particular attention has been paid to aspects that will be of increasing importance in the future, i.e. molecular biology and gene polymorphisms that may explain many of the diverse individual responses to different disease states. At the end of the book, there is a comprehensive list of references, divided according to criteria of evidence-based medicine, to give readers an opportunity to study the relevant papers themselves. We deliberately refrained from incorporating references into the text in order not to interrupt the flow of reading.

This second, fully revised, edition is designed to go beyond subject boundaries in order to serve the welfare of our patients with diseases of the pancreas.

Heidelberg/Bochum/Magdeburg/
Rochester, Minn.
in 2004

Markus W. Büchler
Waldemar Uhl
Peter Malfertheiner
Michael G. Sarr

Neoplasms of the Pancreas

| | |
|-----|---------------------------------------|
| 126 | Characteristic Cases 1–3 |
| 132 | An Atypical Case |
| 134 | Definition and Classification |
| 136 | Pancreatic Carcinoma |
| 156 | Periampullary Carcinoma |
| 160 | Endocrine Pancreatic Neoplasms |

Case 1

Male, 72, married, 2 children, teacher

History

Four weeks previously, the patient noticed his urine was becoming increasingly brown in color. Two weeks later, his wife found that he had icteric sclerae. The patient finally consulted his doctor because of excruciating pruritus. No weight loss.

Findings

Marked jaundice and multiple skin scratch marks. His abdomen was soft, and a round palpable mass could easily be felt in the right upper abdomen in the region of the gallbladder (Courvoisier's sign).

Body weight 81 kg (178 lb), height 178 cm (5 ft 10 in). Body temperature 36.5° C (rectal), heart rate 72/min, blood pressure 145/80 mm Hg.

Laboratory Parameters: Hemoglobin 11.8 g/dl, leukocytes $7.8 \times 10^9/l$, AST 80 U/l, ALT 64 U/l, alkaline phosphatase 718 U/l, γ -GT 365 U/l, bilirubin 158 mg/dl, INR 1.3.

Ultrasonography

On ultrasonography, there was a dilated gallbladder with dilatation of intra- and extrahepatic bile ducts. No stones in the gallbladder or any space-occupying lesion could be seen. The pancreatic duct was diffusely dilated.

CT with Contrast Medium

CT showed dilatation of the intrahepatic bile ducts with the hepatic parenchyma of normal size and density. The gallbladder was dilated as was the common bile duct (1.4 cm) all the way distally (intrapancreatically) down to near the papilla. There was a suspicion of mass close to the papilla without evidence of metastases.

ERCP

The papilla of Vater was distended and a mass 1.5 cm in diameter was found at the papilla. Using contrast medium the common bile duct was dilated to 1.4 cm but without stones; there was stenosis in the region of the papilla. The pancreatic duct was markedly dilated. A plastic stent was inserted for decompression of the bile ducts. Biopsy of the papilla showed a moderately differentiated adenocarcinoma.

Diagnosis

Periampullary carcinoma (papilla).

Management

Preoperative evaluation for surgery.

Course

Preoperative cardiopulmonary risk assessment. Therapy with vitamin K. Laparotomy with removal of the neoplasm via a pylorus-preserving pancreaticoduodenectomy. Final histology: periampullary carcinoma, moderately differentiated, UICC stage T₂N₀M₀. Discharged from hospital after 3 weeks in good condition on regular diet.

Prognosis

5-year survival of 30–40%.

Case Record

| | |
|--------------------|--|
| History | 4-week history of brown discoloration of urine and increasing jaundice with pruritus |
| Diagnosis | Periampullary carcinoma (papilla) |
| Findings | Painless obstructive jaundice; palpable gallbladder (Courvoisier's sign) |
| Laboratory results | Alkaline phosphatase 718 U/l, γ -GT 365 U/l, bilirubin 158 mg/dl, INR 1.3 |
| Ultrasonography | Dilated gallbladder and intrahepatic and extrahepatic bile ducts |
| CT | Suspected mass in the region of the papilla without evidence of metastases |
| ERCP | Papillary neoplasm 1.5 cm in diameter with dilatation of the entire biliary tree; pancreatic duct dilated; insertion of a plastic endoprosthesis (stent); biopsy of the papilla (adenocarcinoma) |
| Treatment | Pylorus-preserving pancreaticoduodenectomy, lymph node dissection |
| Prognosis | Stage T ₂ N ₀ M ₀ ; 5-year survival of 30–40% |



CT. Mass with uptake of contrast medium (arrow) in the region of the papilla.



