Pancreatic Tumours

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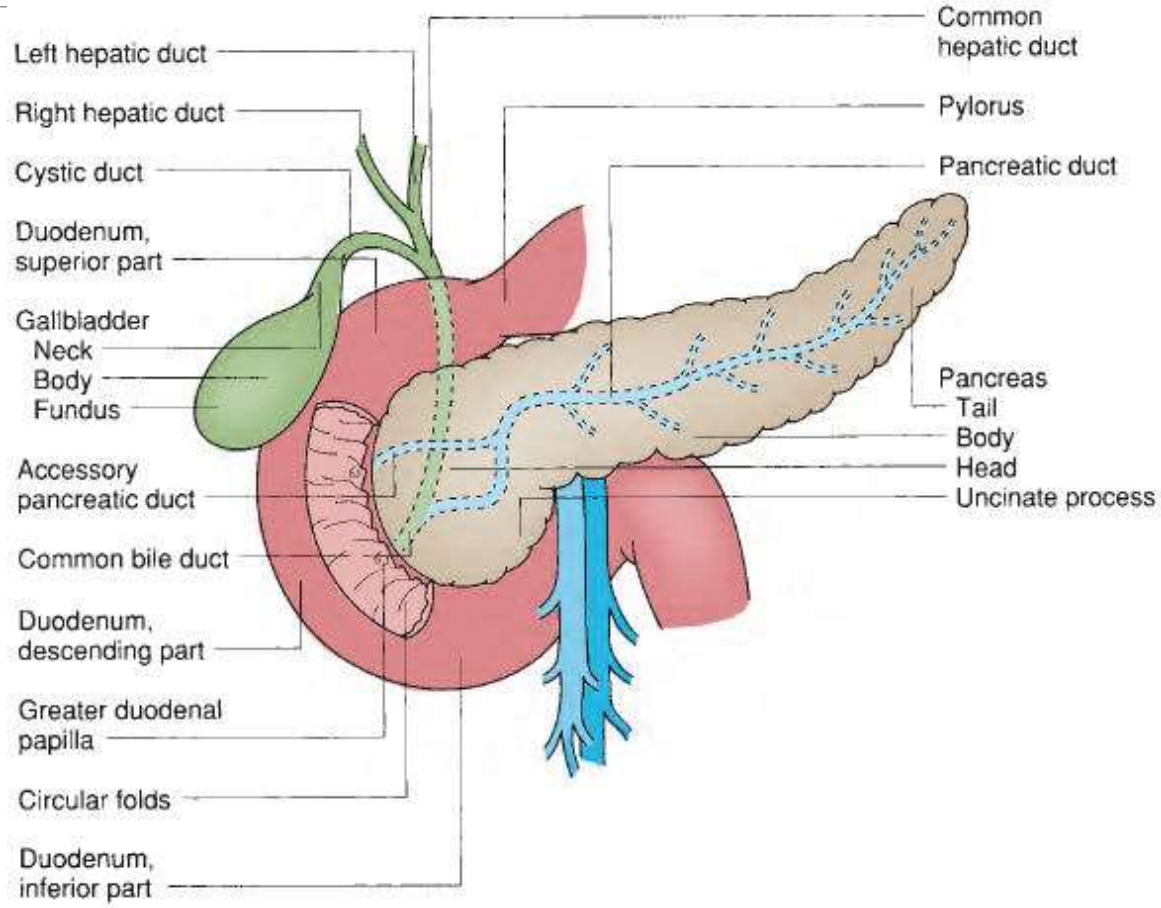
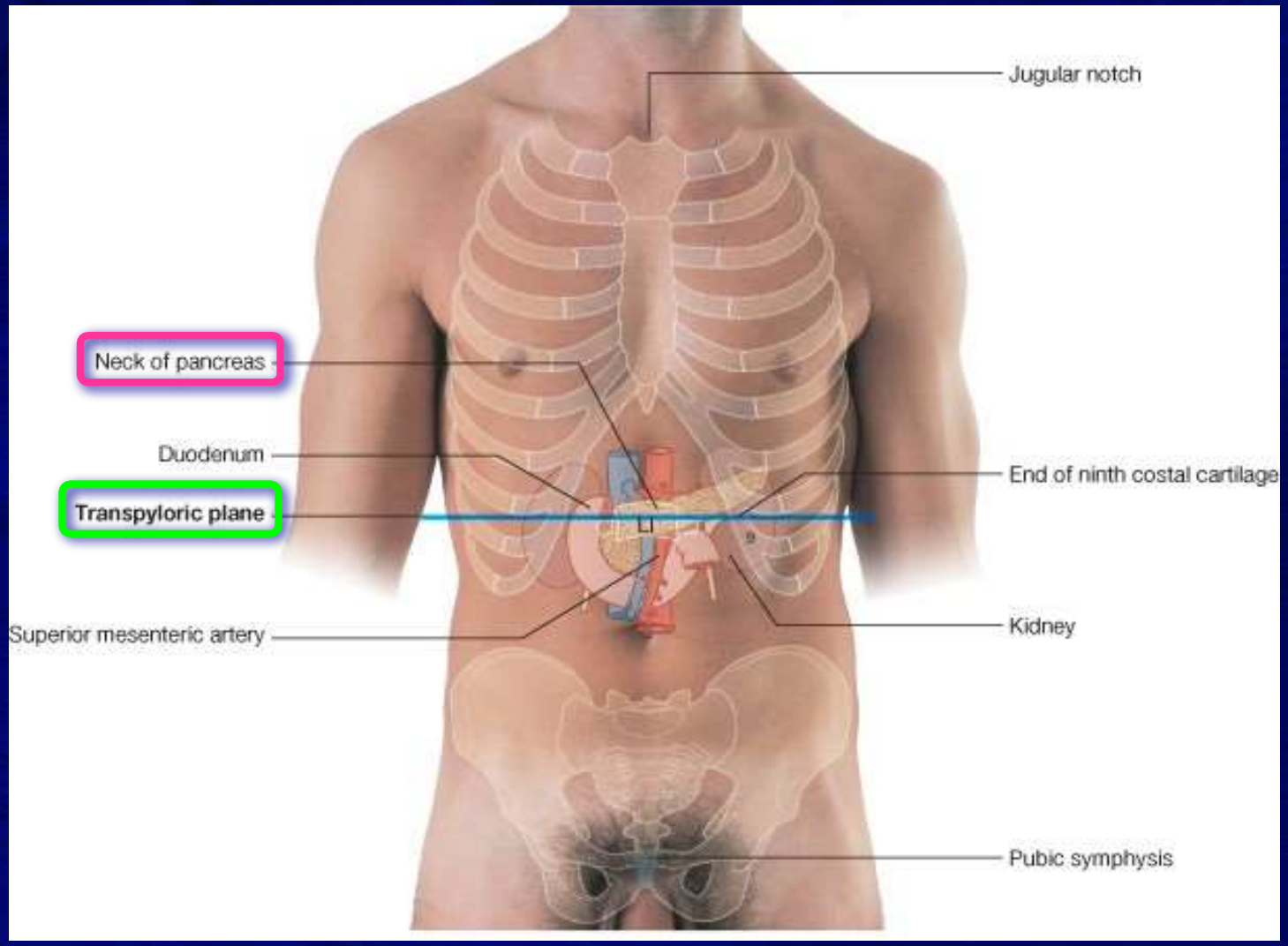
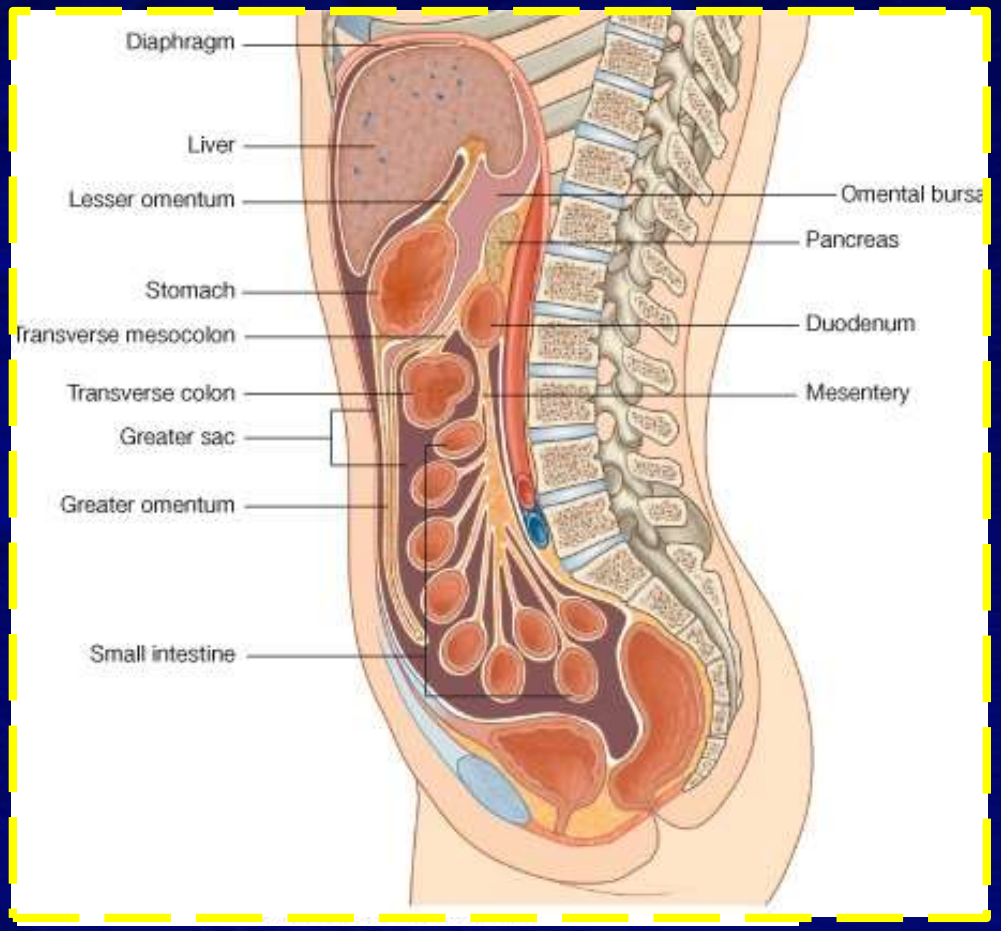


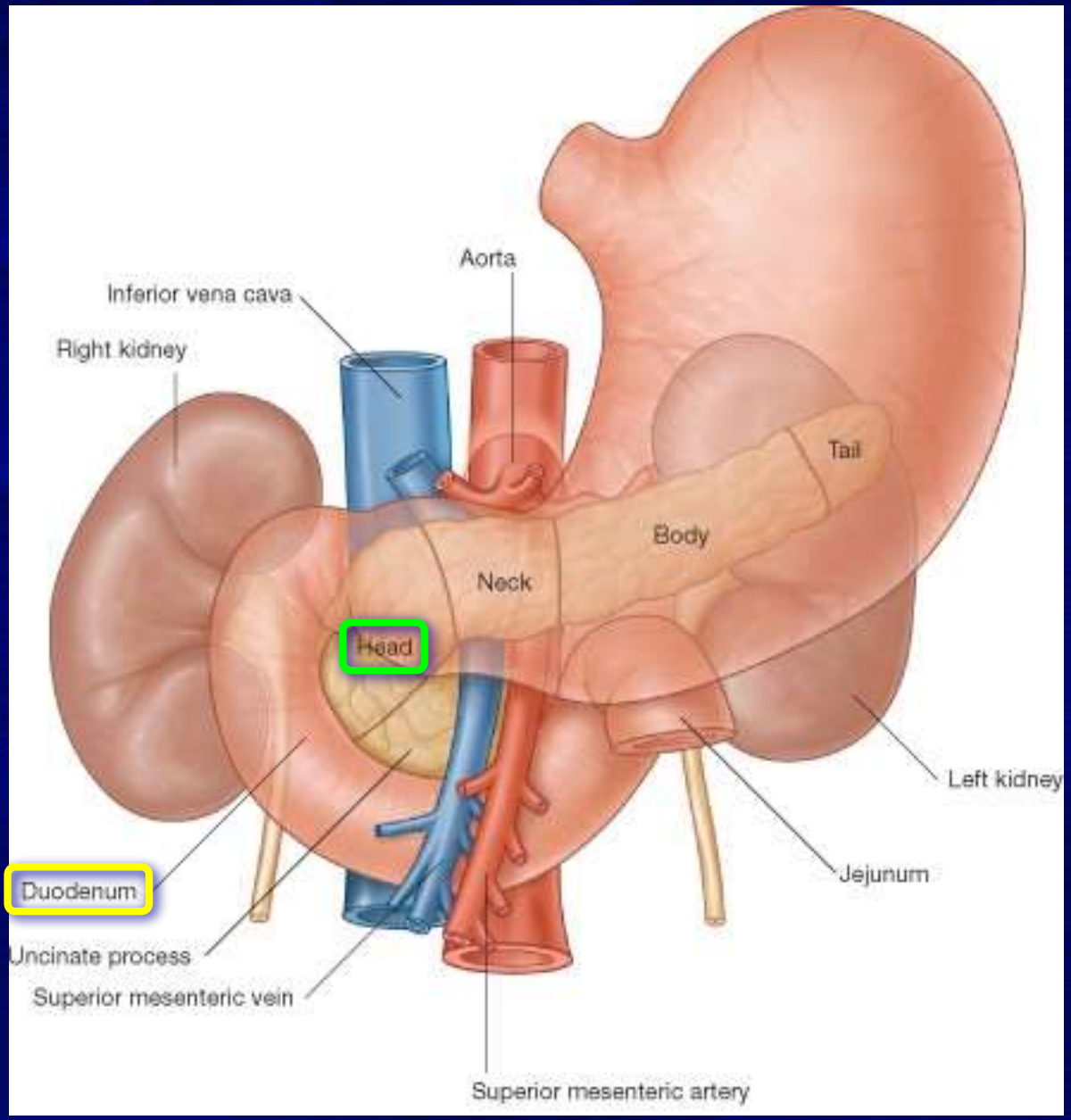
Pancreas anatomy



- The **pancreas** is an elongated structure that lies in the epigastrium and the left upper quadrant.
- It crosses the **transpyloric plane.**



