MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE

UZHHOROD NATIONAL UNIVERSITY

DEPARTMENT OF ONCOLOGY

Pancreatic cancer

Methodical instructions for 5, 6 year medical students' individual training

Uzhhorod – 2022

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PANCREATIC CANCER

I. Topic actuality:

According to recent studies (American cancer society ,2022) pancreatic cancer is the third leading cause of death in Unites States in both genders (male:25 970, female:23 860). Also, its 4th leading cause of cancer deaths in western countries. which shows us a real fact of bad prognosis and poor work up due to late diagnosis in most of the cases. Pancreatic cancers can arise from both the exocrine and endocrine portions of the pancreas. 95% develop from the exocrine portion of the pancreas and adenocarcinomas account for 75% of all pancreas cancers. Patients with carcinoma of the pancreas are mostly asymptomatic in early stages of the disease. Also present with many different symptoms, some of them related to local pathology such as pain as well as enzymes and hormones insufficiency which may be treated symptomatically for long time by patient of by mistake of medical professional, and some of them related to advanced such as weight loss and mechanical jaundice. Despite the poor prognosis of patients with pancreatic cancer, surgical resection is still the only potentially curative treatment for the disease which can not be frequently offered but only for resectable cases.

II. Teaching aim:

2.1. The student must know:

- epidemiology
- classification
- risk factors
- Clinical presentation
- Clinical workup and staging
- Modern methods of diagnosis
- Treatment
- Follow-up
- prognosis

2.2. The student should be able to:

- Put clinical diagnosis, stage of disease, make a plan of examination and make differential diagnosis of pancreatic cancer and other pancreatic and biliary pathologies.
- Put algorithm of treatment, Assess prognosis of patient.

III. Basic level of knowledge and skills:

- classification and presentation of benign and malignant tumors of the pancreas.
- risk factors, premalignant hereditary syndromes of pancreatic neoplasms.
- methods of investigation and work-up of pancreatic cancer.

IV. The **program of self-preparation of the students**:

№	Task Maintenance	Task maintenance concrete definition
1.	Collecting history.	1. risk factors and family history of pancreatic cancer. 2. epidemiology 3 classification of pancreatic neoplasms 4 common presentation and complains
2.	Work up and treatment plan.	1 differential diagnosis of pancreatic neoplasm. 2 modern methods of investigation, metastatic work-up. 3 staging of pancreatic cancer. 4 treatment plans for local, locally-advanced and metastatic pancreatic cancer. 5 prognosis of pancreatic cancer

V. Short methodical instructions for practical study work.

- After introductory teacher's word, control of the level of knowledge and skills of the students, their approach to pancreatic cancer.
- The group carried out the individual educational tasks.
- The students acquaint with work of the department in oncological clinic.

VI. Content of the topic

Overview

The tumors of the pancreas can be of exocrine and of endocrine origin. Exocrine tumors include Benign exocrine neoplasms ex: adenoma, cystadenoma, lipomas, fibromas, hemangiomas, lymphangioma and neuroma. they are rare and have no significant clinical presentation unless they become palpable or give a pressure to adjacent structures and causes symptoms, they also can be solid, cystic or both.

While malignant exocrine neoplasm includes ductal adenocarcinoma, which accounts for 90% of pancreatic tumors and 2\3rd are located in the head of pancreas, and cystadenocarcinoma.

Endocrine tumors are less common than exocrine tumors and are generally benign insulinoma, glucagonoma and less commonly gastrinoma, somatostatinomas, VIPoma (vasoactive intestinal polypeptide)

Incidence and epidemiology

Pancreatic cancer was the fourth most fatal cancer in men after lung, colorectal, and prostate cancers Similarly, pancreatic cancer was found to be the fourth most fatal cancer in women after lung, breast and colorectal cancers. But 8th in incidence worldwide. And with a life expectancy of 5% at 5 years. the prognosis of this cancer has not much improved over the past 20 years, and incidence and mortality rates are very similar as the disease mostly diagnosed at advanced stage.

the peak incidence being at 60–80 years. It usually arises in elderly patients with a mean age at onset of 71 years for men and 75 years for women. The majority of patients with pancreatic cancer progress to either metastatic or locally advanced disease in the asymptomatic phase. Surgical excision is the definitive treatment with a 5-year survival rate (after resection) of 20%, but it is only possible in 15%–20% of the patients. The opportunity to detect pancreatic cancer, while it remains curable, depends on the ability to identify and screen high-risk populations before their symptoms arise.

Risk factors

The main acquired risk factors for pancreatic cancer are cigarette smoking. exposure to chemical and heavy metals such as beta-naphthylamine, benzidine, pesticides, asbestos and benzene. Also increased BMI and obesity (Tumorigenesis is enhanced by excess adipose tissue, probably through the mechanism of abnormal glucose metabolism). genetic germline accounts for 10 % of all cases of pancreatic cancer

- smoking tobacco
- high dietary fat and meat consumption
- high coffee and/or alcohol consumption
- diabetes mellitus
- chronic pancreatitis
- previous surgery for peptic ulcer disease
- Exposure to industrial carcinogens
- familial cancer syndromes (hereditary pancreatitis, von Hippel-Lindau syndrome, lynch syndrome, ataxia-telangiectasia and others)
- Helicobacter pylori, hepatitis B, and human immunodeficiency virus infection have also been reported to be related to an increase in relative risk of pancreatic cancer.

Table 1: Inherited cancer predisposition syndromes that increase the risk of pancreatic cancer.