Diagnosis of a papillary neoplasm on endoscopy.

Definition and Classification

Our recognition of neoplasms of the pancreas has markedly increased in frequency in the last 60 years. They account for nearly one third of all pancreatic diseases. The increase in neoplastic pancreatic diseases is related in part to the fact that human beings live longer – neoplasms of the pancreas are diseases of the elderly – but also because more are detected due to improved diagnostic techniques. The most frequent neoplasm of the pancreas is pancreatic ductal adenocarcinoma (approximately 80% of all neoplasms), followed by periampullary or ampullary carcinoma, and endocrine neoplasms of the pancreas. These three principal neoplasms will be discussed below in accordance with their clinical importance.

Pancreatic neoplasms are divided according to the WHO classification into benign and malignant neoplasms arising from the exocrine or endocrine portion of the pancreas.

Benign Neoplasms

Benign pancreatic neoplasms are rare. Most arise from the endocrine system. Benign exocrine neoplasms, the next most frequent, are benign cystic neoplasms, such as serous cystadenoma, mucinous cystadenoma, or the rare solid pseudopapillary neoplasm of the pancreas. To date, a few hundred of these benign exocrine neoplasms have been described in the world literature. They may occur in all parts of the pancreas, with a predilection for the body and tail of the pancreas. Women between 40 and 60 years old are most often affected. The clinical features of benign exocrine neoplasms of the pancreas usually includes atypical upper abdominal pain, which sometimes radiates to the back or they may be totally asymptomatic. The slow course and growth character-

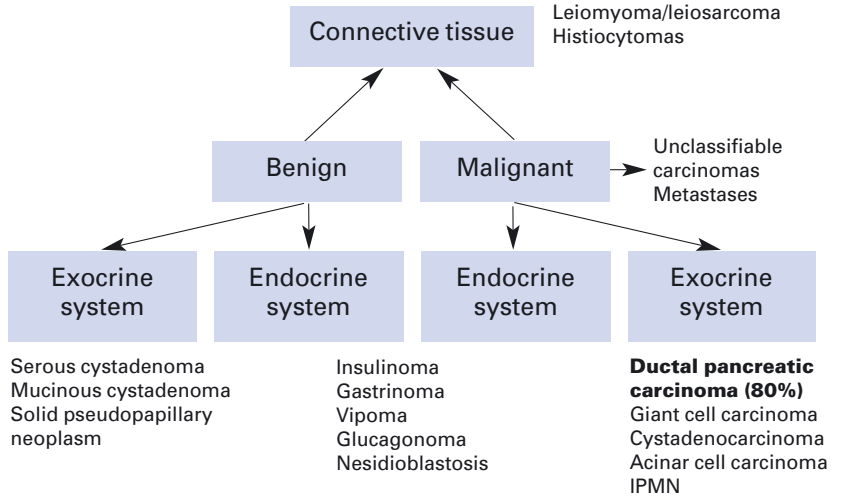
ized by the mass effect of these neoplasms account for the atypical symptomatology. The symptoms generally develop slowly, over a period of years, and are caused on occasion by external compression of the bile duct with jaundice or the duodenum with gastric outflow obstruction. Benign neoplasms of the pancreas should be treated surgically, usually by resection of the affected portion of the pancreas.