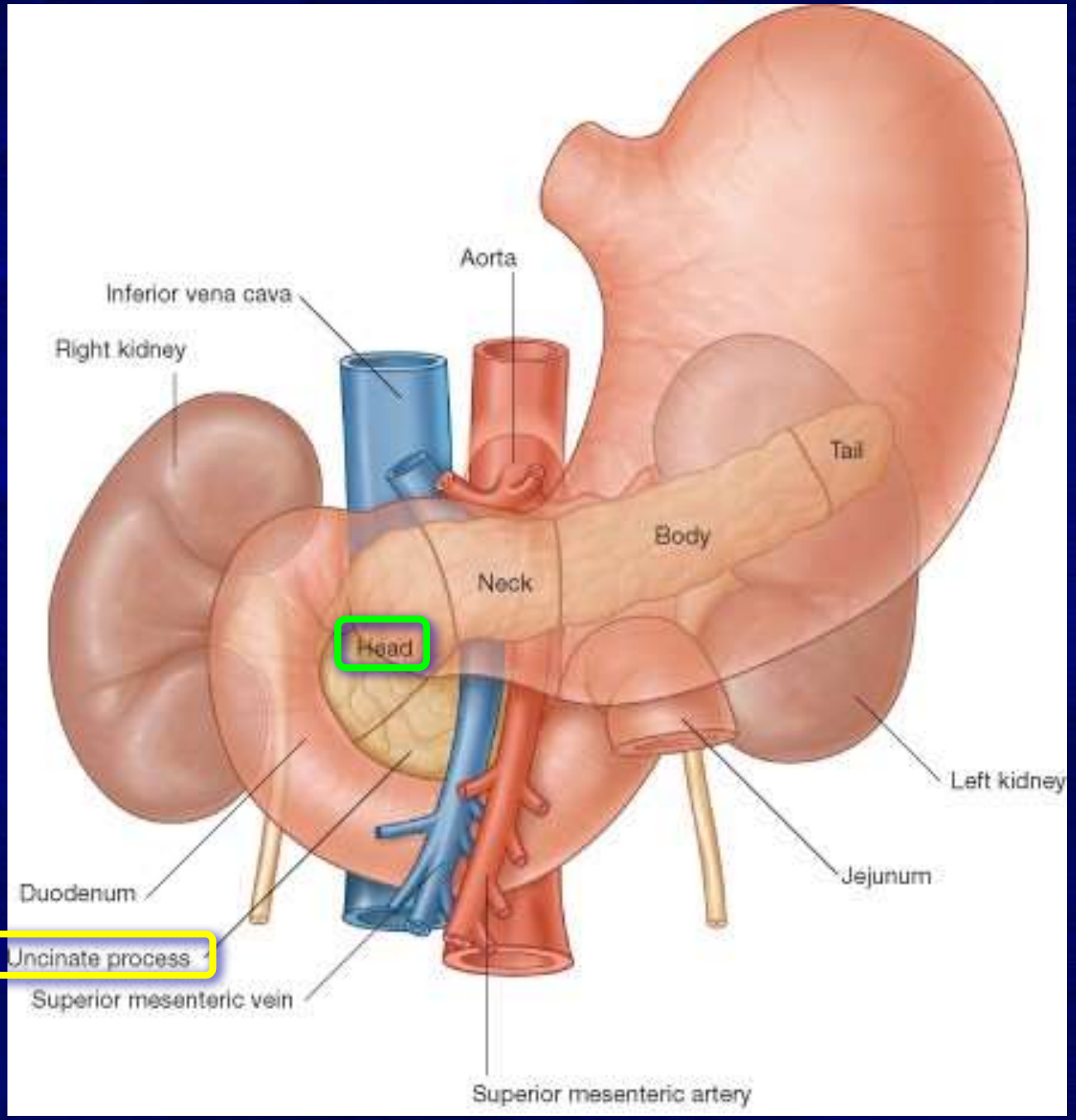
- The **pancreas** is soft and lobulated and
- situated on the posterior abdominal wall *behind the peritoneum.*



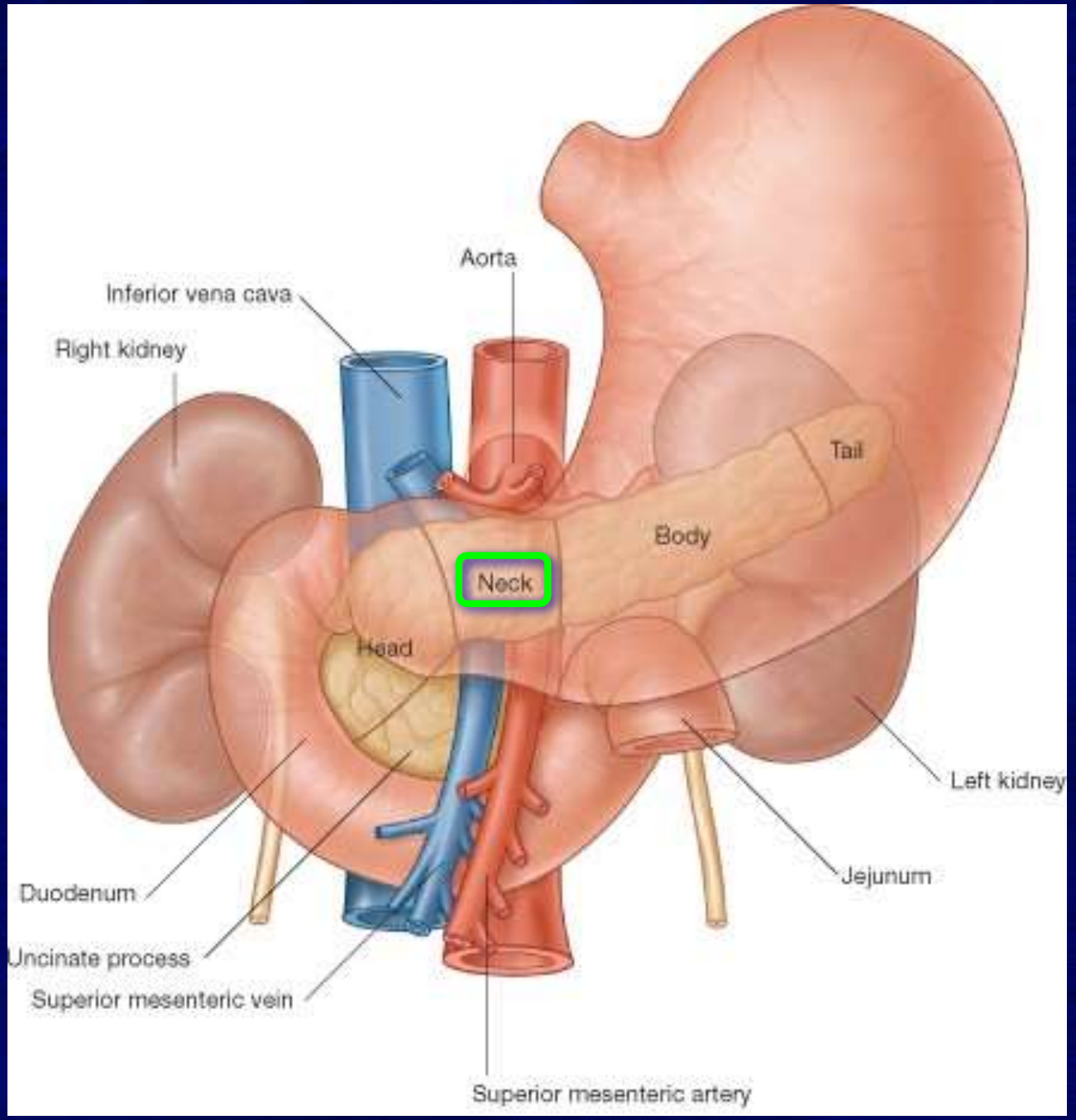
The **pancreas** is divided into a:

- ✓ head,
- ✓ neck,
- ✓ body, and
- ✓ tail.

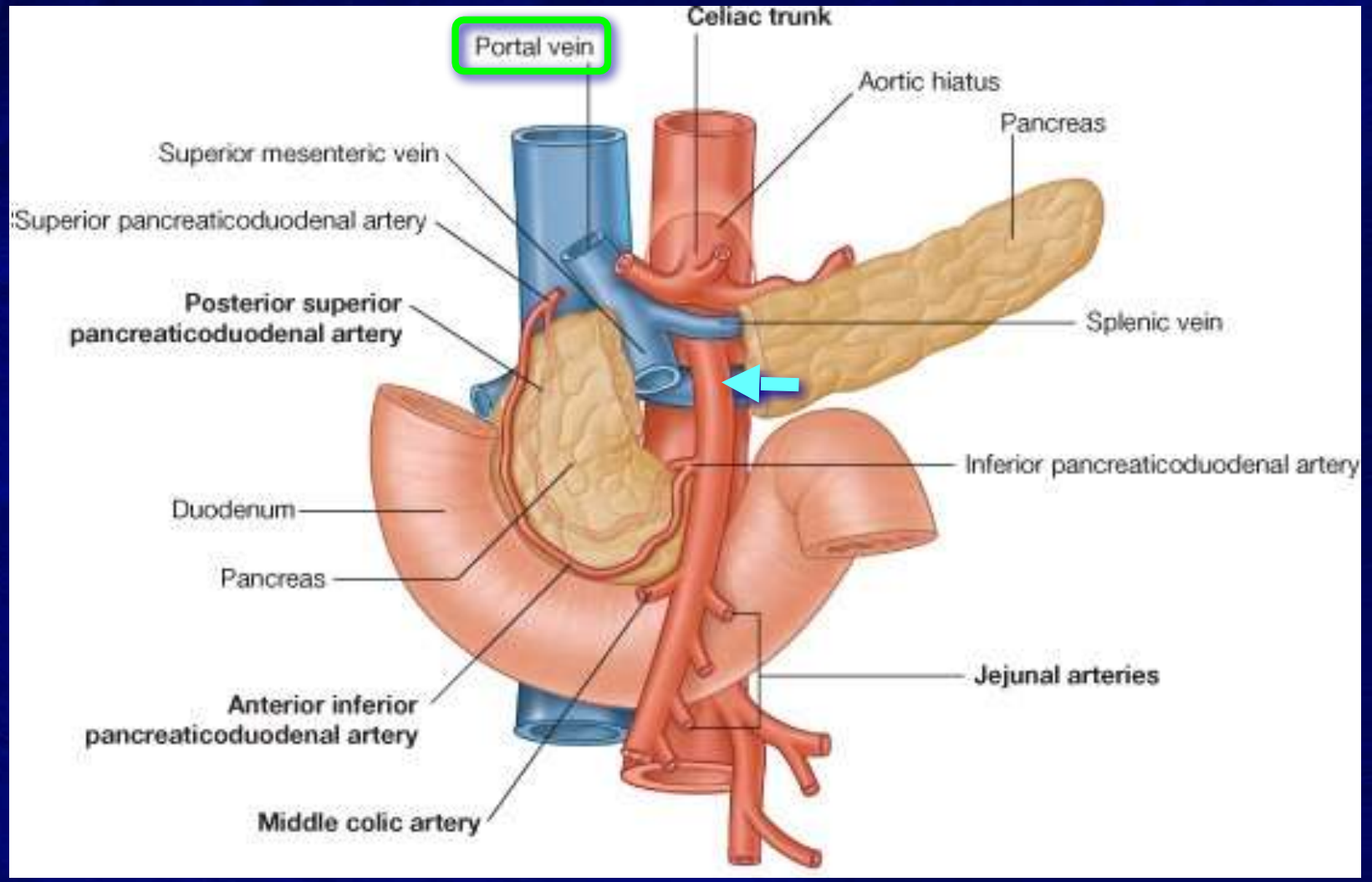
- The **head** of the pancreas is disc shaped and lies within the concavity of the *duodenum.*



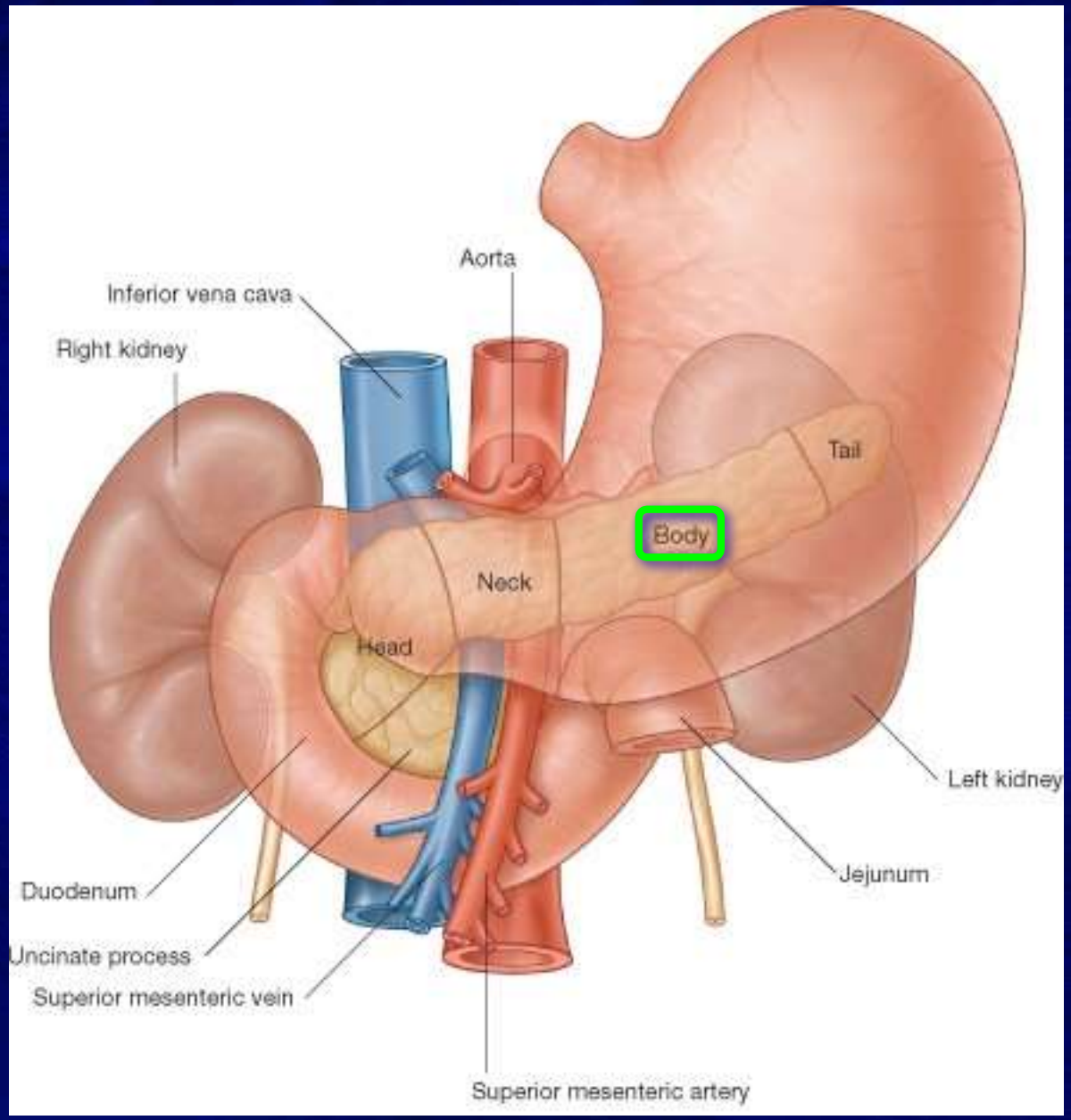
A part of the head extends to the left behind the superior mesenteric vessels and is called the **uncinate process.**