Syndrome	Gene(s)	Risk of pancreatic cancer	Predominant features

Hereditary breast and ovarian cancer	BRCA1 BRCA2	RR, 2.26-3 RR, 3.5-5.9	Malignancies: breast (particularly premenopausal), ovary, male breast, prostate. Malignancies: breast (particularly premenopausal), ovary, male breast, prostate, melanoma (cutaneous and ocular)
Familial atypical multiple mole and melanoma	CDKN2A	RR, 7.4-47.8	Malignancies: melanoma. Other: dysplastic nevi
Hereditary pancreatitis	PRSS1	SIR, 57	Other: chronic pancreatitis
Hereditary nonpolyposis colorectal cancer (lynch syndrome	MLH1 MSH2 MSH6 PMS2 EPCAM	SIR, 0-8.6	Malignancies: colorectal, endometrium, ovary, stomach, small bowel, urinary tract, biliary, brain(glioblastoma), skin(sebaceous)
PJS (peutz-jeghers syndrome)	STK11	SIR, 132	Malignancies: colorectal, small bowel, stomach, breast, gynecological. Other: melanin pigmentation(mucocutaneous), small bowel intussusception.

RR relative risk
SIR standardized incidence ratio

Pathology

Pancreatic cancers arise from both the exocrine and endocrine parenchyma of the gland, however, 95% occur within the exocrine portion and may arise from ductal epithelium, acinar cells, or connective tissue. Germline mutations in BRCA2, p16, ATM, STK11, PRSS1/PRSS2, SPINK1, PALB2, and DNA mismatch repair genes are associated with varying degrees of increased risk for pancreatic carcinoma.

The tumor can be well circumscribed or diffusely infiltrating the pancreas; mostly it is arising in the head and are often associated with a dilated common bile duct, and 20 per cent in the body or tail, the remainder being more diffuse in origin. Carcinoma arises from the ducts (90%) and glandular elements (10 %).

Microscopically, these neoplasms vary from well-differentiated duct-forming carcinomas (which may be so well differentiated that they mimic non-neoplastic glands) to poorly differentiated carcinomas.

Cystic neoplasms represent 10%–15% of cystic lesions of the pancreas. The most commonly encountered cystic neoplasms include: serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (either cystadenoma or cystadenocarcinoma). Mucinous lesions have potential for malignant. The non-mucinous lesions have no malignant potential

The tumor infiltrates diffusely through the gland, or might grow along the pancreatic duct system, eventually reaching the common bile duct and ampulla of Vater. The capsule can be breached leading to invasion of the stomach, duodenum, spleen, aorta and retroperitoneal tissues.

Molecular biology

Multiple combinations of genetic mutations are commonly found in pancreatic cancers and can be classified as follows:

- Mutational activation of oncogenes, predominantly KRAS found in >90% of pancreatic cancers.
- Inactivation of tumor suppressor genes such as TP53, p16/CDKN2A, and SMAD4
- Inactivation of genome maintenance genes, such as hMLH1 and MSH2, which control the repair of DNA damage. Most of these mutations are somatic aberrations.

Spreading of pancreatic tumors:

- Local invasion
- Lymphatic
- Hematological
- Via peritoneal and omental ascites
  Regional lymph nodes are frequently involved and include the pancreaticoduodenal, gastroduodenal, hepatic, superior mesenteric and coeliac groups. The distant metastases most commonly seen in the liver, lung, skin and brain.

Staging

Tis (carcinoma in situ) is very early stage pancreatic cancer. It hasn't grown into the deeper layers of tissue within the pancreas. It is uncommon for pancreatic cancer to be diagnosed this early.

T1 cancer is inside the pancreas and is 2cm or less in greatest dimension.

- T1a means the cancer is no more than 0.5cm
- T1b means the cancer is more than 0.5cm but less than 1cm
- T1c means the cancer is between 1cm and 2cm

T2 means the cancer is more than 2 cm in greatest dimension

T3 tumor extends beyond the pancreas

T4 tumor invades visceral vessels (celiac axis and superior mesenteric artery)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M0 means the cancer has not spread to other areas of the body such as the liver or lungs.

M1 means the cancer has spread to other areas of the body.

Clinical presentation

Patients with carcinoma of the pancreas are mostly asymptomatic in early stages of the disease. Also present with many different symptoms. These include abdominal and back pain, weight loss, anorexia and fatigue.The most common presenting symptoms associated with tumors located in the right side of the pancreas (head, neck include jaundice (75%), weight loss (50%), abdominal pain (40%), or nausea (10%). Jaundice occurs as a result of obstruction of the common bile duct and is often associated with pruritus. Other symptoms or findings associated with an obstructed bile duct include acholic stools and dark-colored urine. An obstructed pancreatic duct may induce acute pancreatitis and result in exocrine insufficiency associated with steatorrhea or endocrine insufficiency causing DM. Patients with left-sided tumors (body or tail) typically experience abdominal pain (which radiates to the back), back pain, and nausea and weight loss.

Signs

- Palpable gallbladder Courvoisier Sign a palpably enlarged gall bladder in a jaundiced patient is mostly due to pancreatic tumor
- Palpable Left supraclavicular LNs. (Troiser's sign)
- Abdominal Ascites usually with pruritis.
- Palpable abdominal masses (Big pancreatic tumor)
- Enlarged liver with nodular surface.
- Sister Merry Joseph's node

Differential diagnosis

Gallstones are a common cause of obstructive jaundice and abdominal pain, although they are not commonly associated with systemic symptoms and are not a cause of glucose intolerance. Benign tumors such as a glucagonoma, gastrinoma or VIPoma should also be considered

According to NCCN guidelines, Chronic pancreatitis and other benign conditions are possible differential diagnoses of patients suspected of having pancreatic cancer. Autoimmune pancreatitis, a rare form of chronic pancreatitis also known as lymphoplasmacytic sclerosing pancreatitis, is a heterogeneous disease that can present with clinical and radiologic characteristics of pancreatic cancer, such as jaundice, weight loss, an elevated CA 19-9 level, and the presence of diffuse pancreatic enlargement, a pancreatic ductal stricture, or a focal pancreatic mass ,peripheral rim surrounding the pancreas although focal enlargement of the pancreas is observed in some cases, histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis , an elevated level of serum lgG4 specifically is the most sensitive and specific laboratory indicator.