Malignant Neoplasms

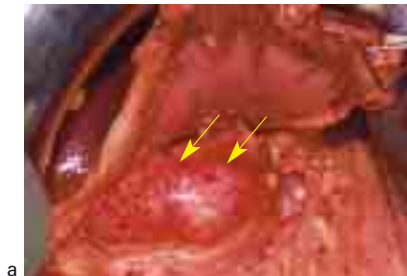
The most frequent cancer of the pancreas is ductal pancreatic carcinoma (80% of all patients). A series of rare malignant neoplasms arise from exocrine tissue (5–10%), such as giant cell carcinoma, cystadenocarcinoma, acinar cell carcinoma or the recently increasingly recognized intraductal papillary mucinous neoplasm (IPMN) of the pancreas. IPMN is an intraductally growing mucin-producing neoplasm which leads to dilatation of the pancreatic duct and is characterized histologically by papillary formation with cell atypia. Clinically, these neoplasms are usually asymptomatic, but can also present as recurrent pancreatitis or masquerade as chronic pancreatitis with pain and steatorrhea. However, in more than 30% of patients they transform into invasive carcinoma. These neoplasms are being recognized with increasing frequency and currently account for 10 to 15% of all resections for pancreatic neoplasms.

Connective tissue neoplasms, such as leiomyosarcoma or histiocytoma, as well as neurogenic neoplasms or metastases, occur extremely rarely in the pancreas.

Classification



Macroscopic Preparations



a

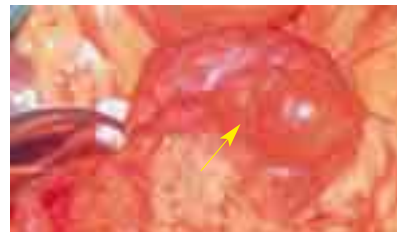


b

Serous cystadenoma of the pancreas involving the whole pancreas (atypical case of page 132). Intraoperative site (a; arrows = neoplasm) and dissected specimen (b).



Surgical preparation. Carcinoma of the head of the pancreas with infiltration of the bile duct (probe).



Cystadenocarcinoma. Intraoperative site with cystic space-occupying lesion (arrow) in the body of the pancreas.

Pancreatic Carcinoma

As in the past, carcinoma of the pancreas presents major diagnostic and therapeutic problems. In most patients, the diagnosis is made too late. Apart from resection in the early stages, therapeutic options are limited. Thus, the aim for the future is to be able to diagnose this neoplasm early in order to improve the extremely poor prognosis.

Epidemiology

Carcinoma of the pancreas appears to have an increasing incidence throughout the world. It is more frequent among males (male:female ratio of 1.5-2:1). In Western industrialized countries, the frequency is currently 10 cases per 100,000 inhabitants. In the United States, approximately 25,000 new cases are recorded each year, while in Germany the figure is 6,000–8,000. Carcinoma of the pancreas is the 4th most common cause of cancer-related mortality for males (after carcinoma of the bronchus, prostate and large intestine). The highest incidences, of up to 20 cases per 100,000 inhabitants, are found among African-American males, while the lowest incidences – approximately 1 case per 100,000 inhabitants – are found in India, Singapore and Kuwait.

Carcinoma of the pancreas is typically a disease of old age, with a peak incidence between the ages of 60 and 80. While the incidence in 30-year-olds is 0.1 case per 100,000 inhabitants, among 80-year-olds the incidence is about 200 cases per 100,000.