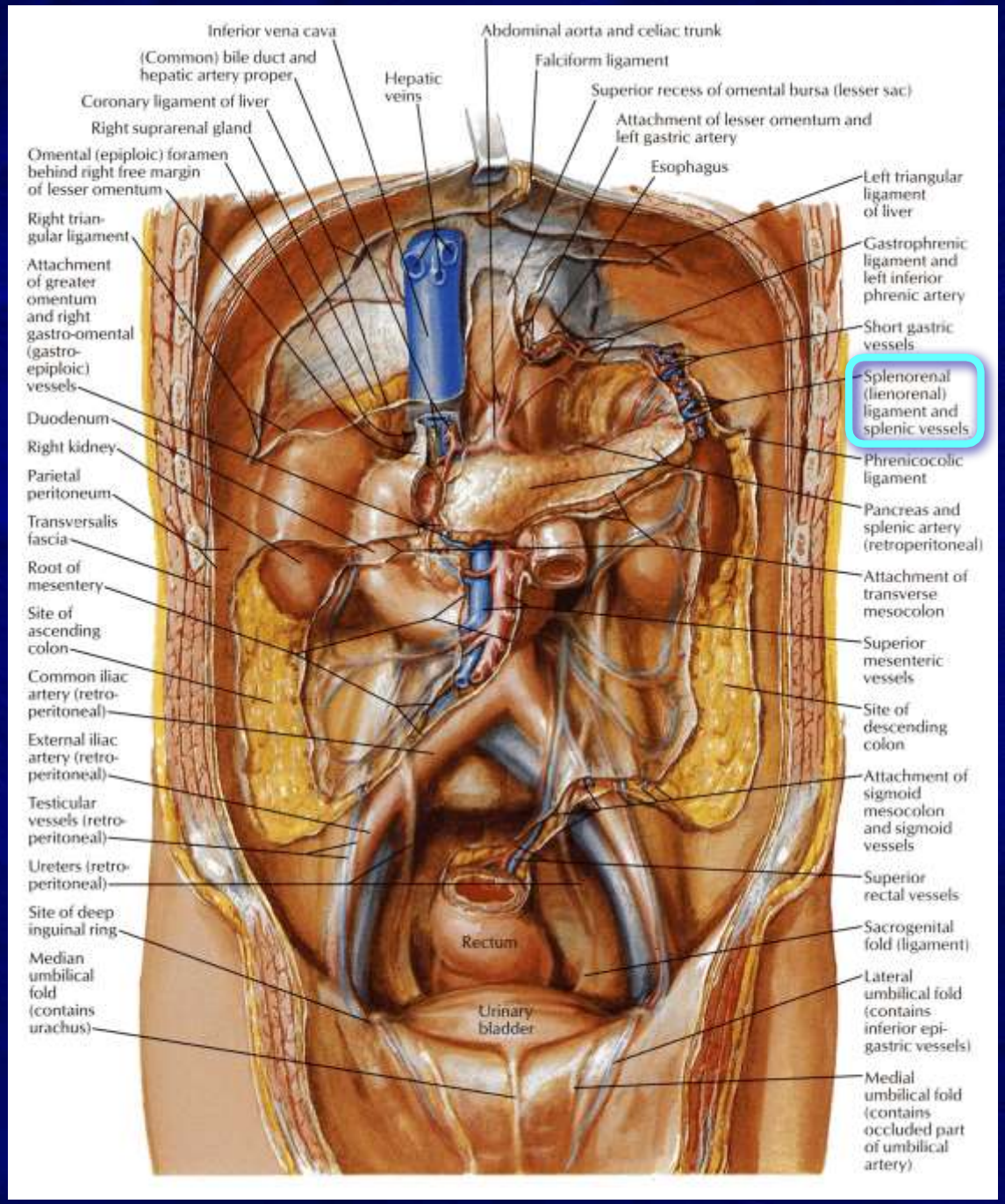
The **neck** is the constricted portion of the pancreas and connects the head to the body.



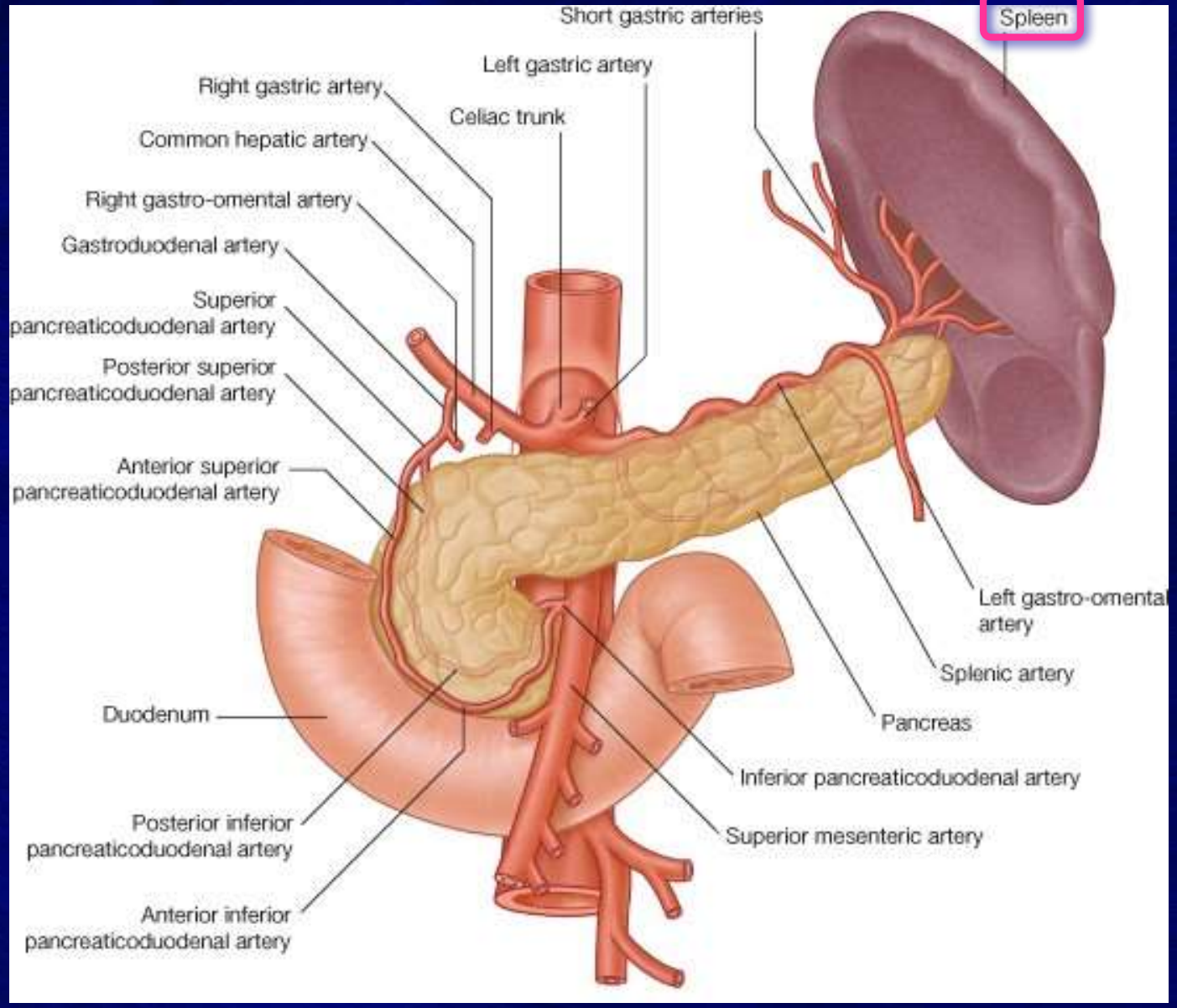
- The **neck** lies:
- *in front* of the beginning of the **portal vein** and
- the the origin of the **superior mesenteric artery** from the aorta.



- The **body** runs upward and to the left across the midline.
- It is somewhat triangular in cross section.

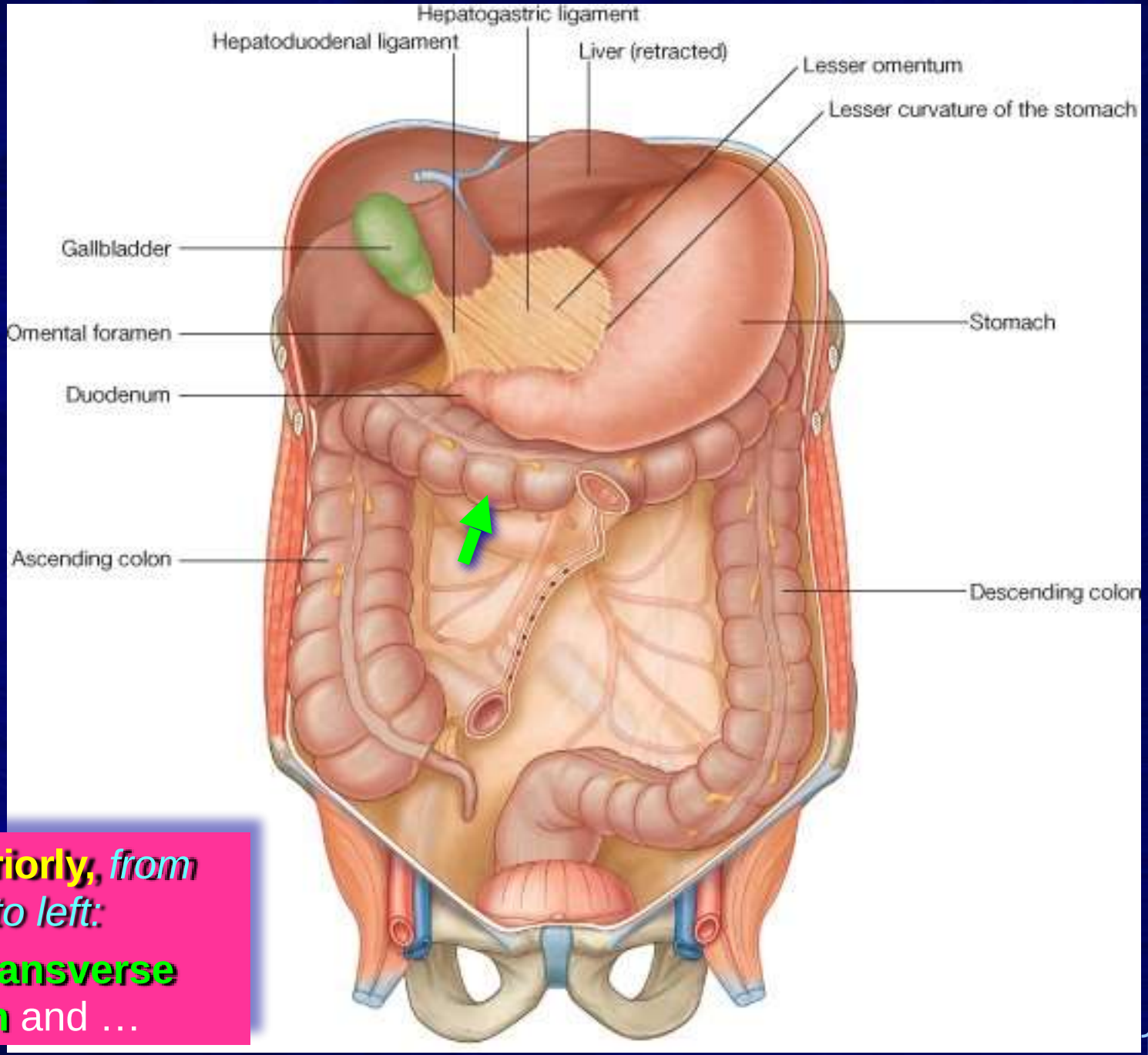


- The **tail** *passes forward* in the **splenicorenal ligament** and …



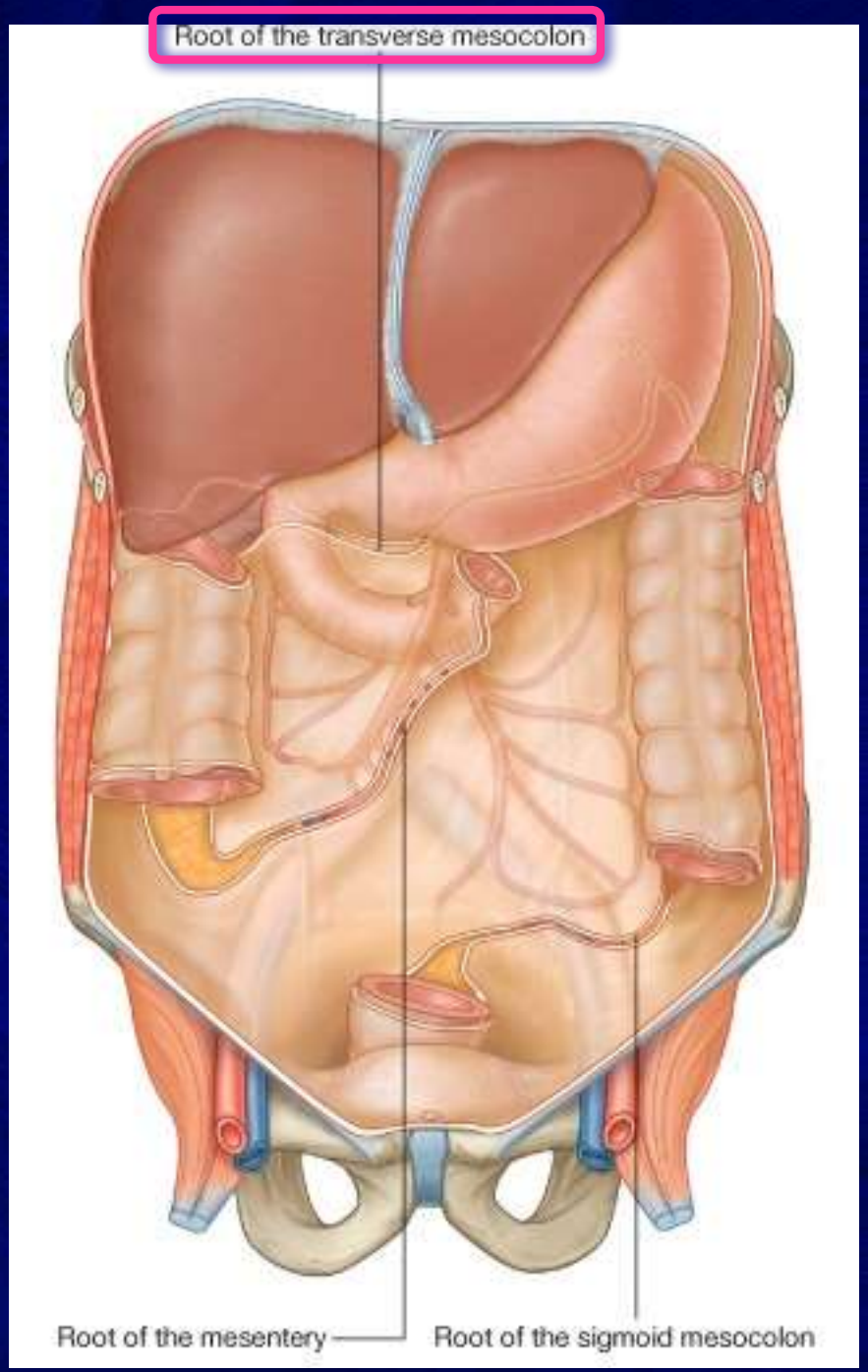
- … comes in contact with the hilum of the **spleen.**