Investigations

Early symptoms of pancreatic cancer result from a mass effect. Approximately 60%–70% of pancreatic cancer arises in the head of the pancreas, 20%–25% in the body and the tail, and the remaining 10%–20% diffusely involve the pancreas. Tumors located in the body and the tail are likely to be diagnosed at a more advanced stage than tumors located in the head, as these can develop symptoms related to an obstruction of the common.

In many cases of pancreatic head tumors in elderly patients presents with mechanical jaundice dur to common bile duct obstruction.

Lab rotary investigations

Liver function tests These will demonstrate the degree of obstructive jaundice, characterized by raised total serum bilirubin, elevated alkaline phosphatase and γ-glutamyl transferase with normal or slightly elevated liver transferases (ALT).

Clotting profile There will be derangement of vitamin K-dependent clotting factors. This is reflected in a prolongation of the international normalized ratio (INR), and will show clinically as bruising and a tendency to prolonged bleeding.

CA 19-9 is not useful for the primary diagnosis of pancreatic cancer. An increase in serum levels is seen in almost 80% of the patients with advanced disease CA 19-9 has a significant value as a prognostic factor and can be used as a marker to measure disease burden and potentially guide treatment decisions.

A preoperative serum CA 19-9 level ≥500 UI/ml clearly indicates a worse prognosis after surgery.

Imaging work-up

The imaging work-up must determine the tumor size and precise burden, as well as arterial and venous local involvement. All these factors are part of the TNM classification

transabdominal ultrasound mostly would be the initial workup for patients presents with mechanical jaundice

Endoscopic ultrasound (EUS) is now largely used in the staging of adenocarcinoma. EUS valuable in the detection of vascular invasion (Sen 85%, Sp 91%) and prediction of resectability (Se 90%, Sp 86%). The great advantage of EUS is its ability to provide tissue samples, via fine-needle aspiration, that allow up to 95% diagnostic accuracy. EUS also be used to evaluate the periampullary lesions, separates invasive from noninvasive lesions. On EUS, malignant cystic lesions may present as a hypoechoic cystic / solid mass or as a complex system, and they are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions can also be done with EUS (e.g., celiac neurolysis, removal of ascites).

Endoscopic retrograde cholangiopancreaticogram (ERCP) A side-viewing endoscope is passed into the duodenum allowing cannulation of the ampullary duct under direct vision. With an image intensifier, a cannula is advanced into the main pancreatic duct and contrast injected to opacify the pancreatic duct system and extrahepatic biliary tree. Gallstones will appear as filling defects in the ducts while pancreatic carcinoma will lead to distortion and obstruction of the pancreatic ducts and extrinsic compression of the common bile duct. Duodenal and pancreatic aspirates collected through the endoscope can be sent for cytology. (ERCP) is considered as pathognomonic when it shows a double stop on the main bile and pancreatic ducts. However, ERCP had little diagnostic value over CT or MRI for the evaluation of patients with pancreatic cancer. ERCP allows for stent placement and can be used to palliate biliary obstruction when

surgery is not elected or if surgery must be delayed. However, biliary decompression in those without symptomatic hyperbilirubinemia receiving upfront surgery may be avoided.

Computed tomography (CT) of the abdomen This characteristically shows dilatation of the common bile duct associated with a mass lesion in the head of the pancreas, a discrete mass in the body or tail of the pancreas, or diffuse enlargement of the pancreas. All patients considered suitable for radical surgery should undergo this investigation as it is the best way of defining the extent of local invasion, presence of enlarged regional lymph nodes and liver metastases. It also facilitates a fine needle biopsy when a definitive diagnosis cannot be made by less invasive procedures.

Radiological studies should include computed tomography (CT) angiography at the pancreatic arterial and portal venous phases. In the majority of cases, pancreatic adenocarcinoma appears in the pancreatic arterial phase on CT examination, as a hypoattenuating homogeneous mass with indistinct margins. The interruption (with or without dilatation) of the biliary duct is fundamental to specify tumor extension. The presence of calcifications is very unlikely but a cystic part of the tumor can exist, especially when the tumor originates from a degenerating cystic pancreatic lesion. Extra-pancreatic local extension has to be delineated: enlarged lymph nodes (especially in the retro portal space), hepatic or peritoneal nodules are the main metastatic sites.

Each vessel—superior mesenteric artery (SMA), coeliac axis, and common hepatic artery—has to be assessed individually with attention paid to local encasement or abutment and a possible anatomic variant, as these can be crucial for the surgical decision making. The portal vein (PV) and the superior mesenteric vein (SMV) are the major trunks; any local involvement, thrombus, or hazy attenuation of the fat surrounding the vessel.

