Clinical manifestation , diagnose and staging of exocrine pancreatic cancer

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- The commonly used term "**pancreatic cancer**" usually refers to a **ductal adenocarcinoma** of the **pancreas** (including its subtypes), which represents approximately **85 percent** of all pancreatic neoplasms.
- Of the several subtypes of ductal adenocarcinoma, **most have a similar poor long-term prognosis**, with the **exception** of **colloid carcinomas**, which have a **better prognosis**, and **adenosquamous cancers**, which have a **worse prognosis** than other subtypes.

- **More than 95 percent** of **malignant neoplasms** of the **pancreas** arise from the **exocrine elements**. **Neoplasms** arising from the **endocrine** pancreas (ie, **pancreatic neuroendocrine** [islet cell] tumors) comprise no more **than 5 percent** of pancreatic neoplasms.

- **CLINICAL PRESENTATION** — The most common presenting symptoms in patients with exocrine pancreatic cancer are **pain**, **jaundice**, and **weight loss**.

- the most frequent symptoms at diagnosis were:
- ●Asthenia – 86 percent
- ●Weight loss – 85 percent
- ●Anorexia – 83 percent
- ●Abdominal pain – 79 percent
- ●Epigastric pain – 71 percent
- ●Dark urine – 59 percent

- ●Jaundice – 56 percent
- ●Nausea – 51 percent
- ●Back pain – 49 percent
- ●Diarrhea – 44 percent
- ●Vomiting – 33 percent
- ●Steatorrhea – 25 percent
- ●Thrombophlebitis – 3 percent

- The most frequent signs were:
- ●Jaundice – 55 percent
- ●Hepatomegaly – 39 percent
- ●Right upper quadrant mass – 15 percent
- ●Cachexia – 13 percent
- ●Courvoisier's sign (nontender but palpable distended gallbladder at the right costal margin) – 13 percent
- ●Epigastric mass – 9 percent
- ●Ascites – 5 percent

- The **initial presentation** of **pancreatic cancer** varies according to **tumor location**.
- Approximately **60 to 70 percent** of **exocrine pancreatic cancers** are **localized** to the **head** of the **pancreas**, while **20** to **25 percent** are in the **body/tail**

- Compared with tumors in the body and tail of the gland, **pancreatic head tumors** more often present with **jaundice**, **steatorrhea**, and **weight loss**.

- **Pain** is one of the **most frequently** reported **symptoms**, even with **small** (<2 cm) **pancreatic cancers**.
- The **pain** associated with **pancreatic cancer** is **usually insidious in onset**.
- It is generally **epigastric**, **radiating** to the **sides** and/or **straight** through to the **back**.
- It may be **intermittent** and made **worse** by **eating** or **lying supine**. It is frequently **worse** at **night**.

- **Lying** in a **curled** or **fetal position** may **improve** the **pain**.
- **sever back pain** should raise suspicion for a **tumor arising** in the **body** and **tail** of the **pancreas**.
- Rarely, **pain** develops very **acutely**, as a result of an **episode** of **acute pancreatitis** due to **tumoral occlusion** of the **main pancreatic duct**

- **Jaundice**, which is usually **progressive**, is most often due to **obstruction** of the **common bile duct** by a **mass** in the **head** of the **pancreas**, causing **hyperbilirubinemia**.
- **Jaundice** may be **accompanied** by **pruritus**, **darkening** of the **urine**, and **pale stools**.

- **Jaundice** is a relatively **early sign** in **tumors** arising from the **pancreatic head**, and **pancreatic tumors** that **present** with **painless jaundice** have been ascribed a relatively more **favorable prognosis** compared with those that present with **pain** and **obstructive jaundice**.
- **Jaundice secondary** to a tumor in the **body** or **tail** typically **occurs later** in the **course** of the **disease** and may be **secondary** to **liver metastases**.

- **A recent onset of diabetes mellitus** may be noted.
- **Diabetes** is **common** in the **age** group where **pancreatic cancer** occurs, but in up to **25 percent**, the disease may be heralded by **new-onset (two years or less)** diabetes.

- Unexplained **superficial thrombophlebitis**, which may be **migratory** (classic **Trousseau's** syndrome).
- There is a particularly high incidence of **thromboembolic** events (both **venous and arterial**), particularly in the setting of **advanced disease.**

- Multiple **arterial emboli** resulting from **nonbacterial thrombotic endocarditis** may occasionally be the presenting **sign** of a **pancreatic cancer.**
- **Thromboembolic complications** occur **more commonly** in patients with tumors arising in the **tail** or **body** of the **pancreas** .

- **Skin manifestations** occur as **paraneoplastic** phenomena in some patients. As an example, both **cicatricial** and **bullous pemphigoid** are described, even as a **first sign** of **disease**
- Rarely, erythematous subcutaneous areas of **nodular fat necrosis**, typically located on the **legs** (**pancreatic panniculitis**), may be evident, particularly in patients with the **acinar cell** variant of **pancreatic cancer**.