Relations

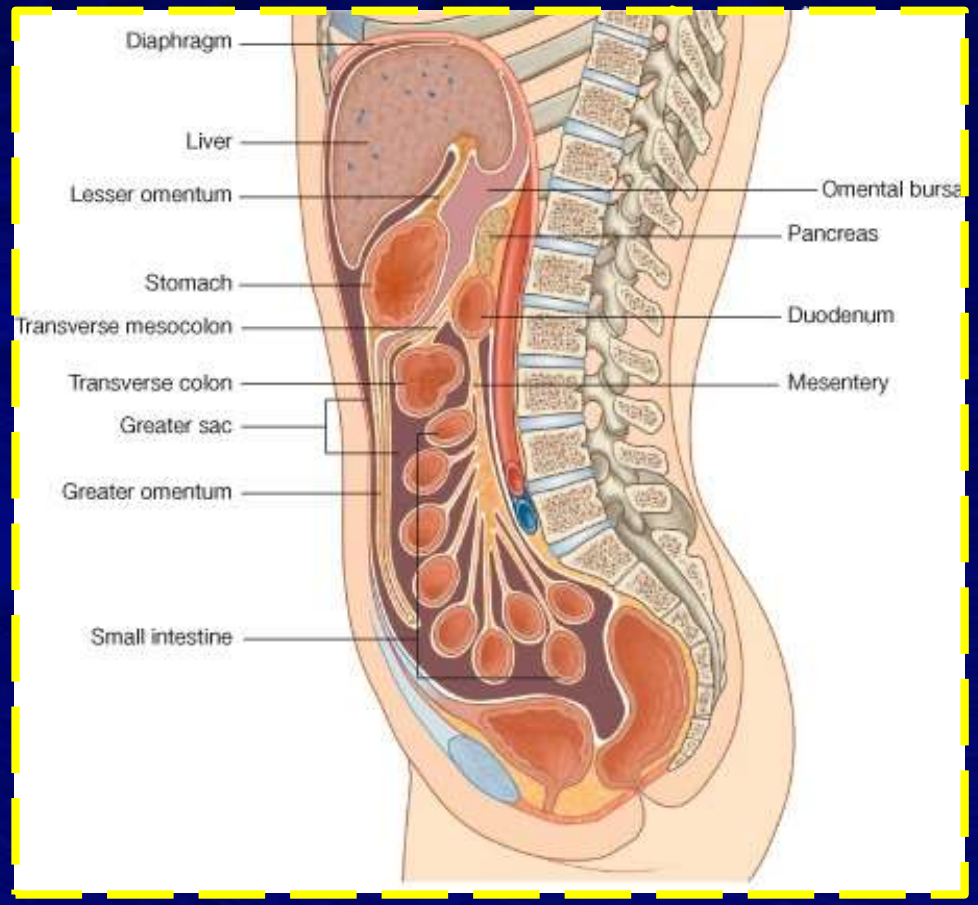


Anteriorly, *from right to left:*

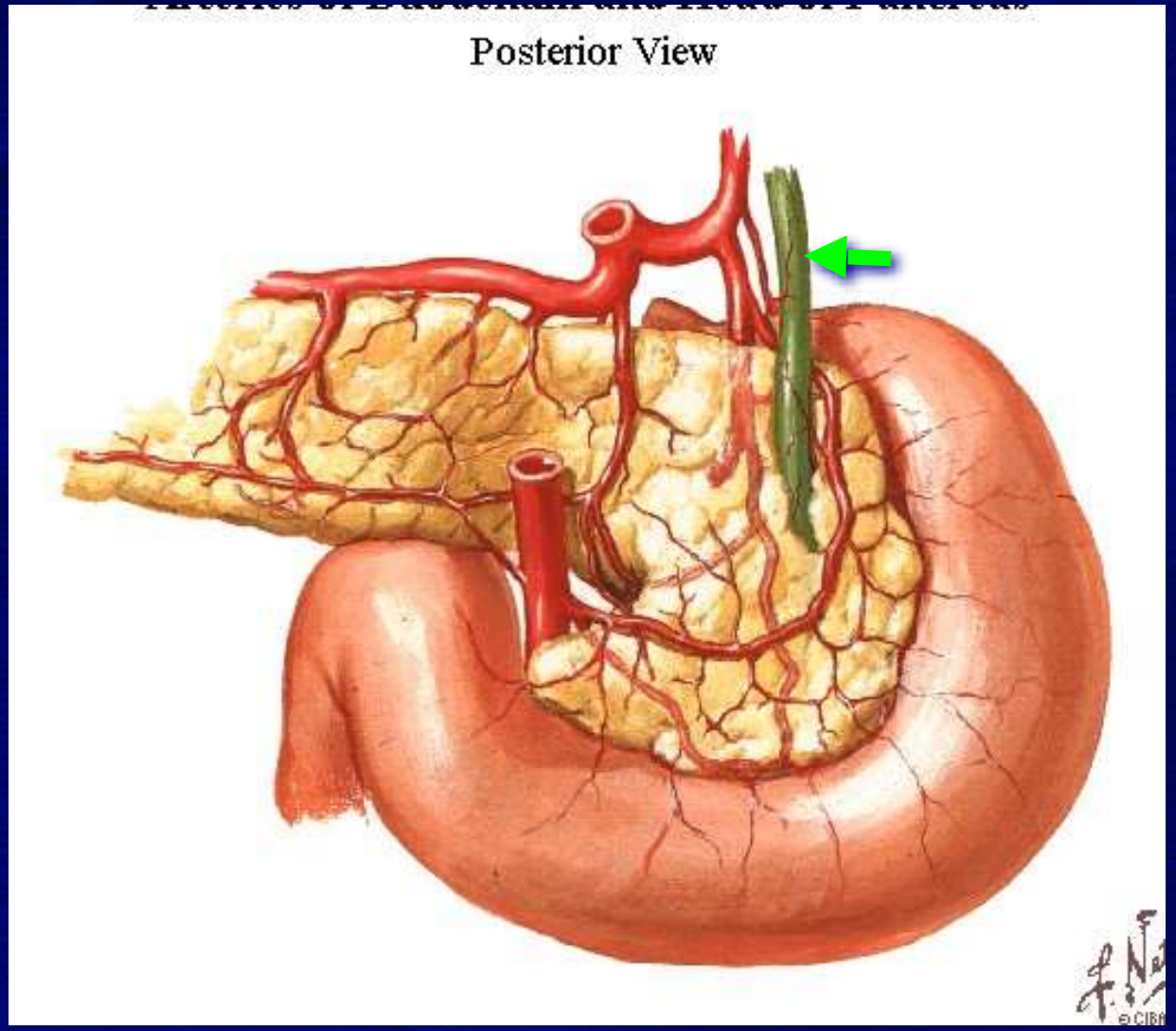
- the **transverse colon** and …



- … the **attachment of the transverse mesocolon,**

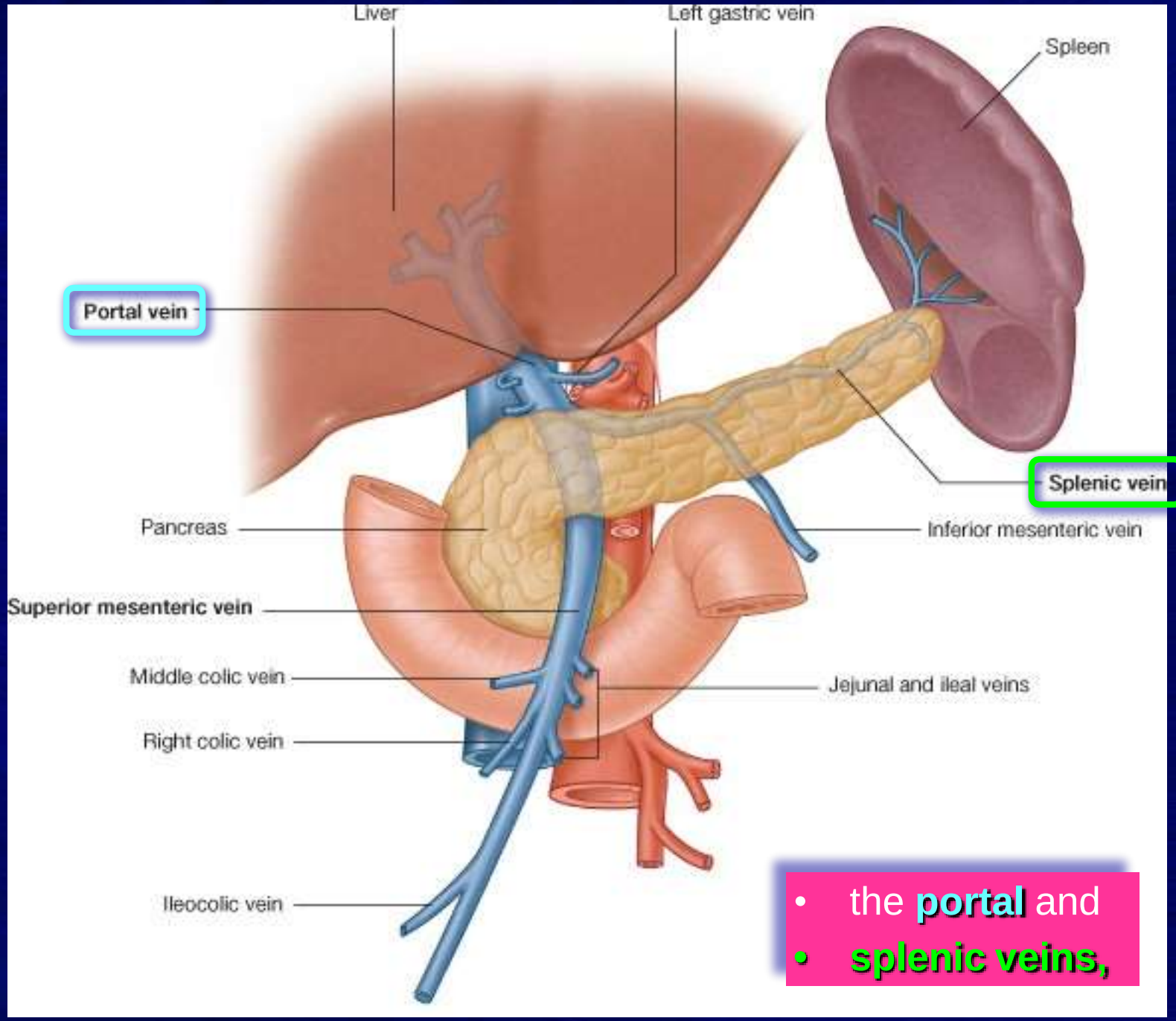


- the **lesser sac,** and
- the **stomach.**

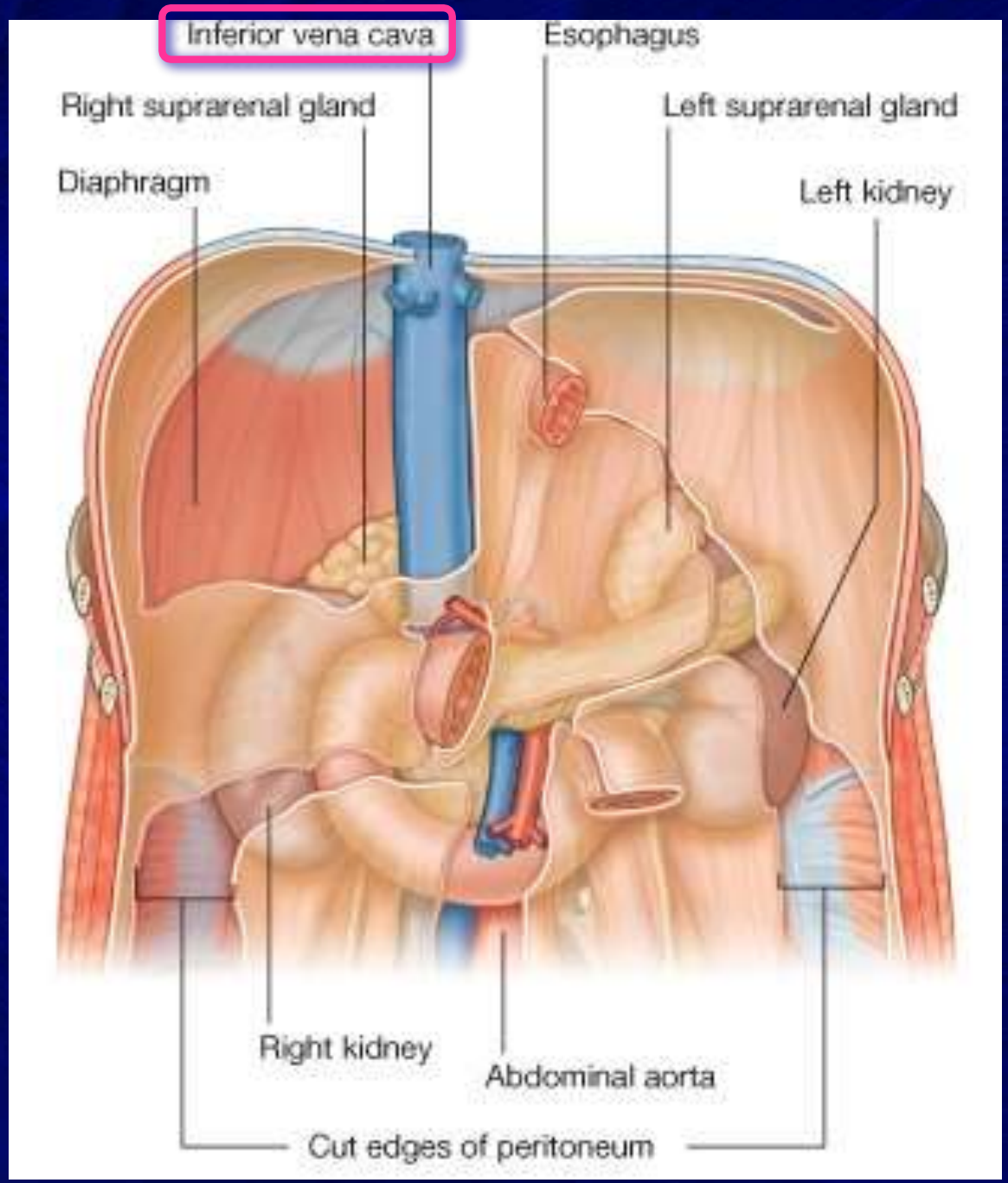


Posteriorly, *from right to left:*