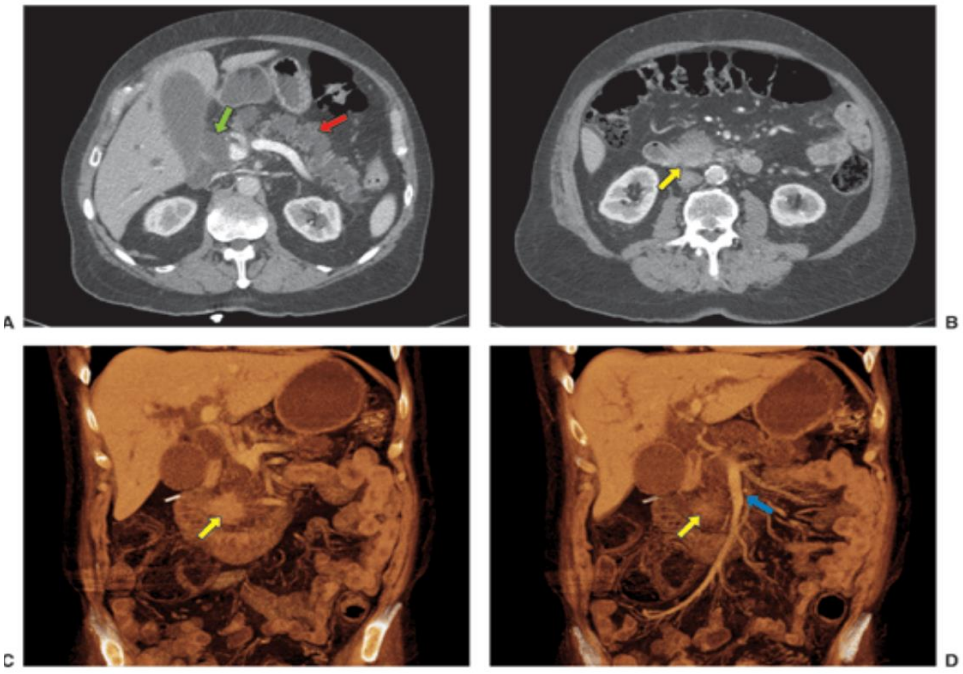


Figure1 :Slices from a triphasic CT scan in a patient with resectable pancreatic cancer. (A) late arterial phase. Double duct sign with dilated common bile and pancreatic ducts, and an atrophic pancreatic body. (B) Mass (C) Coronal reconstruction, venous phase, with the mass apparent,and(D) clearly away from the superior mesentric-portal vein axis

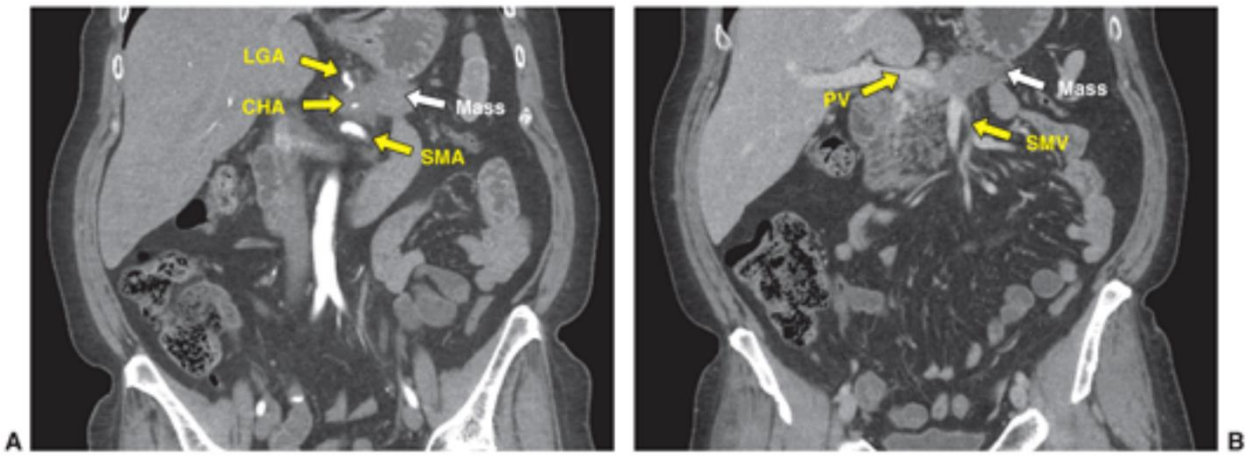


Figure2: CT scan of a locally advanced stage 3 carcinoma of pancreatic body. Coronal images, (A) The arterial phase. Visceral arteries named are left gastric artery (LGA). Common hepatic artery (CHA). And superior mesenteric artery (SMA). (B) The venous phase. the portal splenic confluence is completely occluded.

Magnetic resonance imaging (MRI) The superior soft tissue resolution of MRI is best exploited when curative surgery is contemplated. It is useful for clarifying the local extent of tumor infiltration with regard to adjacent anatomical structures that cannot be sacrificed, and may be of use in surgical planning. When assessing vessel involvement, the use of magnetic resonance imaging (MRI) is left to expert discretion. It shows equal benefit to CT scanning with no superiority demonstrated in studies [13]. However, MRI is useful for solving problems such as the detection of hepatic lesions that cannot be characterized by CT MRI and magnetic resonance cholangiopancreatography may also be preferable for cystic neoplasms of the pancreas and to evaluate biliary anatomy.

Percutaneous transhepatic cholangiography (PTC) A needle is passed through the skin into a dilated extrahepatic bile duct under ultrasound control and a cholangiogram obtained by injecting contrast into the biliary tree. It will visualize any gallstones in the biliary tree, and in the case of carcinoma confirm blockage of the common bile duct by extrinsic compression at the level of the pancreas. PTC also provide a therapeutic benefit while biliary obstruction from pancreatic cancer is usually best palliated by the endoscopic stent placement.

Positron emission tomography (PET) This is now routinely performed to complete whole body staging prior to curative surgery. Careful patient selection is vital for radical surgery where morbidity and mortality are very high. It has the advantage of disclosing the presence of metastatic disease at occult sites in the body (e.g. peritoneal cavity) and can show of active cancer in abdominal lymph.

According to NCCN guidelines the use of PET / CT following a standard CT protocol showed increased sensitivity for detection of metastatic disease when compared with the standard CT protocol. According to a study, the sensitivity of detecting metastatic disease for PET / CT alone (61%,), standard CT alone (57%), and the combination of PET / CT and standard CT were (87%).

Laparoscopy\Laparotomy

Laparoscopy is another potentially valuable diagnostic tool for staging; it can identify peritoneal, capsular, or serosal implants or studding of metastatic tumor on the liver that may be missed

even with the use of a pancreatic CT protocol. The yield of laparoscopy is dependent on the quality of preoperative imaging and the likelihood d of metastatic disease.

Laparotomy Occasionally, it is not possible to make a diagnosis from less invasive investigations. If there are no metastases detected during staging and the tumor is otherwise operable, laparotomy is justified with a view to radical.

Biopsy is indicated for patients requiring a diagnosis, such as patients initiating chemotherapy or chemoradiation. EUS-guided fine-needle aspiration allows preoperative tissue confirmation of malignancy, but fear of tumor cell dissemination along the needle track has limited its use. A recent study has indicated that it could be carried out without consequence on efficacy of surgery. It must be recommended, especially in doubtful cases. Percutaneous biopsy of a liver metastasis can be used in metastatic disease, but percutaneous biopsy of the pancreas is contra-indicated in potentially resectable cases.