Etiology

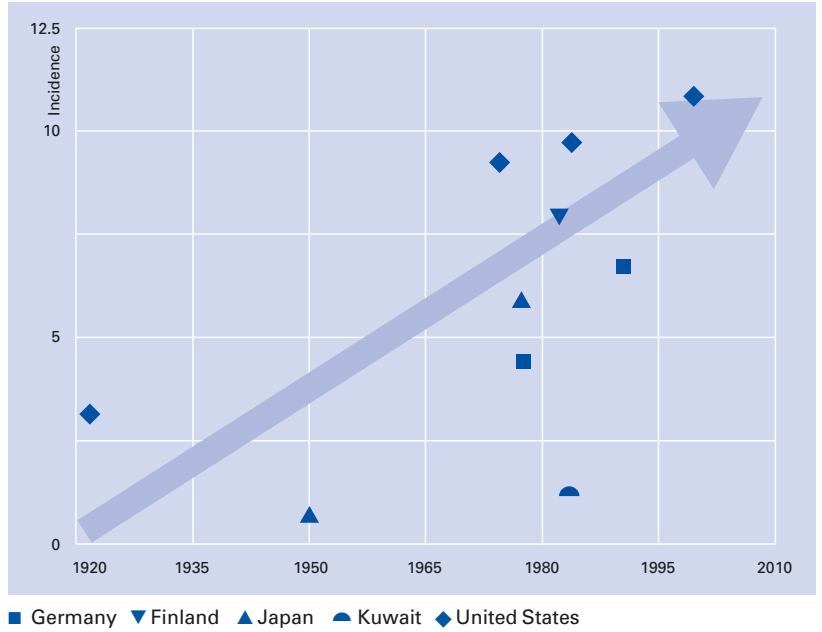
The etiology of carcinoma of the pancreas is not known. Factors that favor its occurrence include smoking and a diet with a high fat content.

No association has been shown between a high consumption of alcohol or coffee and carcinoma of the pancreas. Insulin-dependent diabetes mellitus also does not represent a risk for carcinoma of the pancreas; however, new onset of diabetes mellitus in a nonobese patient older than 40 years should alert the physician to the possibility of an underlying pancreatic cancer. In animal studies, carcinoma of the pancreas may be induced by long-term treatment with carcinogens, such as azaserine or nitrosamines. We therefore assume that these or other carcinogens are also involved in humans as cofactors in the development of carcinoma of the pancreas. This is also supported by the occurrence of this disease in advanced age.

Genetic Predisposition and Factors

Studies to date have shown that in about 10% of patients with carcinoma of the pancreas there is a genetic predisposition. Various diseases, with their known genetic alterations, have now been directly associated with the development of carcinoma of the pancreas. Hereditary pancreatitis, acquired in an autosomal dominant manner, involves a 70- to 100-fold increased risk, while long-standing chronic alcohol-induced pancreatitis shows a 5- to 15-fold increased risk of carcinoma. Patients with cystic fibrosis have a 5-fold increased risk of the occurrence of pancreatic carcinoma. Through epidemiologic studies, certain nonpancreatic diseases show an increased risk of carcinoma of the pancreas, e.g. the Peutz-Jeghers syndrome (by up to 132 times), dysplastic nevus syndrome (by 13–65 times), familial breast carcinoma (by 3.5–10 times), and familial polyposis coli (by 4.5 times).

**Incidence per
100,000
Inhabitants**



**Carcinoma of the
Pancreas:
Nutritional and
Toxic Risk Factors**

| Risk factors | Increase in risk of carcinoma, % |
|---|----------------------------------|
| Smoking | 14–33 |
| High-fat diet | 12–36 |
| Carcinogens (azaserine, nitrosamine) | ? |
| Coffee | no association |

Carcinoma of the pancreas that occurs with increased frequency among family members (at least 3 first-degree relatives) involves an approximately 57-fold increased risk. The genetic cause of hereditary carcinoma of the pancreas was recently localized on the long arm of chromosome 4. The increased risk of familial pancreatic cancer may possibly be decreased by treatment with β -carotene, COX II inhibitors, or stopping smoking.

The molecular pathogenesis of carcinoma of the pancreas has been investigated intensively. Activation of the transforming oncogene K-ras and inactivation of tumor suppressor genes have been identified in pancreatic tissue and pancreatic secretions. K-ras is dominantly inherited on chromosome 12 and is believed to transform cells into malignancies. The tumor suppressor genes include p53, the best known one, which is activated in response to DNA injury and is involved in its repair. Other tumor suppressor genes are DPC4, CDKN2, BRCA-2 and SMAD4. The fact that these genes are secreted in pancreatic secretion enables them to be used potentially in molecular diagnosis and screening. The accuracy of brush cytology during ERCP with identification of K-ras or p53 is about 85% for the presence of a carcinoma of the pancreas.

This new field of research offers hope that further genes and their penetrance will be identified, and thus their clinical importance described. Specific precautions and/or treatments (prophylactic surgery, gene therapy) will then need to be established in the future.