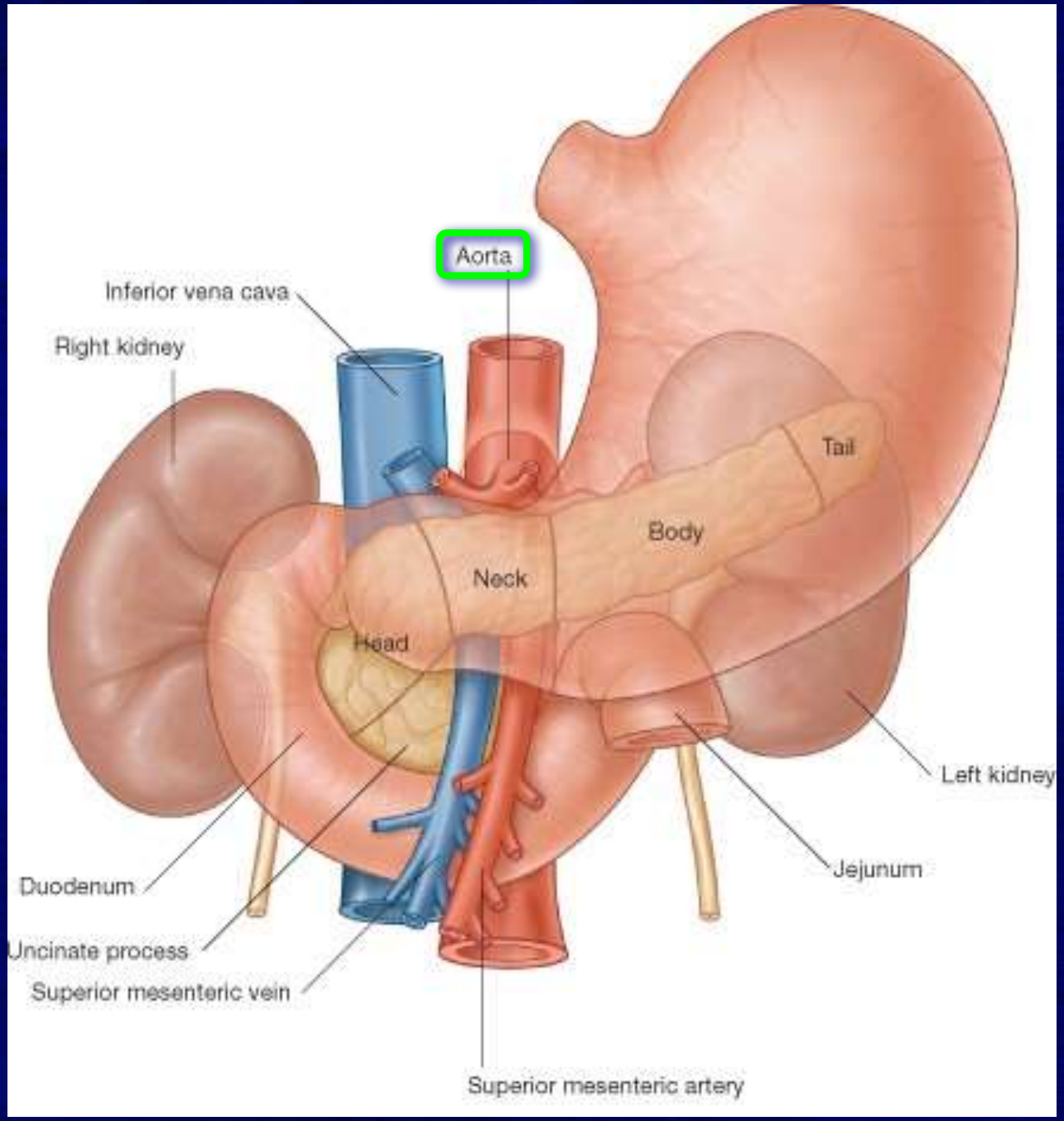
- the **bile duct,**



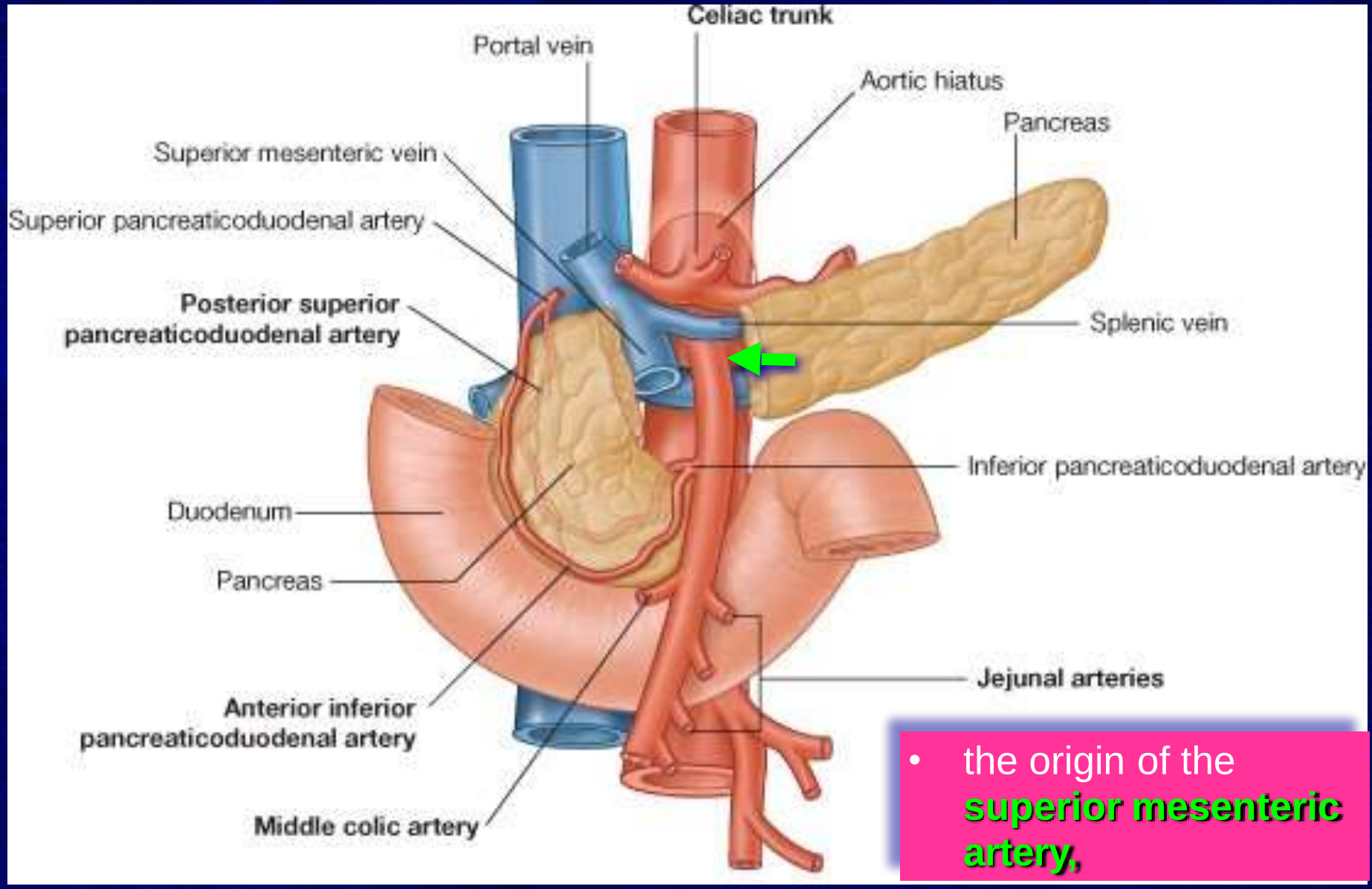
- the **portal** and
- **splenic veins,**



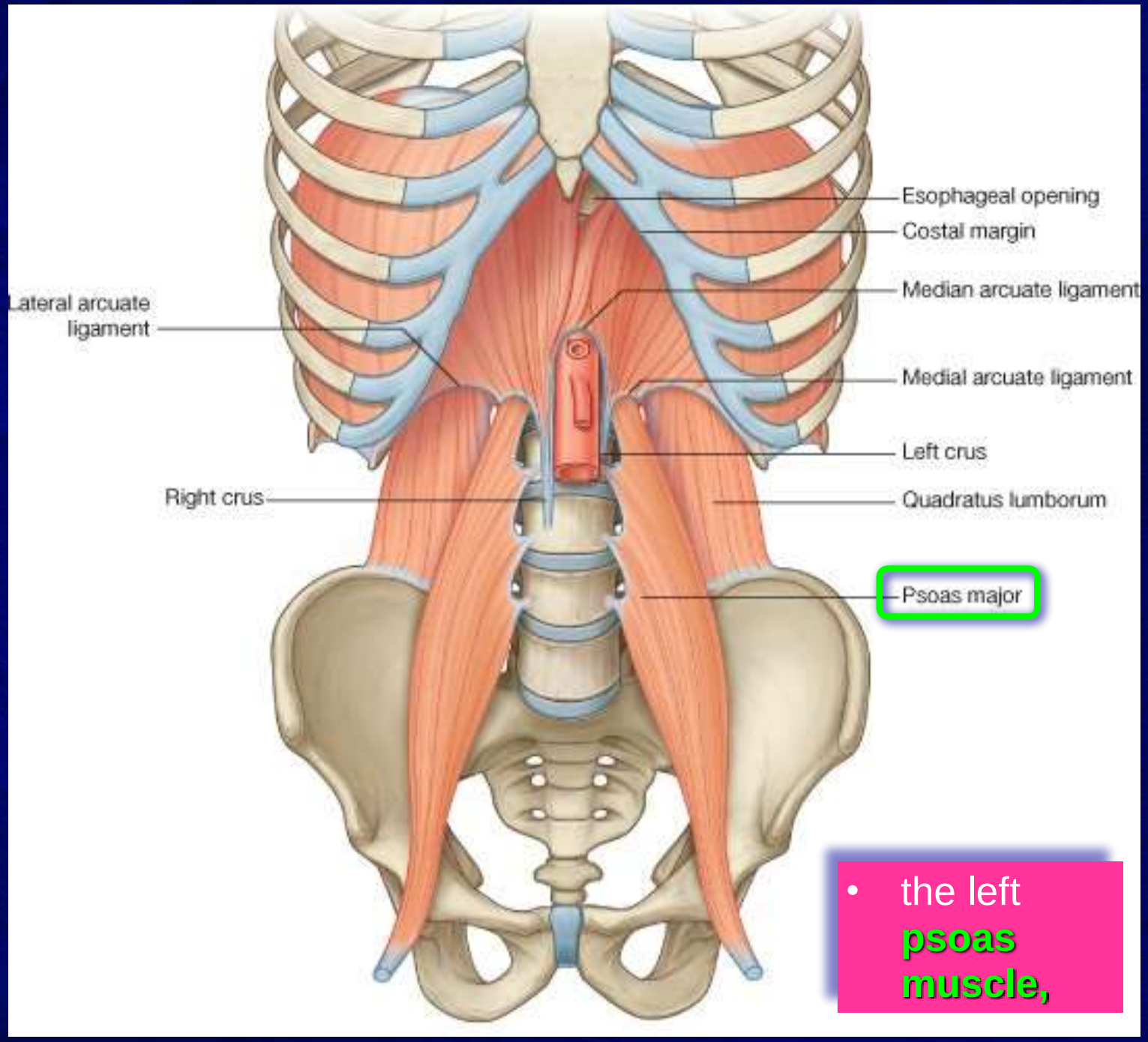
- the **inferior vena cava,**


Aorta
Inferior vena cava
Right kidney
Tail
Body
Neck
Head
Left kidney
Jejunum
Duodenum
Uncinate process
Superior mesenteric vein
Superior mesenteric artery