According to NCCN guidelines, Biopsy and a pathologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy and for patients staged with locally advanced pancreatic cancer or metastatic disease. A pathologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either EUS guidance (preferred) or CT. EUS-FNA is preferable to CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety , and potentially lower risk of peritoneal seeding with EUS-FNA when compared with the percutaneous approach.

Intraductal biopsies can be obtained via endoscopic Cholangioscopy.

If biopsy does not confirm malignancy, at least 1 repeated biopsy should be performed; B EUS-guided FNA and a core needle biopsy at a high-volume center is preferred, although new methods are being developed for diagnosis of pancreato-biliary malignancies when repeat biopsy is needed, Core needle biopsy is recommended, if possible, for a patient with borderline resectable disease.

Treatment

At the end of the staging procedures, the tumor can be categorized as resectable, borderline resectable, locally advanced or metastatic disease. A treatment decision must be taken in accordance with these findings, including general and nutritional status considerations.

resectability criteria: An expert consensus group has developed criteria to define tumor resectability, to improve patient selection and the rate of R0 resections. According to the degree of contact between the tumor and the vessels (PV or SMV, SMA, coeliac trunk, and common hepatic artery), tumors are classified as resectable, borderline resectable or locally advanced. For patients with resectable tumors, upfront surgery remains the standard of care. Patients with borderline resectable tumors have a high probability of R1 resection and, as such, should not be considered as good candidates for upfront surgery. Patients with locally advanced or metastatic disease have to be considered as having unresectable tumors. These criteria.

Treatment of localized disease

Surgical resection is the only potentially curative treatment of pancreatic adenocarcinoma. However, at diagnosis, <20% of patients have a resectable tumor. The main goal of surgery is to achieve negative (R0) resection margins. After radiological evaluation, only patients with a high probability of R0 resection are good candidates for upfront surgery. surgery is routinely

recommended to all resectable patients unless the patient is interested in participating in neoadjuvant therapy clinical trials or is not medically fit for surgery.

More accurate radiographic diagnosis is one strategy to identify patients who have locally advanced or micro-metastatic disease, as these patients would not benefit from aggressive up-front surgery. Resectable disease with a very high CA 19-9 level without biliary obstruction can be suggestive of systemic micro-metastases, thus these patients may benefit from up-front systemic therapy prior to local therapy (radiation or surgery). Nonetheless, the subset of patients who underwent curative surgery after neoadjuvant therapy had a much longer survival (if they did not progress prior to surgery) compared with those who had up-front surgical resection.

Postoperative (adjuvant) therapy is considered to be the standard of care for resected pancreatic cancer. a combination of chemotherapy and radiation is favored in the adjuvant setting. However, the sequence of chemotherapy and radiation therapy is individualized. Patients with a close or positive resection margin (R1 resection) are treated with chemoradiation therapy (CRT) first, followed by further adjuvant chemotherapy. Patients with node positive disease (regional lymph node metastasis) are treated with 4 to 6 months of systemic chemotherapy first, followed by CRT if there is no evidence of disease at the completion of chemotherapy. Individuals with T1/T2 tumors and N0 resections are usually given 6 months of chemotherapy alone, though some patients also elect to receive adjuvant radiation therapy, these patients are often treated with two cycles of gemcitabine-based chemotherapy, followed by chemoradiation, and concluded by another two cycles of gemcitabine-based chemotherapy. Or 5-FU folinic acid after potentially curative surgical resection.

Borderline Resectable PC

There is a general consensus that patients with borderline resectable pancreatic cancer will benefit from receiving neoadjuvant chemotherapy with chemoradiation prior to surgical resection. Without neoadjuvant therapy, the risk for borderline resectable tumors to have a positive resection margin is high due to the tumor involvement of adjacent vascular structures. It is known that R1 or R2 resection has a significantly poorer survival comparing to R0 resection. By contrast, with neoadjuvant therapy, the rate of margin-negative resections is approximately 80% to 90% with comparable or better survival comparing to initially resectable tumor patients. However, with neoadjuvant therapy, most of the retrospective analyses demonstrated that the resectability rate of borderline resectable tumors is less than initially resectable patients. Therefore, better strategies of chemotherapy or chemoradiation for neoadjuvant therapy remain to be established for borderline resectable tumors. In general, both treatment modalities are considered to be part of neoadjuvant therapy.

Locally Advanced The standard of care is 6 months of gemcitabine.

A study was published almost 30 years ago and demonstrated that radiation concurrently with 5-fluorouracil (5-FU) prolonged the median overall survival from 5.7 months (with radiation alone) to 10.1 months. Since this time, 5-FU combined with radiation therapy has been the standard treatment option for this population. Subsequently, most research efforts were made in testing the role of systemic chemotherapy in addition to chemoradiation, A minor role of chemoradiation in this subgroup of patients has been observed.

The role of systemic chemotherapy in locally advanced pancreatic cancer is emphasized by the high risk of microscopic systemic disease at the time of diagnosis and/or the rapid development of metastases during the course of radiation. In the last decade, induction chemotherapy with a gemcitabine-based combination was tested in multiple single-arm clinical trials.