- Signs of metastatic disease may be present at presentation. **Metastatic disease** most commonly affects the **liver**, **peritoneum**, **lungs**, and less frequently, **bone**. Signs of advanced, incurable disease include the following:
- ●An abdominal mass.
- ●Liver metastases.
- ●Ascites.
- ●Left supraclavicular lymphadenopathy (Virchow's node)

- ●A **palpable periumbilical mass** (**Sister Mary Joseph's node**) or a **palpable rectal shelf** are present in some patients with widespread disease.

- **Common abnormalities** include an **elevated serum bilirubin** and **alkaline phosphatase** levels, and the presence of **mild anemia**.

- The **majority of pancreatic lesions** discovered on **radiographic** studies performed **for another reason** are **cystic**, and **many** of these **represent intraductal papillary mucinous neoplasms**.

- **DIAGNOSTIC APPROACH** —In general, the diagnostic evaluation of a patient with suspected pancreatic cancer includes **serologic evaluation** and **abdominal imaging**.

- **Initial testing — All patients** presenting with **jaundice** or **epigastric pain** should have an assay of serum **aminotransferases**, **alkaline phosphatase**, and **bilirubin** to determine if **cholestasis** is **present**.
- In addition, patients with **epigastric pain** should be evaluated for **acute pancreatitis** with a **serum lipase.**

- An additional test that can be useful is measurement of the tumor marker carbohydrate antigen 19-9 (**CA 19-9**).
- The **next step** in the patient's evaluation is **abdominal imaging**.

- **Jaundice** — For patients with **jaundice**, the initial imaging study is often transabdominal **ultrasound** (US).
- It also has **high sensitivity (>95 percent) for detecting** a **mass** in the **pancreas**, although **sensitivity** is **lower** for **tumors <3 cm.**

- CT has the advantage of providing **information** on potential **resectability** and the **presence** or **absence** of **metastatic desease.**

- **Epigastric pain and weight loss — Abdominal CT** is the preferred initial imaging test in patients presenting with **epigastric pain** and **weight loss,** but **without jaundice**.

- **Subsequent testing if initial imaging is positive** — If a **pancreatic mass** is seen on **transabdominal US**, an **abdominal CT scan** is typically next obtained to confirm the **presence** of the **mass** and to **assess disease extent.**

- If the **CT appearance** is **typical** for a **pancreatic cancer**, **enough information** is provided to assess **resectability**, and the **patient** is **fit** for a **major operation**, additional testing (including **biopsy**) **may be unnecessary** before **surgical intervention**.
- On the other hand, if the **diagnosis** is in **doubt**, **resectability** is **uncertain**, or if a **therapeutic intervention** is **needed**, **additional procedures** may be **indicated**.

- Endoscopic ultrasound (**EUS)-guided** or **percutaneous biopsies** of a **pancreatic mass** can be obtained if **histologic confirmation** is **needed**, though this is **not always required** in patients who **appear** to have **potentially resectable disease** and who have **typical imaging findings**.
- **EUS** may also be used as an **alternative** to **contrast-enhanced** multi-phase helical **CT** for the staging of pancreatic cancer.

- if the **suspicion** for **pancreatic cancer** remains **high** (eg, in a patient with **profound weight loss** or who has **risk factors** for **pancreatic cancer**, such as **hereditary pancreatitis** or **chronic pancreatitis**), an **EUS** is a reasonable next step to exclude a **small pancreatic cancer** .
- Any lesions that are visible only on **EUS** should be **biopsied** to confirm the diagnosis **prior** to **surgical exploration**.

- On **US**, a **pancreatic carcinoma** typically appears as a **focal hypoechoic hypovascular solid mass** with **irregular margins**. **Dilated bile ducts** may also **suggest** the **presence** of a **pancreatic tumor**.

- **Abdominal CT** — A **mass** within the **pancreas** is the **most common CT finding** of **pancreatic cancer**, although **enlargement** of the **whole gland** is **sometimes** seen .

- The **typical CT appearance** of an exocrine **pancreatic cancer** is an ill-defined **hypoattenuating mass** within the **pancreas** although **smaller lesions** may be **isoattenuating**.

- **Dilation** of both the **pancreatic duct** and the **common bile duct**, commonly referred to as the "**double duct sign**" is present in approximately **62 to 77 percent** of cases of pancreatic cancer **but is not diagnostic** for a **pancreatic head malignancy** Approximately **50 percent** of **ampullary carcinomas** have a double duct sign, and it can also occasionally be seen with **benign adenomas** and **autoimmune pancreatitis**.

- **Carbohydrate antigen 19-9** — The reported **sensitivity** and **specificity** rates of **CA 19-9** for **pancreatic cancer** range from **70 to 92,** and **68 to 92** percent, respectively .
- However, **sensitivity** is closely **related** to **tumor size**.
- **CA 19-9 levels** are of **limited sensitivity** for **small cancers** .