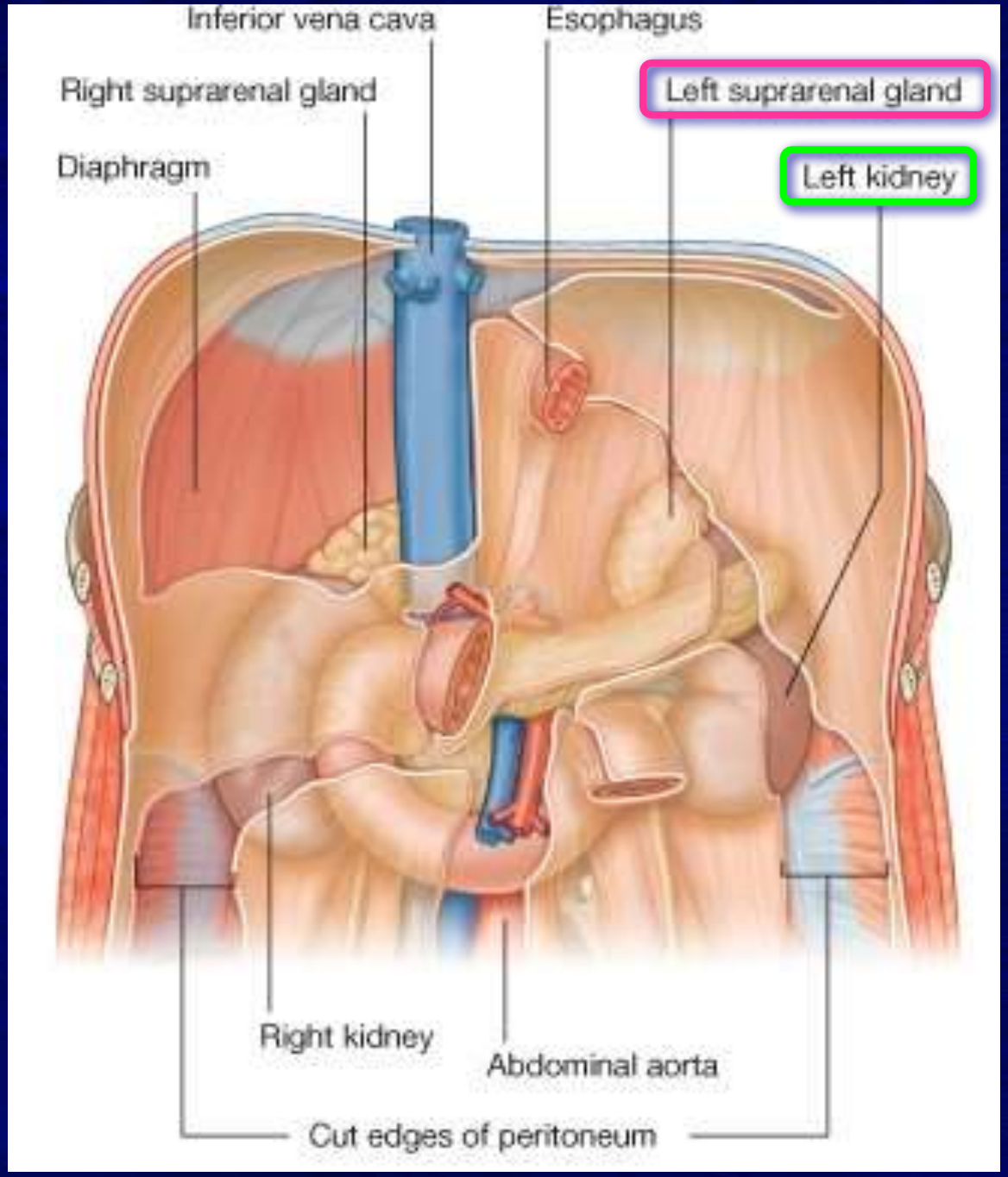
- the **aorta,**



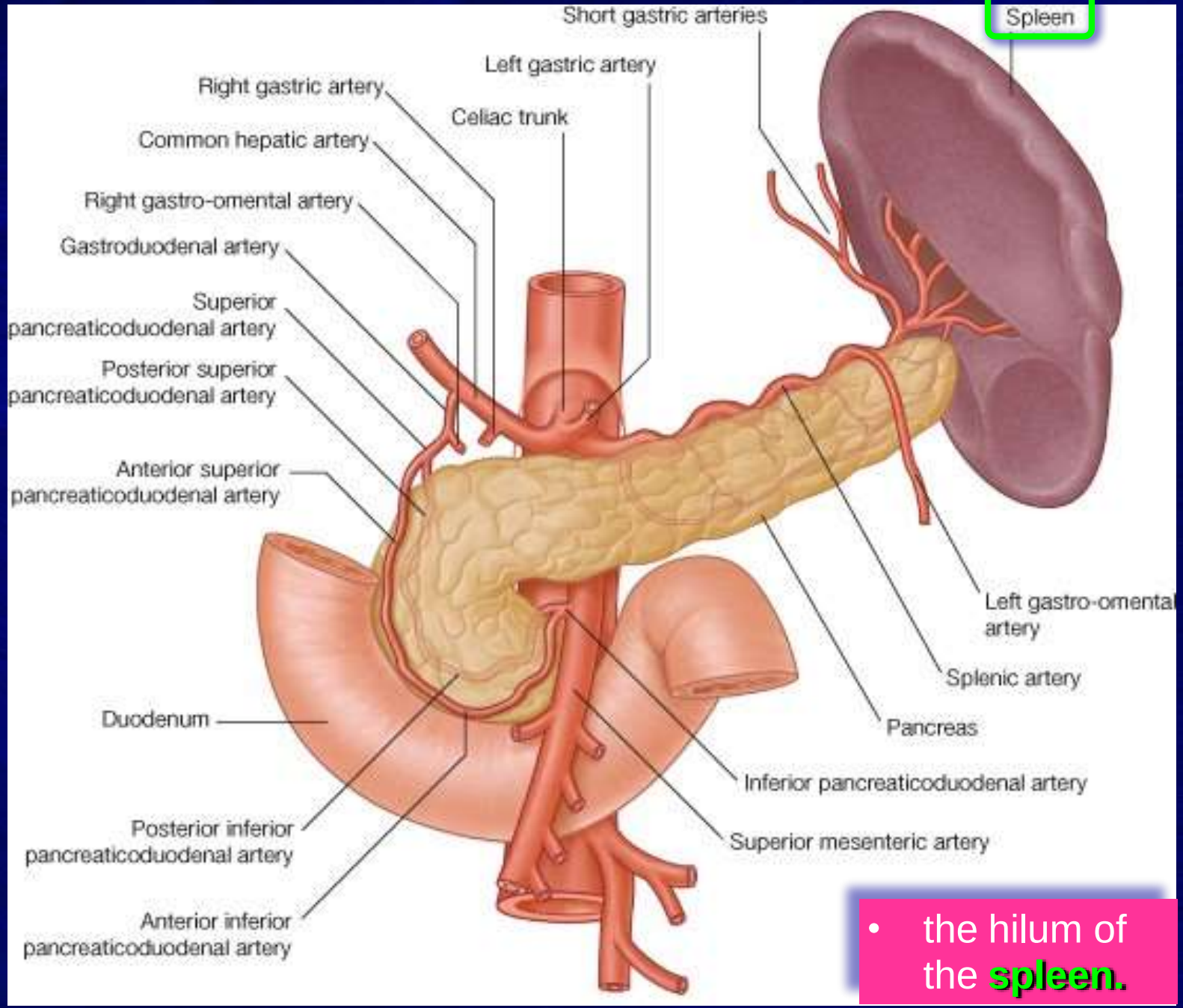
- the origin of the **superior mesenteric artery,**



- the left **psoas muscle,**

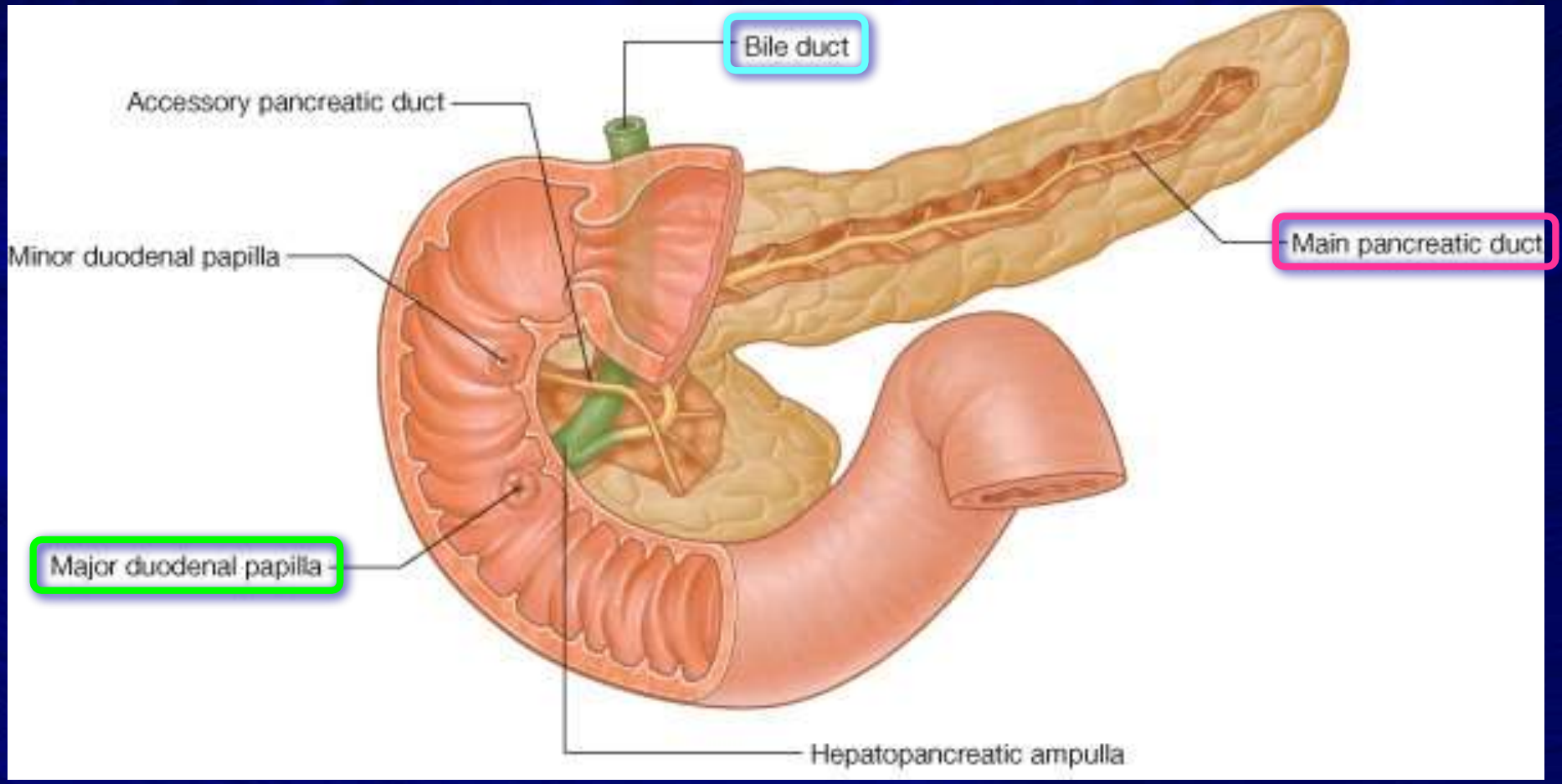


- the **left suprarenal gland,**
- the **left kidney,** and …

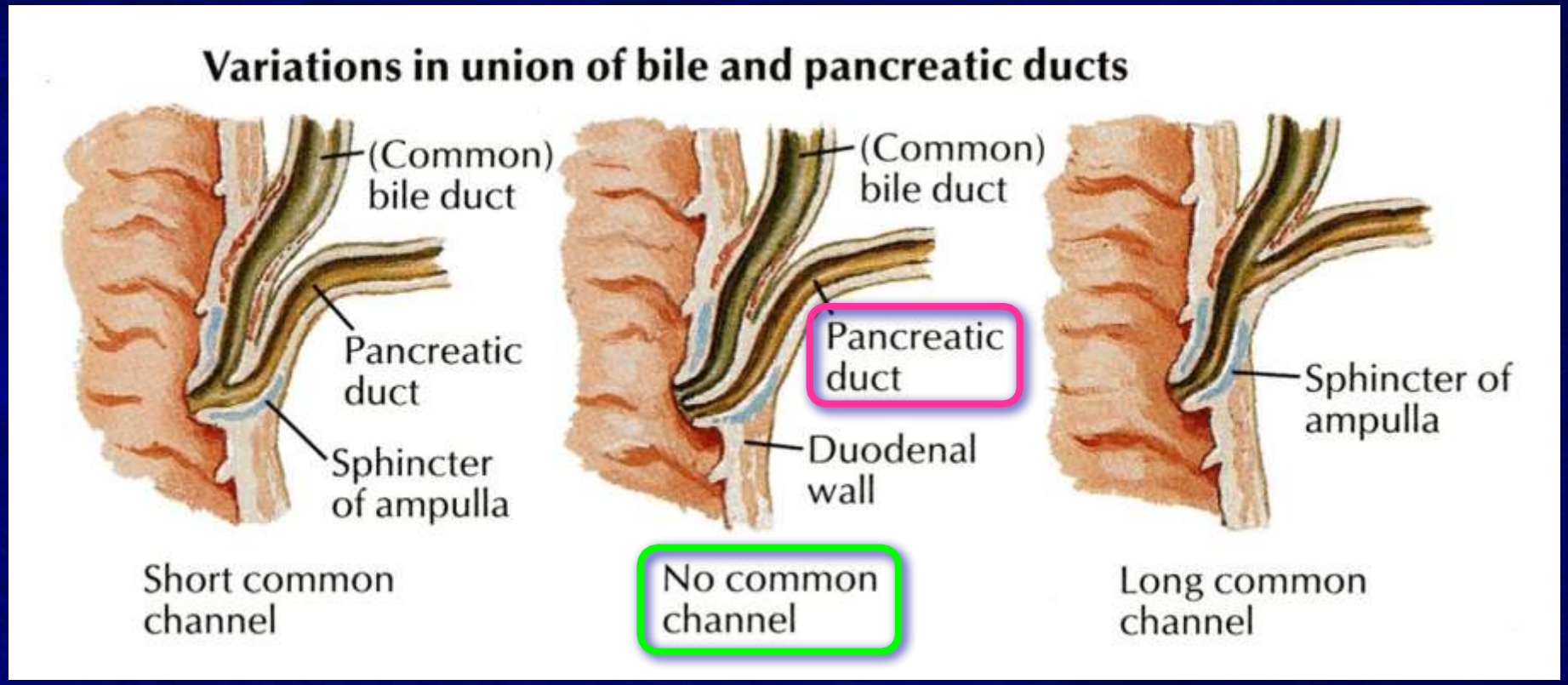


- the hilum of the **spleen**.

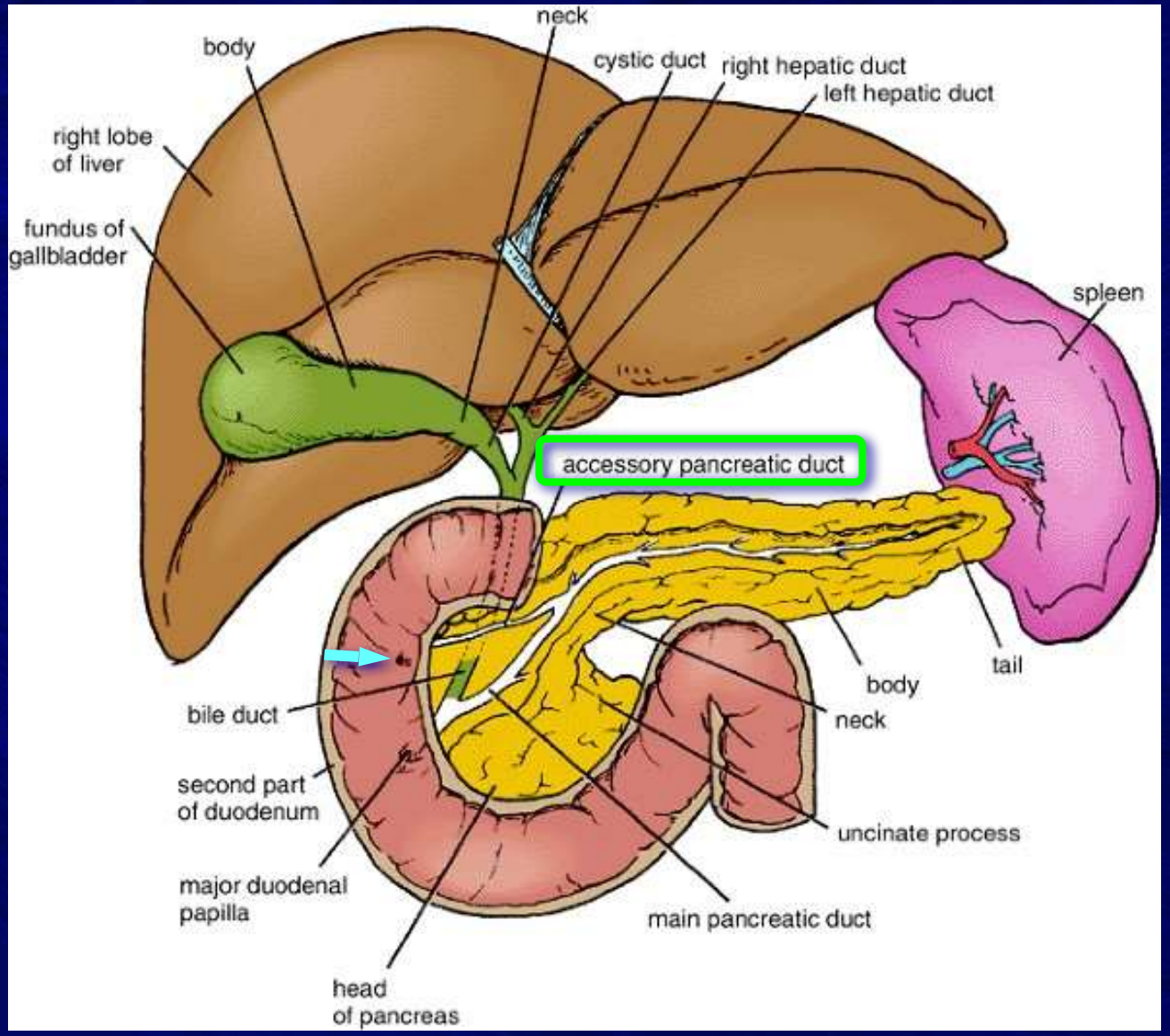
Pancreatic Ducts



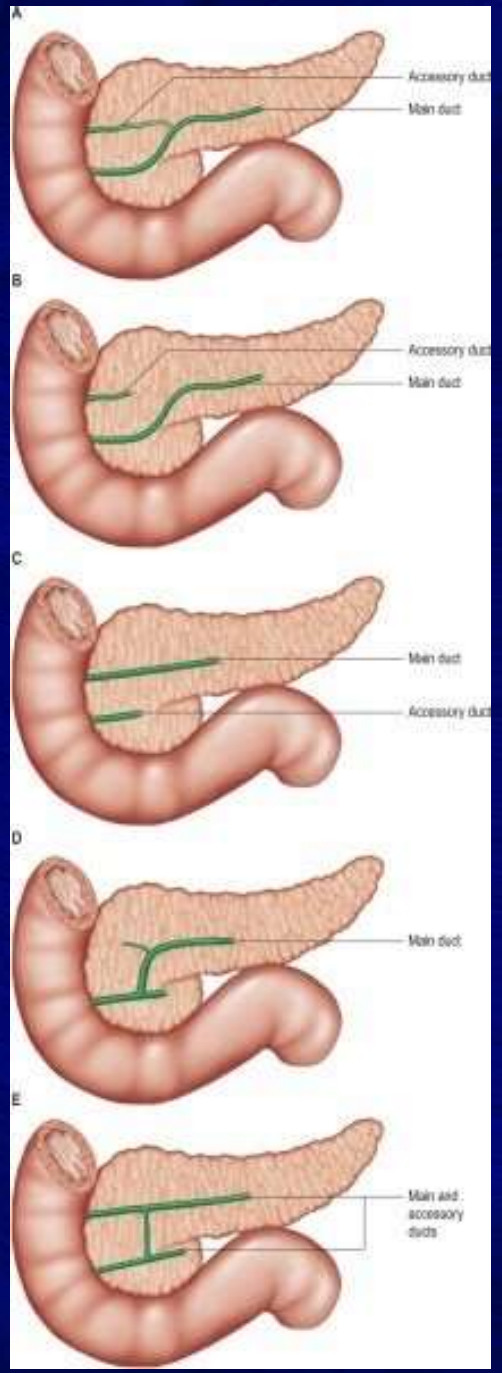
- The **main duct of the pancreas** begins in the tail and runs the length of the gland, receiving numerous tributaries on the way.
- It opens into the *second part* of the duodenum at about its middle *with the bile duct* on the **major duodenal papilla**.