Metastatic disease

palliative and supportive care Before even considering systemic chemotherapy with gemcitabine chemotherapy combinations with cytotoxic agents such as irinotecan, 5-FU, cisplatin, oxaliplatin and capecitabine. gemcitabine and capecitabine is superior to gemcitabine alone.

patients with metastatic pancreatic cancer may need interventions to provide relief of biliary and/or duodenal obstruction, malnutrition, and pain. In the event of a biliary obstruction due to a pancreatic tumor, the endoscopic placement of a metallic biliary stent is strongly recommended. The endoscopic method is safer than percutaneous insertion and is as successful as surgical hepatojejunostomy. Duodenal obstruction is preferentially managed by endoscopic placement of an expandable metal stent when possible, and is favored over surgery. Pain is also considered to be a major priority in these patients and it is observed in almost all patients with advanced pancreatic carcinoma. It must be managed aggressively following standard guidelines on pain treatment, without any major specificity due to the location of the disease. However, radiotherapy can be used at this stage to control the coeliac pain induced by a primary pancreatic tumor. Oral supplementation of pancreatic enzyme has been suggested to help control pain; though this has never been proven by a randomized study and should not be considered as a reason to prescribe such drugs. The input of a pain control specialist is often mandatory.

Coeliac plexus block (CPB) can lead to pain control and frequently to a decrease in the total amount of systemic drugs and their side-effects. The endoscopic method is safer than percutaneous insertion and is as successful as surgical hepatojejunostomy.

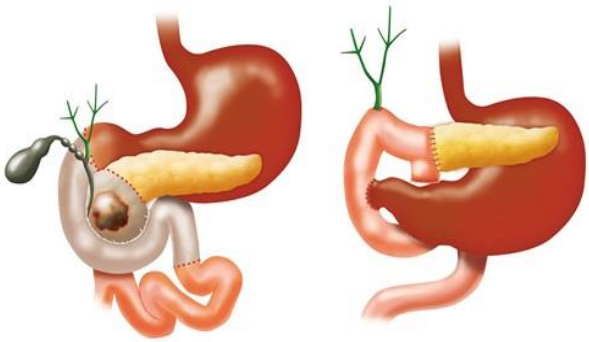
Biological therapy the orally delivered tyrosine kinase inhibitor erlotinib (Tarceva®) inhibits the intracellular pathways involved in cell signaling and, when combined with gemcitabine chemotherapy, yields a 7 per cent 1-year survival advantage in those with locally advanced or metastatic disease.

Principles of surgery

Curative resection Approximately 20% of patients with pancreas cancer are candidates for a potentially curative resection

Types of surgical interventions

Whipple surgery (pancreatico-duodenectomy) : is the primary surgical treatment for pancreatic cancer that occurs within the head of the gland. During this procedure, surgeons remove the head of the pancreas, most of the duodenum (a part of the small intestine), a portion of the bile duct, the gallbladder and associated lymph nodes. In some cases, the surgeon may remove the body of the pancreas, the entire duodenum and a portion of the stomach. Reconstruction consists of attaching the pancreas to the jejunum (pancreatojejunostomy), the common bile duct to the jejunum (choledochojejunostomy), and the stomach to the jejunum (gastrojejunostomy), to allow bile, digestive juices and food to flow.



www.hopkinsmedicine.org

Figure 3: whipple's operation

pylorus-sparing pancreaticoduodenectomy. For those patients with localized disease and small cancers (<2cm) with no lymph node metastases and no extension beyond the capsule of the pancreas.

distal pancreatectomy and splenectomy for Patients with resectable tumors in the body or tail of the pancreas.

Total pancreatectomy

Lymphadenectomy Standard lymphadenectomy for pancreatoduodenectomy should resect the following lymph nodes: • Suprapyloric • Infrapyloric • Anteriosuperior group along the common hepatic artery • Along the bile duct • Around the cystic duct • On the inferior portion of the head of pancreas • On the right lateral side of SMA.

For tumors of the body and tail of the pancreas, removal of the following lymph nodes is recommended: • At the splenic hilum • Along the splenic artery • The inferior margin of pancreas. Standard lymphadenectomy should involve the removal of ≥15 lymph nodes to allow adequate pathologic staging of the disease. The total number of lymph nodes examined and lymph nodes ratio (number of involved lymph nodes/number of lymph nodes examined) should be reported in the pathologic analysis.

Common bile duct draining and supportive care for patients with obstructive jaundice.

Role of chemotherapy

Chemotherapy may be used at any stage of pancreatic cancer to kill cancer cells. Chemotherapy drugs are usually administered in cycles, with alternating periods of treatment and recovery. They may be given alone or in conjunction with radiation therapy or surgery.

According to the American Cancer Society, the following chemotherapy drugs may be used to treat pancreatic cancer:

- Gemcitabine
- 5-fluorouracil (5-FU)
- Irinotecan (Camptosar)
- Oxaliplatin (Eloxatin)
- Albumin-bound paclitaxel (Abraxane)
- Capecitabine (Xeloda)
- Cisplatin
- Paclitaxel (Taxol)
- Docetaxel (Taxotere)
- Irinotecan liposome (Onivyde)

Neoadjuvant chemotherapy: Chemotherapy can be given before surgery ,and sometimes along with radiation to try to shrink the tumor so it can be removed with less extensive surgery.

Adjuvant chemotherapy: Chemotherapy can be used after surgery alone or with radiation to try to kill any cancer cells that have been left behind or have spread but can't be seen, even on imaging tests. If these cells were allowed to grow, they could form new tumors in other places in the body. This type of treatment might lower the chance that the cancer will come back later.

In patients with **metastatic disease**, the combination of gemcitabine and erlotinib has led to a significantly higher median survival and 1-year survival than has the use of gemcitabine alone. This has led to US Food and Drug Administration (FDA) approval of erlotinib for use in combination with gemcitabine in advanced, unresectable pancreatic cancer. The recommendation that this combination should now constitute standard therapy for metastatic or unresectable local disease is premature and problematic. The improvements in response rates seen, although significant, were not great and were obtained with no small amount of patient toxicity.

The combination should be used with considerable care, and the use of gemcitabine alone should still be considered as appropriate therapy for patients with metastatic disease. Gemcitabine alone should also be considered as appropriate therapy for patients with unresectable disease; there is no meaningful significant benefit obtained to adding radiotherapy in this situation. Such an addition simply increases toxicity.