- **CA 19-9 levels** also have **low specificity,** especially in **jaundiced** patients.
- **CA 19-9** is frequently **elevated** in patients with **cancers** other than **pancreatic cancer** and **various benign pancreaticobiliary disorders** .

- The **degree** of **elevation** of **CA 19-9** (both at **initial presentation** and in the **postoperative setting**) is **associated** with **long-term prognosis** .
- Among patients who appear to have **potentially resectable pancreatic cancer**, the magnitude of the **preoperative CA 19-9** level can also help to **predict** the **presence** of **radiographically occult metastatic disease.**

- **Serial monitoring** of **CA 19-9** levels (once **every one** to **three months**) is **useful** to follow **patients after potentially curative surgery** and for those who are **receiving chemotherapy** for **advanced disease**.

- **Imaging studies** — **Imaging studies** play an **important role** in the **staging** and **management** of **pancreatic cancer**.
- **Abdominal computed tomography** — A "**pancreatic protocol**" (**multi-phase**, **contrast-enhanced thin-slice**) **CT** of the **abdomen** and **pelvis** is used to assess disease **extent** and **resectability**.

- **Definitions of unresectable and borderline resectable disease —**
- In general, pancreatic cancers can be categorized along a continuum from **resectable** to **unresectable** .
- A pancreatic cancer is categorically **unresectable** if **distant metastases** are **present** in the **liver**, **peritoneum**, **omentum**, **extraregional lymph nodes**, or any **extra-abdominal site**.

- **Local unresectability** is usually (but not always) due to **vascular invasion**, particularly of the **SMA** .
- **many surgeons** would **consider** a **pancreatic cancer** to be **locally advanced** and **unresectable** if it is associated with **encasement** (**more** than **one-half** of the **vessel circumference**) of the **SMA** or **celiac artery**, or if there is **occlusion** of the **SMV** or **SMV-portal vein confluence without suitable vessels above** and **below** the **tumor** to **allow** for **reconstruction**.

- ●Head of pancreas/uncinate lesions:
- Solid tumor contact with the SMA >180 degrees
- Solid tumor contact with the celiac axis >180 degrees
- Solid tumor contact with the first jejunal SMA branch
- Unreconstructable SMV or portal vein due to tumor involvement or occlusion (can be due to tumor or bland thrombus)
- Contact with the most proximal draining jejunal branch into the SMV

- ●Body and tail lesions:
- Solid tumor contact of >180 degrees with the SMA or celiac axis
- Solid tumor contact with the celiac axis and aortic involvement
- Unreconstructable SMV or portal vein due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

- ●For all sites:
- Distant metastases
- Metastases to lymph nodes beyond the field of resection
- Most of these patients will be managed with initial chemotherapy, with or without chemoradiotherapy. If a sufficient downstaging response is obtained, subsequent surgical exploration can be considered.

- There is less consensus on the definition of "borderline" resectable pancreatic cancer . Some reserve the term "borderline resectable" for cases where there is focal (less than one-half of the circumference) tumor abutment of the visceral (superior mesenteric, celiac) arteries or short-segment occlusion of the SMV or SMV-portal vein confluence or hepatic artery.

- ●For tumors of the head or uncinate process:
- Solid tumor contact with the SMV or portal vein of >180 degrees with contour irregularity of the vein or thrombosis of the vein, but with suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction.

- Solid tumor contact with the inferior vena cava.
- Solid tumor contact with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction.
- Solid tumor contact with the SMA ≤180 degrees.

- ●For tumors of the body/tail:
- Solid tumor contact with the celiac axis of ≤180 degrees.
- Solid tumor contact with the celiac axis >180 degrees without involvement of the aorta and with an intact and uninvolved gastroduodenal artery, thereby permitting a modified Appleby procedure (although some members of the consensus committee preferred this criterion to be in the unresectable category).

- **Most patients** with **borderline resectable disease** are **referred** for **neoadjuvant therapy prior** to **surgical exploration**.

- We also use **staging laparoscopy** in **patients** with **advanced vascular involvement** (but not yet **complete encasement** or **occlusion** of the **major vessels**).
- Other **indications** for a **staging laparoscopy prior** to **open laparotomy** include a **high preoperative CA 19-9 level** (although the optimal threshold is not established ;we use **>1000 units/mL**) and **high-quality imaging** that is in any way **suggestive** of **occult metastatic** disease.
- At some institutions, diagnostic laparoscopy is **performed** if **neoadjuvant therapy** is to be **recommended**.

- **Focal chronic pancreatitis** and **autoimmune pancreatitis** are the **two benign processes** that are **most commonly mistaken** for **pancreatic malignancy** on **CT** or **US**.
- **Serologic testing for IgG4** or **EUS-guided biopsy** may be recommended.