Pathologic Anatomy

Ninety percent of all pancreatic carcinomas arise from the ductal epithelium; about 80% of all

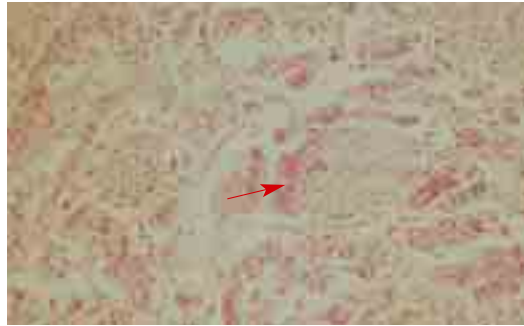
pancreatic carcinomas arise in the head of the pancreas, and 80% have already metastasized at the time of diagnosis, i.e. it is a very aggressive cancer. Particularly typical for the biology of the tumor is invasion of the intrapancreatic nerve sheaths, which also causes the characteristic back pain. Lymphatic metastases occur in two thirds of patients. In the case of hematogenous metastasis, the liver is affected in 80% of patients. Next in frequency of metastasis are the lungs and peritoneal surfaces; the adrenal glands, kidneys, pleura, and skeleton are more rarely affected. Histologically and on electron microscopy there are three grades of tumor differentiation: grade 1 is a highly differentiated carcinoma (40% of tumors), grade 2 is a moderately differentiated adenocarcinoma (approximately 50%), and grade 3 is a poorly differentiated or undifferentiated adenocarcinoma (approximately 10%).

Molecular Biology

Carcinoma of the pancreas is characterised by particularly aggressive and invasive growth, together with a poor overall survival of patients. The last 15 years have seen intensive research worldwide on the study of the tumor biology and especially the control of growth and metastases of pancreatic carcinoma. After transformation, neoplastic cells need 'growth factors', which bind to receptors on the cell surface. These factors include amongst others epidermal growth factor (EGF), transforming growth factors (TGF- α , - β) and fibroblast growth factors (BFGF), which have receptors of the same name on the tumor surface (e.g. EGF receptor).

In terms of tumor biology, malignant growth is characterised by various features: (a) auton-

Pathologic Anatomy



Histologic preparation. Carcinoma of the pancreas (arrow) with infiltration of nerves.

Carcinoma of the Pancreas: Genetic Predisposition

| Disease | Gene | Remarks | Increase in risk of carcinoma, % |
|--|--|---|----------------------------------|
| Chronic pancreatitis | disease-modulating genes SPINK1, CFTR (others) | genetic and environmental factors (alcohol) | 5–15 |
| Hereditary pancreatitis | PRSS1 (approx. 70%) | autosomal dominant, point mutations, approx. 80% penetrance | 70–100 |
| Familial carcinoma of the pancreas | 4q32–34 | autosomal dominant, reduced penetrance | 56 |
| Cystic fibrosis | CFTR | autosomal recessive, point mutations, mutations in 5% | approx. 5 |
| Familial atypical multiple-mole melanoma | CDKN2A CDK4 | autosomal dominant, point mutations | 13–65 |
| Peutz-Jeghers syndrome | STK11/LKB1 | autosomal dominant | ≤132 |
| Familial breast carcinoma | BRACA2 | autosomal dominant, reduced penetrance, point mutations | 3.5–10 |
| Familial polyposis coli | APC 8 (approx. 80%) | autosomal dominant, point mutations | 4.5 |