Prognosis

According to the American Cancer Society, for all stages of pancreatic cancer combined, the one-year relative survival rate is 20%, and the five-year rate is 9%. These low survival rates are attributable to the fact that fewer than 20% of patients' tumors are confined to the pancreas at the time of diagnosis; in most cases, the malignancy has already progressed to the point where surgical removal is impossible.

In those cases where resection can be performed, the average survival rate is 23 to 36 months. The overall five-year survival rate is about 10%, although this can rise as high as 20% to 35% if the tumor is removed completely and when cancer has not spread to lymph nodes.

FUNCTIONING ENDOCRINE TUMORS OF THE PANCREAS

These are much less common than adenocarcinoma. The beta cell tumors secrete (Insulin) and called INSULINOMAS. Another functioning tumor secrete (Gastrin) called GASTRINOMA which come from the islet's cells.

Pathology

The actual islet cell lesion may be one of the following: (1) generalized hyperplasia; (2) discrete adenoma; (3) generalized adenomatosis; and (4) carcinoma.

As part of the multiple endocrine neoplasia syndrome they may be associated with tumors in other endocrine glands, especially thee anterior pituitary, the parathyroid and the adrenal cortex.

Alpha cell	Glucagon	Glucagonoma
Beta cell	Insulin	Insulinoma
Delta cell	Somatostatin	Somatostatinoma

Delta-2-cells	VIP	WDHA (VIPoma)
G-cells	Gastrin	ZES (Gastrinomaa)

INSULINOMA:

The commonest islet cell tumor and arise from the beta cell and may be situated anywhere on the surface or within the substance of the pancreas.

Most tumors are benign adenomas but 15% are low grade carcinomas and secrete (insulin).

Clinical manifestations

Whipple described a triad of features which typify the (insulinomas):

1. Fasting produces fainting.

2. During these "attacks" there is hypoglycemia.

3. The attacks may be relieved by ingestion of glucose.

attacks are always associated with hypoglycemia and occur at irregular intervals, often with progressively increasing frequency and severity.

epigastric discomfort, nervousness, 'feeling unwell', trembling, sweating, dizziness, episodes of inarticulate speech and uncoordinated movements and, in extreme cases, fits indistinguishable from epilepsy.

Diagnosis

- Measurement of blood sugar during an attack. serum levels of less than 2.8 mmol/litre
- Overnight fasting serum glucose and insulin level (before & after overnight). Insulin levels are estimated by radio-immuneoassay. The hypoglycemia should inappropriate levels of serum insulin (greater than 6 1. miccro units/dl) and elevated C-peeptide levels.
- Pre-operative localization of the tumor very important identification at operation can be difficult. a. [Combination CT Scan and selective angiography] with rapid injection (5—7 ml/second) of intravenous contrast.
- Intra-Operative localization using portable Sonographic probe.
- Endoscopic ultrasound the diagnosis of the characteristic 'blush' noted be documented and associated with at the site of the tumor.

Treatment

- If the tumor is localized surgical resection is the treatment of choice.
- If the tumor could not be localized during surgery (Intra operative U/S can be done to localize the tumor) then it is resected.
- Subtotal distal resection for multiple tumors is appropriate.
- With negative exploration it is appropriate pancreatectomy distal to the superior mesenteric vessels.
- The Hypoglycemic attacks may be relieved by diazoxide or streptozotocin. `

GASTRINOMA: (Zollinger-Elison Syndrome)

The tumor arising from the islets cell of langhans in the pancreas and in the duodenal wall. The majority (60%) of these tumors are malignant. They may be associated with (MEN 1) syndrome which are Parathyroid Hyperplasia, and Pituitary Adenoma.

Gastrinoma give rise to ZE Syndrome which consist of triad (hypersecretion of gastric acid, severe peptic ulceration and the presence of non-beta cell tumor of the pancreas or duodenum).

Clinical manifestations

The disease presents as peptic ulcer disease in over 90% have a typical pain more severe and less response to medical treatment.

All complications of peptic ulcer disease are present in (ZE-Syndrome) as acute hemorrhage, perforation and recurrent ulceration.

Multiple ulcerations be present at the same time in the duodenum, stomach, esophagus and even the jejunum.

Diagnosis

Severe peptic ulcer disease doesn't respond to medical treatment, Multiple peptic ulcers or ulcers in unusual locations such as the distal duodenum or jejunum, Peptic ulcer disease associated with diarrhea

Recurrent peptic ulcer disease following an acid reducing ooperation (surgery), peptic ulcer is associated with MEN- 1 Syndrome and Marked elevation of serum Gastrin.

Localization - the 'gastrinoma triangle' (confluence of the cystic duct and common bile duct superiorly, junction of the second and third parts of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially) and suggested that 80—90 per cent of gastrinoma would be found within this triangle. This is, indeed, the case. A high percentage of tumors will be found in the duodenal wall and these are often quite small (4—6 mm).

Treatment

Medical therapy for control of the acid hypersecretion in patient with ZE-Syndrome, PPI, Omeprazole is considered the antisecretory drug of choice for all gastrinoma patients. And octreotide. Surgical Treatment: by Tumor excision, Total Gastrectomy.

Patient with metastases should have chemotherapy prior and after gastrectomy. Gastrinoma patient with MEN 1 Syndrome and documented hyperparathyroidism should have parathyroidectomy performed prior to removal of gastrinoma.

VII. QUESTIONS FOR SELF-CONTROL:

1. Epidemiology and risk factors of pancreatic cancer.
2. Pathology of pancreatic cancer, modes of spreading.
3. Histological classification of pancreatic tumors, benign and malignant neoplasms of the pancreas.
4. Clinical presentation, history, symptoms and signs.
5. Pancreatic cancer staging, diagnostics, modern methods of investigations.
6. Differential diagnosis of pancreatic cancer.
7. Principles of treatment of pancreatic cancer, treatment of localized and advanced pancreatic cancer.

8. Surgical treatment of pancreatic cancer, types of surgeries. Role of radiotherapy in treatment of pancreatic cancer.
9. Role systemic therapies in pancreatic cancer treatment. adjuvant and neoadjuvant chemotherapy.
10. Functional endocrine tumors of the pancreas.