- Sometimes the **main duct**
- *drains separately* into the duodenum.



- The **accessory duct** of the pancreas, when present, drains the upper part of the head and then
- opens into the duodenum a short distance above the main duct on the **minor duodenal papilla**.



The accessory duct frequently *communicates (A, E)* with the main duct.

Variations in the ductal anatomy of the pancreas.

A, Normal (50%).

B, Absence of communication between normally sited accessory duct and main ducts (10%).

C, Persistance of complete ventral and dorsal ducts with separate drainage (5%).

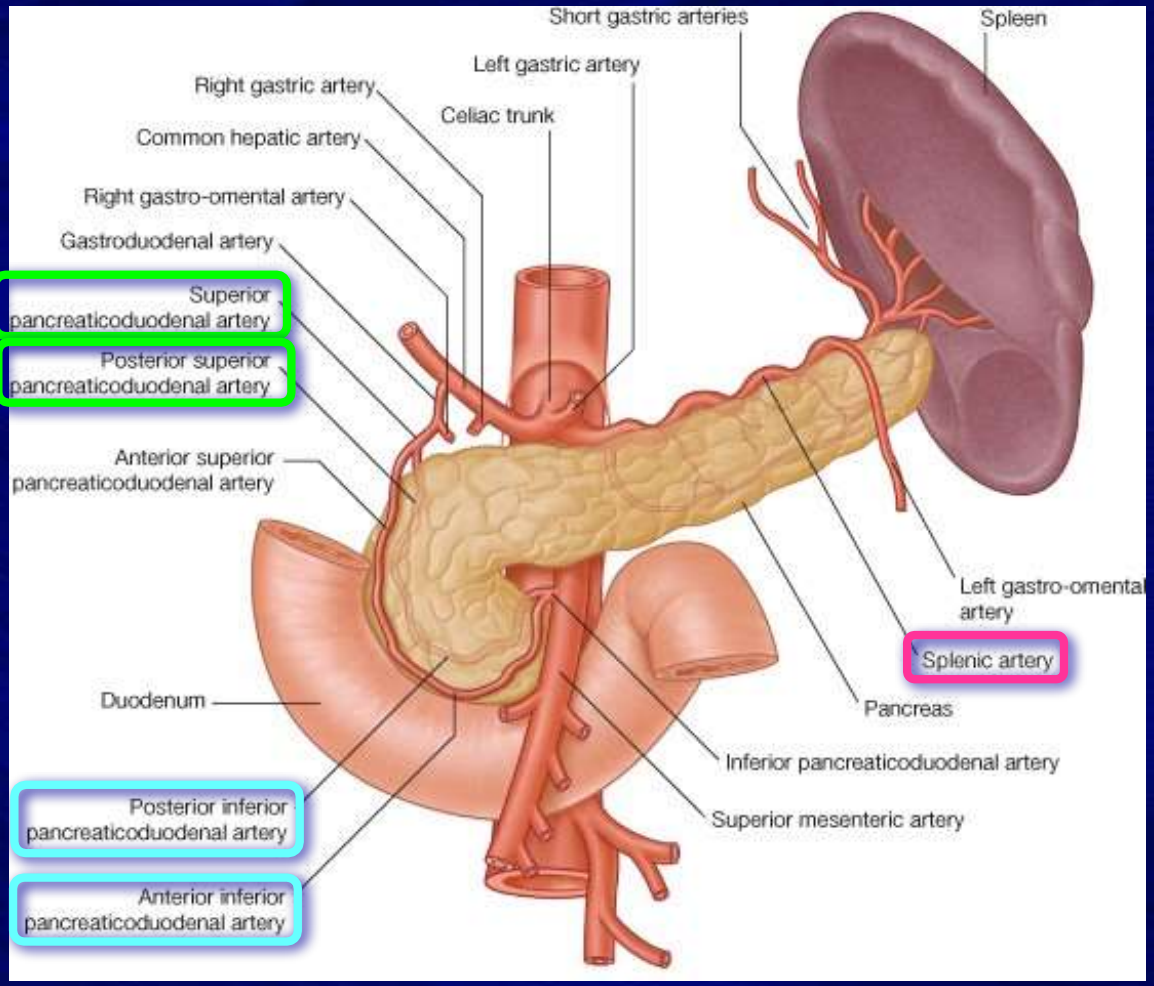
B and **C** are both forms of 'pancreas divisum'.

D, Absence of accessory duct (20%).

E, Conjoined drainage of persistant ventral and dorsal ducts (<5%).

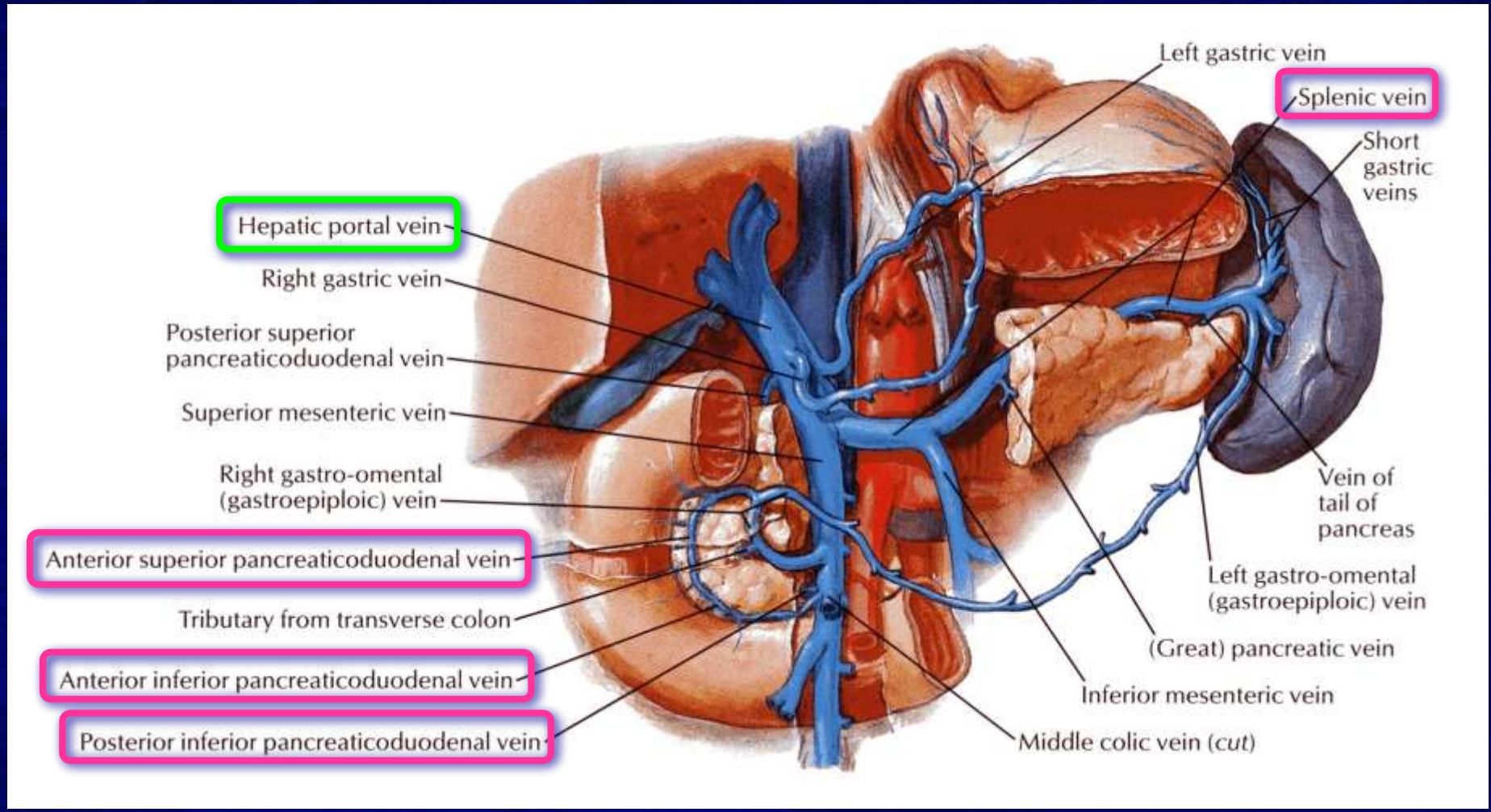
Blood Supply

Arteries



- The **splenic** and
- the **superior** and
- **inferior pancreatico-duodenal arteries** supply the pancreas.

