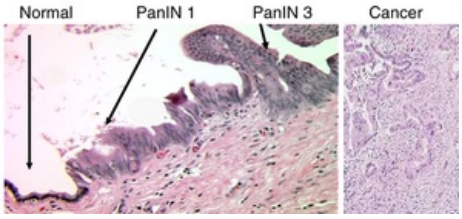
Pancreatic carcinoma

Pancreatic carcinoma is a malignant tumor arising from the exocrine part of the pancreas, most often it is a solid **adenocarcinoma**, less often cystic tumors (< 5%). The origin of the malignant elements is mainly from the epithelium of the **pancreatic ducts**, approximately one percent are from acini cells. Macroscopically, it is a resistant nodule of a yellowish color with central necrosis or vascularization.



Development of pancreatic cancer from pancreatic duct epithelium PanIN1 is epithelial hyperplasia, PanIN3 is carcinoma in situ (does not pass through the basement membrane)

In addition to its increasing incidence in the population, which has not yet been satisfactorily explained, it has a **high mortality rate**, even in cases of early detection of malignancy. It affects men slightly more often than women. In recent years, it has been ranked fourth in terms of mortality (after lung cancer, colorectal cancer and breast cancer). Only 4% of patients live to five years after diagnosis, and the majority do not live beyond one year. Nowadays, the disease is often diagnosed at an advanced stage. Clinically, it is often asymptomatic for a long time or the symptoms are so subtle that they do not attract the attention of the patient or the treating physician. The tumor markers commonly used in the diagnosis do not have significant diagnostic value as they are not specific for pancreatic cancer.

External risk factors

Age

It represents the strongest risk factor. Under the age of 30, the disease is rare, after this age the incidence rises sharply and the peak is reached in the seventh and eighth decades

Smoking

A significant risk factor for the development of the disease, it is associated with a two- to threefold increase in the risk of malignancy. The mechanism is based on the action of tobacco **N-nitrosamines** directly on target cells or by their secretion into bile with possible reflux into the pancreatic ducts. Passive smoking has not been confirmed as a risk factor.

Alcohol

Alcohol is currently confirmed only as an indirect risk factor for developing cancer. It is possible through its ability to induce chronic pancreatitis, which is a recognized as an endogenous risk factor.

Dietary factors

High intake of meat, cholesterol and fried foods are risk factors as well. On the other hand, vegetables, fruits, fiber, vitamin C and other antioxidants prevent the development of cancer..

Internal risk factors

Chronic pancreatitis

Chronic inflammation induces genetic changes in the tissue and the simultaneous healing process exposes the defective cells to growth factors produced by activated macrophages. These are TNF-α, IL-1, IL-6, IL-8, EGF, PDGF, TGF-α, TGF-β (transforming growth factor). Growth factors induce cell proliferation (they accelerate cell division and thus increase the likelihood of stabilizing genetic mutations in the cell population), angiogenesis and desmoplastic response. TGF-α inhibits the processes leading to apoptosis through activation of NF-κB (nuclear factor kappa B), which acts as a transcription factor but also stimulates the production of reactive nitrogen oxide, cyclooxygenase-2 (COX-2) and induces IL-8 expression. COX-2 increases the amount of anti-inflammatory prostaglandins, which are able to facilitate cell proliferation and angiogenesis during inflammation and carcinoma, in addition it inhibits apoptosis. Reactive oxygen and nitrogen forms (produced by neutrophil granulocytes or generated by COX-2 activity) are directly related to DNA structural defects. **People with chronic pancreatitis have a 16 times higher risk of developing pancreatic cancer compared to the healthy population.** The time interval between the diagnosis of chronic pancreatitis and pancreatic cancer is 6-13 years. The increase in risk is mainly influenced by the duration of chronic pancreatitis and smoking.

Diabetes mellitus

The risk is represented by type 2 diabetes mellitus, that is insulin resistance of target cells. In this situation, there is even an overproduction of insulin. Tumor cells often overexpress the insulin receptor. Its overactivation stimulates, among others things, mitosis.

Familial burden

This refers to families in which a mutation in a proto-oncogene, mismatch repair gene or tumor suppressor gene is present and inherited. Typical examples include mutations in the p53 gene (Li Fraumeni syndrome), MMR genes (Lynch syndrome), inherited BRCA2 mutations, and a syndrome that links pancreatitis, diabetes mellitus and pancreatic cancer to a previously unidentified gene locus.

Hereditary pancreatitis

An autosomal dominantly inherited disorder usually caused by a defect in the trypsinogen gene. Those so affected have a **40 times higher risk of developing cancer** than the healthy population.

Other

Other risk factors include mainly post gastrectomy status, cholelithiasis, cholecystectomy.