VIII. Tasks for verification of concrete teaching aims achievement:

1. A 52-year-old man presents with abdominal pain and weight loss. He describes a dull "gnawing" pain located in the epigastric region radiating to the back. The abdominal examination is normal with no hepatosplenomegaly or masses palpated. A computerized tomography (CT) scan of the abdomen reveals a 3-cm mass in the pancreas. Which of the following statements regarding cancer of the pancreas is true?
    A. tumors of the pancreas are divided almost equally between those arising from the exocrine portion and those arising from the endocrine portion
    B. most endocrine tumors of the pancreas are not symptomatic
    C. the body of the pancreas is the most common site of malignancy
    D. Adenocarcinoma is the most common pancreatic cancer
    E. extension is through local invasion; metastases are a late manifestation
2. All of the following statements regarding pancreatic cancer are true EXCEPT:
    A. Alcohol consumption is not a risk factor for pancreatic cancer.
    B. Cigarette smoking is a risk factor for pancreatic cancer.
    C. Despite accounting for fewer than 5% of malignancies diagnosed in the United States, pancreatic cancer is the fourth leading cause of cancer death.
    D. If detected early, the 5-year survival is up to 20%.
    E. The 5-year survival rates for pancreatic cancer have improved substantially in the past decade
3. A 65-year-old man is evaluated in clinic for 1 month of progressive painless jaundice and 10 lb of unintentional weight loss. His physical examination is unremarkable. A dual-phase contrast CT shows a suspicious mass in the head of the pancreas with biliary ductal dilation. Which of the following is the best diagnostic test to evaluate for suspected pancreatic cancer?
    A. CT-guided percutaneous needle biopsy
    B. Endoscopic ultrasound-guided needle biopsy
    C. ERCP with pancreatic juice sampling for cytopathology
    D. FDG-PET imaging
    E. SerumCA 19-9
4. A 69-year-old African American man presents with weight loss and back pain. Over the past 2 months he has developed hyperglycemia with a fasting glucose of 153 mg/dL. He does not have nocturia. His appetite is decreased; he has noticed mild constipation. The back pain is constant and keeps him awake at night. On examination he appears cachectic and pale. He does not have scleral icterus. Laboratory studies reveal a mild normochromic anemia. Liver and kidney function studies are normal. What diagnostic study is most likely to reveal the cause of his symptoms?
    A. CT scan of the abdomen with IV contrast
    B. Glucose tolerance test
    C. Colonoscopy
    D. Stool studies for malabsorption
    E. Whole-body PET scan

5. A 63-year-old black man presents to the emergency department with abdominal pain, dizziness, and nausea. He reports that he has lost about 20 lb during the past month and a half and that his abdominal pain has just recently become severe. It is midepigastric, gnawing, and radiates to his back. Over the past 3 days, he has had polyuria, but nausea has prevented him from being able to stay hydrated. On examination, the patient is cachectic, has dry mucous membranes, and is orthostatic. His abdomen is tender in the midepigastric region, and there is no palpable mass. Results of laboratory studies are notable for an elevated glucose level of 630 mg/dl and mild renal insufficiency; pancreatic enzyme levels are normal. You diagnose the patient as having diabetes mellitus of new onset, but you are concerned that he may have an underlying pancreatic malignancy. For this patient, which of the following statements regarding pancreatic cancer is false?
    A. Pancreatic cancer is more common in males than in females and is more common in blacks than whites
    B. Tumor size is a very important predictor of resectability, with tumors larger than 4 cm having less than a 10% chance of being resectable and nonmetastatic
    C. EUS is the single most accurate test for imaging and staging pancreatic carcinoma
    D. Risk factors for pancreatic cancer include increasing age, tobacco smoking, chronic pancreatitis, and coffee ingestion
    E. Surgical resection is the only curative modality for pancreatic cancer
6. 80% of all pancreatic cancers account histologically for:
    A. Adeno-squamous carcinoma
    B. Papillary cystic carcinoma
    C. Adenocarcinoma
    D. Giant cell carcinoma
    E. Basal cell carcinoma

7. Clinical Presentation of carcinoma of the head of pancreas is:
    A. Painless obstructive jaundice
    B. Dysphagia and odynophagia
    C. Constipation
    D. Bleeding
    E. Pain
8. The client is diagnosed with cancer of the head of the pancreas. When assessing the patient, which signs and symptoms would the nurse expect to find?
    A. Night sweats and fever
    B. Left lower abdominal cramps and tenesmus
    C. Nausea and coffee-ground emesis
    D. Clay-colored stools and dark urine
9. Tumor marker for pancreatic cancers is:
    A. PSA
    B. CA 125
    C. CA 19-9
    D. AFP
    E. TNF
10. Which one of the following is true about the treatment of pancreatic cancer?
    A. Surgery offers the best chance of cure

B. 10–20 per cent will be long-term survivors
C. Chemotherapy has no role in the management of early pancreatic cancer
D. 5FU is the most active chemotherapy agent
E. Tamoxifen is a useful treatment

Correct answers: 1-D, 2-E, 3-B, 4-A, 5-D, 6-C, 7-A, 8-D, 9-C, 10-A.

IX. Suggested Literature:

IX 1. Basic:

1. NCCN clinical practice Guidelines of pancreatic cancer ,2021.

2. Cancer principles and practice of oncology – DeVita, Hellman and Rosenberg's ,10th edition

3. ANNALS OF ONCOLOGY, ESMO Clinical Practice Guidelines of Pancreatic cancer treatment, 2015.

4. . manual of clinical oncology (Lippincott manual), 7th edition -2017.

IX 2. Additional:

1. Textbook of complex general surgical oncology -SHYNE Y. MORITA, CHARLES M. BALCH, V. SUZANNE KLIMBERG, TIMOTHY M. PAWLIK, MITCHELL C. POSNER, KENNETH K. TANABE, 2018.

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