omous control of growth (EGF, FGFs), (b) resistance of neoplastic cells to growth inhibition (TGF- β), (c) resistance to apoptosis, e.g., pancreatic carcinoma cells have developed intracellular mechanisms that circumvent programmed cell death (EGF, IGF = insulin-like growth factor), (d) induction of neoangiogenesis as an important precondition for tumor growth through growth factors such as vascular epithelial growth factor (VEGF) or fibroblast growth factor (FGF-2), and (e) invasion and metastasis, in order to penetrate the surrounding tissue and to achieve deposition of tumor cells from the primary tumor with the formation of distant metastases. For invasion, growth factors such as TGF- β s, nerve growth factor (NGF) and hepatocyte growth factor (HGF) play an important role, while for metastases, a change in the expression and function of cell adhesion systems (e.g. the loss of E-cadherin expression) is important. Other important molecules that play a leading role in metastasis are proteases, e.g. matrix metalloproteinases or the urokinase/plasminogen system. Deregulated expression of these enzymes leads to the neoplastic cells breaking down the extracellular matrix and being able to better penetrate the surrounding tissue. The positive effects found in animals with the use of matrix metalloproteinase inhibitors have to date not been realized as yet in patients.

In pancreatic carcinoma, the receptors on the cell surface are, in most cases, increased in number and the cell itself also produces greater quantities of growth factors. This type of transformation stimulates further growth with invasion and metastasis, thereby negatively influencing the prognosis of patients. Immunohistochemical studies in human pancreatic carcinoma tissue

showed that patients who overexpressed both the EGF receptor and EGF and/or TGF- α had a significantly shorter postoperative survival than patients who did not have simultaneous overexpression of the receptor and ligand. TGF- β s, in contrast, inhibit the growth of epithelial cells, influence the structure of the extracellular matrix, stimulate angiogenesis, and furthermore have an immunosuppressant effect. Overexpression of TGF- β s in pancreatic carcinoma cells is accompanied by more aggressive tumor growth, which is associated with a markedly reduced survival.

These different families of growth factors and receptors interact with each other in a complex manner, the exact description of which is beyond the scope of this book. In the future, new techniques in molecular biology could, however, result in new treatment strategies for curative and/or palliative treatment of carcinoma of the pancreas, as well as allowing much more sensitive and specific diagnostic techniques. Therapeutic options include, for example, the inhibition of individual components of the EGF family (e.g., tyrosine kinase inhibitors for blockade of the EGF receptor) or other growth factors and their receptors.

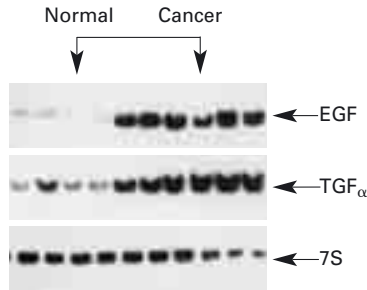
Staging

From the clinical standpoint, it is important that all neoplastic diseases are staged uniformly with regard to their local and distant extent. In accordance with an international agreement (UICC, 1993), the TNM system is now used clinically to classify and describe pancreatic cancer. The T category describes primarily the size and local extension of the primary tumor. For carcinoma of the pancreas, the categories range from T₀ (no identifiable primary site) to T₄ (tumor

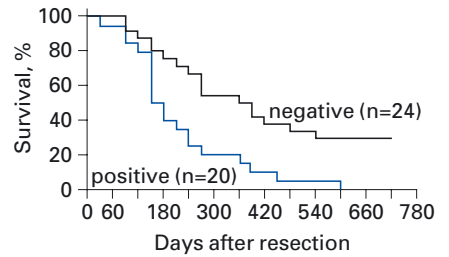
Basic Characteristics of Malignant Growth

| Characteristics of malignant growth | Pancreatic carcinoma |
|-------------------------------------|--|
| Autonomous growth control | Increased expression of EGF, FGF, PDGF, IGF and their receptors |
| Resistance to growth inhibitors | Increased expression of TGF- β s and their receptors, but Smad4 mutations, Smad-6 and Smad-7 hyperexpression |
| Resistance to apoptosis | Increased expression of EGF, IGF and their receptors |
| Angiogenesis | Increased expression of VEGF, FGF-2 and their receptors |
| Invasion and metastases | Increased expression of HGF, TGF- β s, NGF and their receptors |

Molecular Biology



Increased expression of EGF and TGF α in pancreatic carcinoma.



Reduced survival in patients with increased density of growth factors (EGF, EGFR, TGF α).