Molecular genetic mechanisms of pancreatic cancer

For a text on the genetic background of pancreatic cancer, see Molecular genetic mechanisms of pancreatic cancer

Clinical symptomatology

Clinically, the carcinoma may be **asymptomatic** until late stages; symptoms may often be based on the location of the tumor - **obstructive icterus** (in carcinomas of the head of the pancreas), vomiting in duodenal obstruction, **epigastric pain** with propagation to the back, **weight loss**, loss of appetite, **indigestion** (pancreatic insufficiency with steatorrhea), thrombophlebitis migrans of the veins of the lower limbs (paraneoplastic). In the late stages, portal hypertension with the development of esophageal varices or hemorrhagic ascites with spreading to the peritoneum.

Diagnostics

For diagnosis, imaging methods such as ultrasonography (USG), endoscopic ultrasonography (EUS), CT, PET, ERCP are used today. Methods are constantly being sought to detect cancer at an early stage. Peripheral blood testing for tumor markers is offered. Elevated carcinoembryonic antigen (CEA), alpha fetoprotein (AFP) and pancreatic oncofetal antigen (POA) can be detected but are not specific. For this reason, part of the scientific work is focused on the search for an ideal marker that can be obtained from peripheral blood to avoid invasive biopsy or ERCP. Currently, there are procedures that can detect early K-ras gene mutations in circulating metastatic cells (present in the peripheral blood) or detect mutations of the same gene in tumor epithelial cells that enter the stool with the pancreatic juices.

Biological behavior

This tumor is characterized by **perineural spread** (penetration into nerves - usually splanchnic nerves), which is a source of severe pain. In more advanced stages, it can also **spread into the surrounding organs** (bile ducts, duodenum, blood vessels), spreading to the peritoneum is common. It metastasizes to local lymph nodes (nodi lymphatici hepatici - from the head of the pancreas, nodi lymphatici coeliaci et pancreaticolienales - body and tail), **haematogenously into the liver**, later into the lungs and bones.

Current therapy

Surgical treatment

Surgical procedures can be curative - resection or palliative, contraindication to resection is significant tumor penetration into large vessels (v. + a. mesenterica superior, v. portae, even their partial resection is possible) or metastases into the liver and spread to the peritoneum. Despite advanced imaging methods, tumor penetration into blood vessels is often detected only by the surgeon perioperatively. Nerve penetration (usually into the splanchnic nerves) cannot be detected.

Curative interventions

The aim is to cure the patient, they are divided according to the tumor localization and extent of affected area, **after resection it is necessary to monitor the exo- and endocrine functions of the pancreas and, if necessary, to provide substitution** with pancreatic enzymes and insulin

1. resection of the pancreatic cauda (resection of the parenchyma with tumor + regional lymphadenectomy + resection of the duodenum, possibly splenectomy),
2. partial duodenopancreatectomy (**Whipple resection**),
3. total duodenopancreatectomy with gastrojejunal anastomosis.

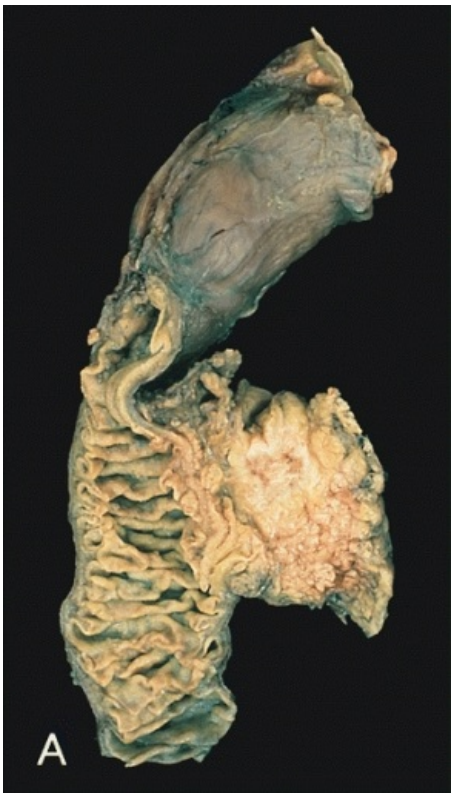
Palliative interventions

in advanced tumors, solves life-threatening complications

1. when obstructive icterus - biliodigestive anastomosis (hepaticojejunal anastomosis),
2. when duodenal stenosis - gastro-jejunal anastomosis,
3. when severe pain - sympathectomy.

Radio and chemotherapy

They generally have very **little efficacy**, these therapies are palliative in most cases. Of the cytostatics, **gemcitabine** (a nucleoside analogue, also tried in combination with other agents) is the standard treatment, but even then patient survival is a few months.



Small adenocarcinoma of the pancreatic head, after Whipple's resection

Conclusion

In conclusion, it is important to say that **the prognosis of this disease is very poor**. The chance to improve it or prolong the patient's life is to catch the malignancy early, which is still not possible due to asymptomaticity. It is important for physicians to identify patients at risk (over 65 years of age, recurrent chronic pancreatitis, smokers, obese, ...) and pay special attention to them.

Summary video

<mediaplayer width='500' height='300'>https://www.youtube.com/watch?v=lQAqPlOAYMM</mediaplayer>

Links

Related articles

- Tumours of the pancreas
- Pancreatitis

References

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