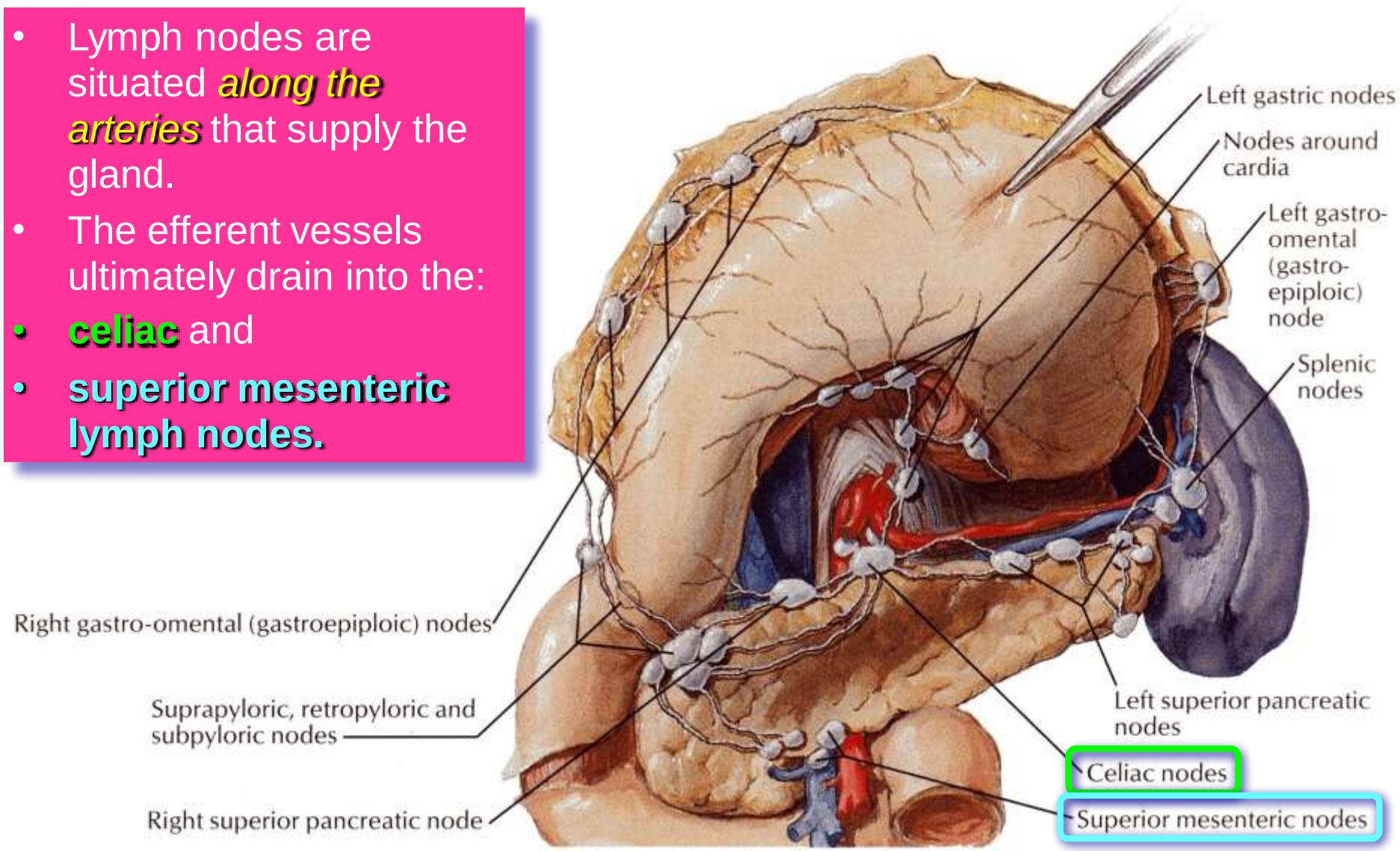
Veins



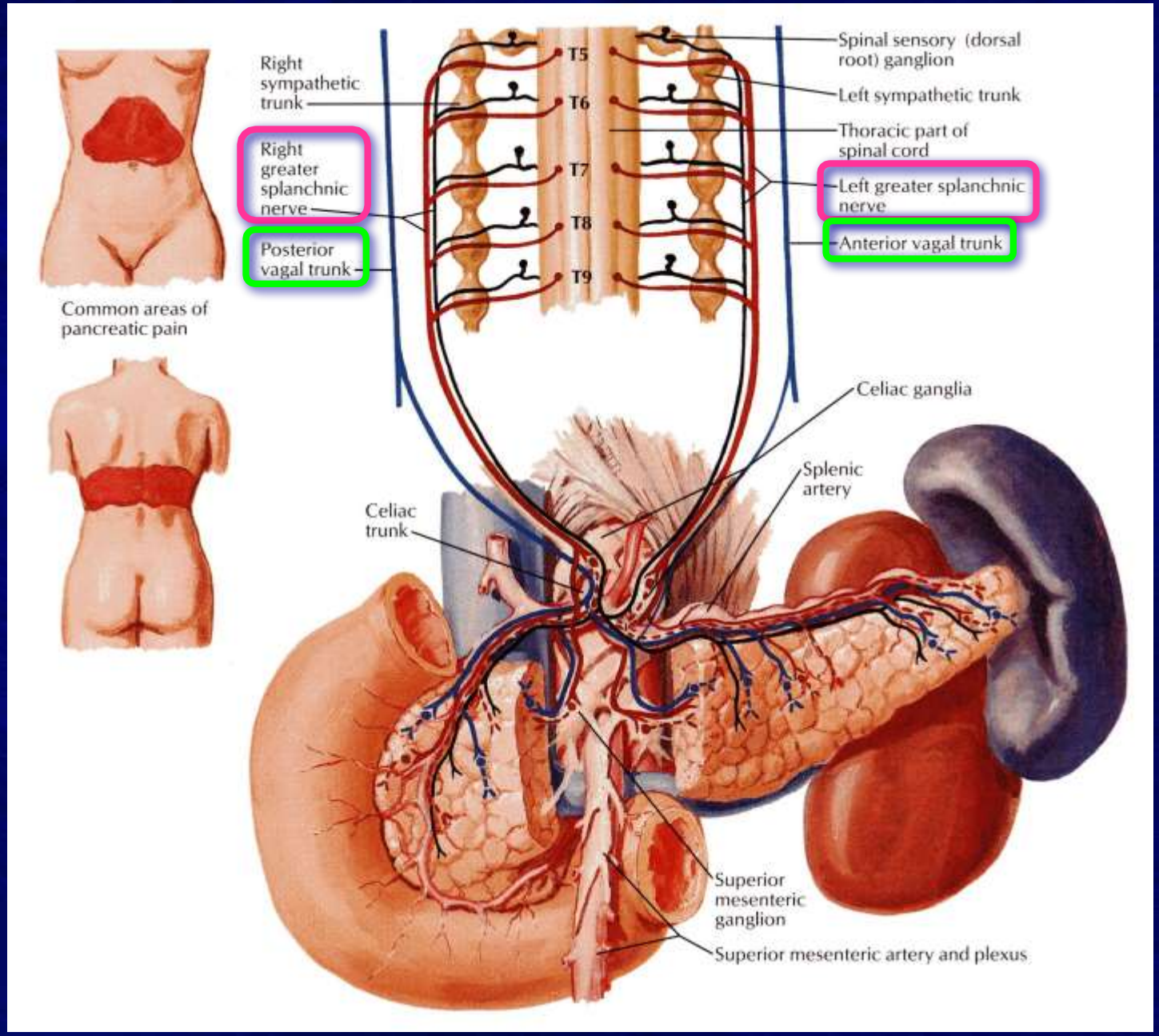
- The **corresponding veins** drain into the **portal system.**

Lymph Drainage

- Lymph nodes are situated ***along the arteries*** that supply the gland.
- The efferent vessels ultimately drain into the:
- **celiac** and
- **superior mesenteric lymph nodes.**



Nerve Supply



Sympathetic and **parasympathetic** (vagal) nerve fibers supply the area.

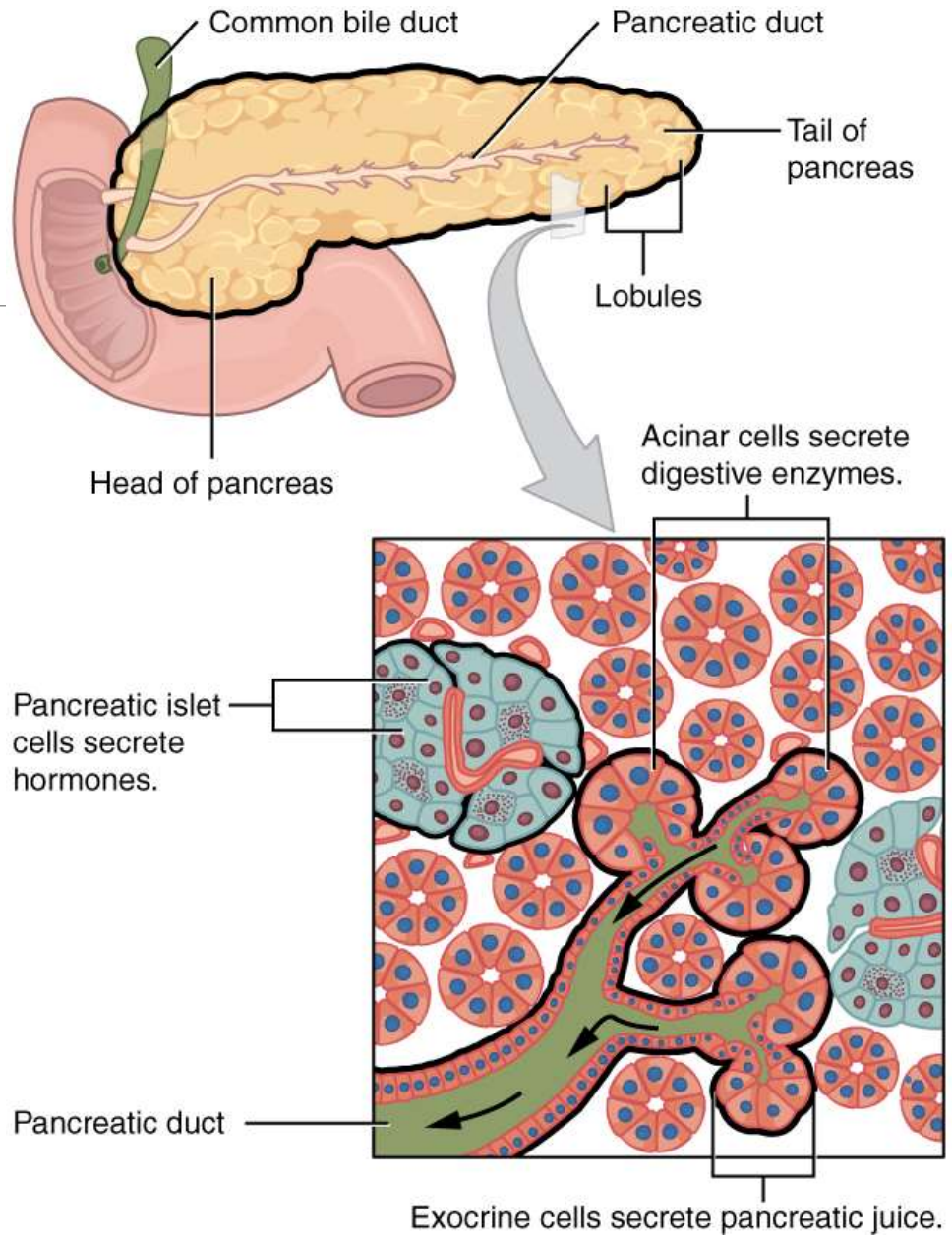
STRUCTURE AND HISTOLOGY

The pancreas has two major components: the exocrine structure and the endocrine structure.

The exocrine structure of the pancreas forms 80-90% of the pancreatic mass, while the endocrine structure forms approximately 2%.

The remainder of the pancreas is composed of extracellular matrix, blood vessels, lymph & nerves.

The exocrine component secretes the enzymes responsible for digestion, and the endocrine component is critical in glucose homeostasis.



Exocrine Structure

The exocrine structure of the pancreas is composed of two main components: the acinar cells and the ductal network.

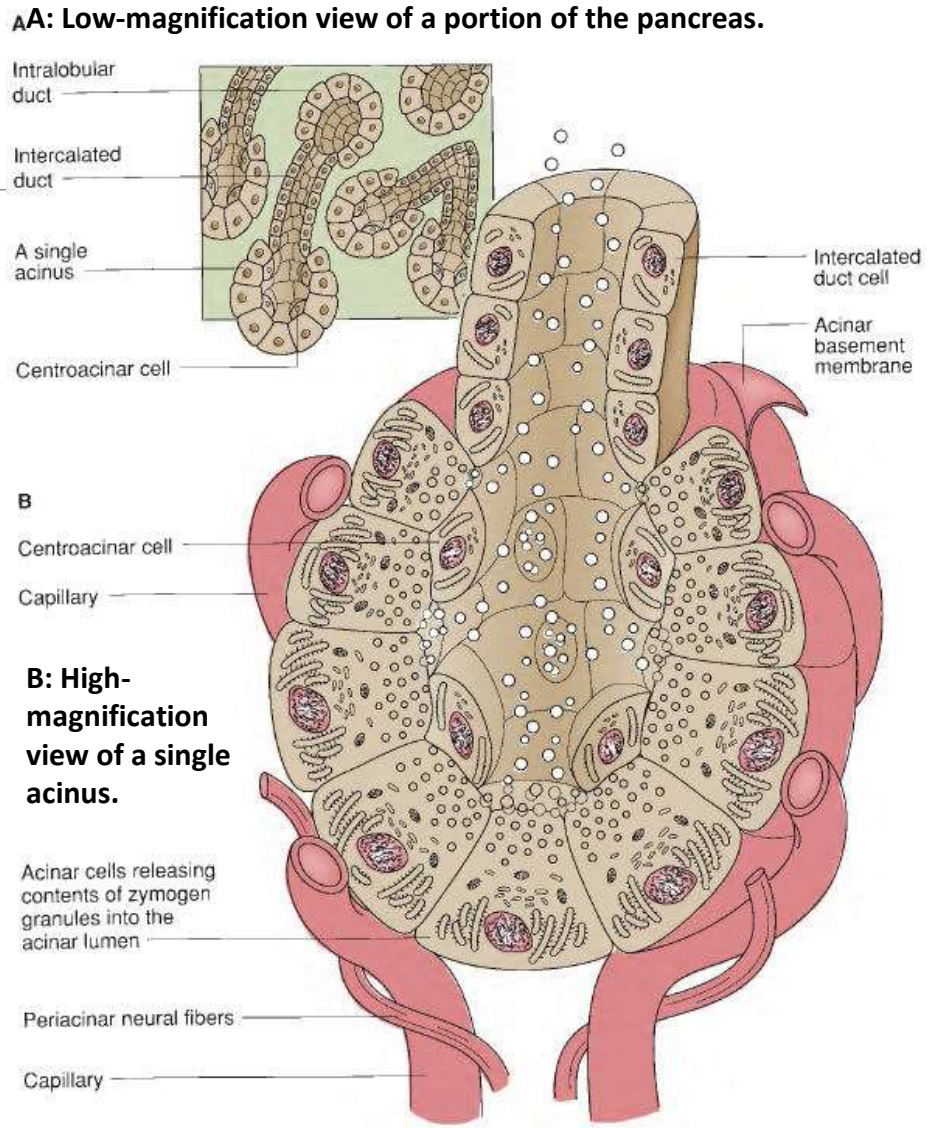
The acinar cells produce and secrete the enzymes responsible for digestion. The role of the ductal system is to carry the digestive secretions to the duodenum.

The acinar cells are pyramidal cells with an apex that faces the pancreatic ductal network. Within the apex of the cells there are numerous zymogen granules, which contain the digestive enzymes for secretion into the ductal system.

20 - 40 acinar cells cluster together to form the functional unit called an acinus.

A second cell type in the acinus, the centroacinar cell, functions to secrete fluid and electrolytes of the correct pH into the pancreatic ductal system.

Histologic anatomy of the acinus.



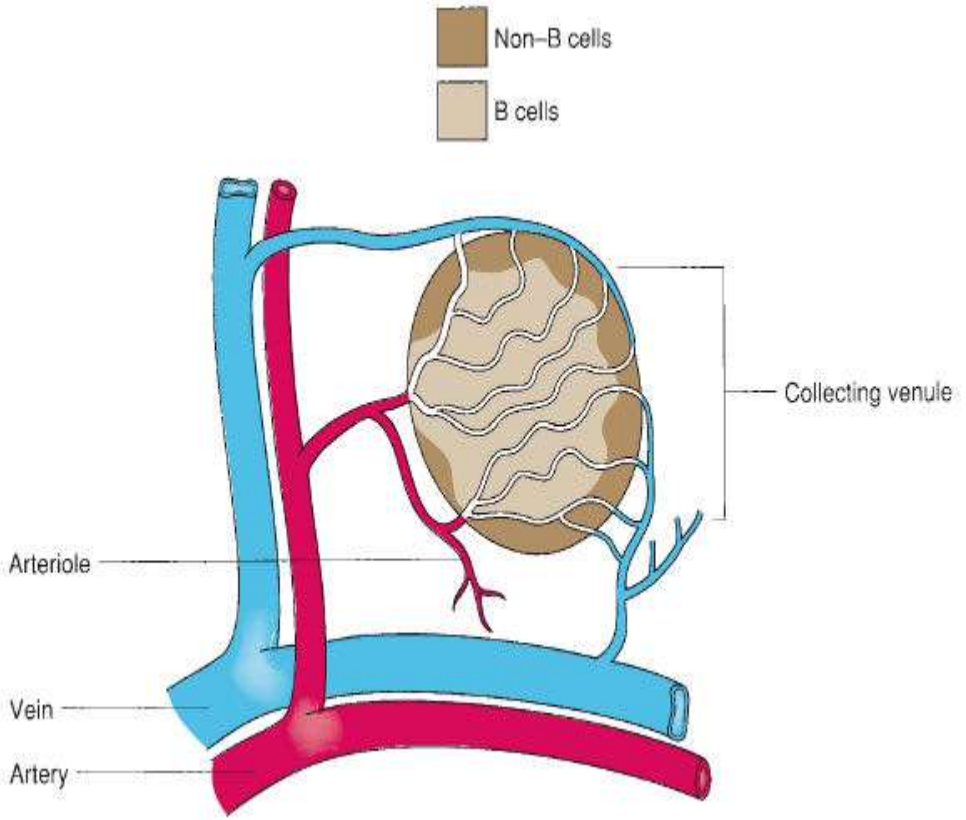
Endocrine Structure

The pancreatic islet cells are of neural crest origin and part of the family of Amine Precursor Uptake and Decarboxylation (APUD) cells.

The islets are composed of four cell types:
Alpha (A) cells (10% of Islet cell mass) secrete glucagon,
Beta (B) cells (70% of islet cell mass) secrete insulin and amylin,
Delta (D) cells (5% of Islet cell mass) secrete somatostatin, and
F cells (15% of Islet cell mass) secrete pancreatic polypeptide.

The distribution of endocrine cell types is not uniform throughout the pancreas:
B and D cells are uniformly distributed throughout the gland.
A cells are concentrated in the body and tail of the pancreas.
F cells are concentrated in the uncinate process.
This distribution is important clinically, since resection of different parts of the pancreas will have varying endocrine effects.

Diagram of a typical islet.



Simplified Classification of Pancreatic Tumors

- **Primary tumors**
  - Exocrine
    - Ductal adenocarcinoma
    - Serous cystic tumor
    - Mucinous cystic tumor
    - Solid-pseudopapillary-mucinous tumor
    - Acinar cell carcinoma
    - Anaplastic carcinoma
    - Pancreatoblastoma
  - Endocrine
    - Insulinoma
    - Gastrinoma
    - Glucagonoma
    - Vipoma
    - Somatostatinoma
    - Nonhyperfunctiong tumor
  - Nonepithelial tumor
    - Lymphoma
    - Teratoma
    - Lymphangioma
    - Lipoma
    - Neural tumors
- **Secondary tumors**

The most common of all

WHO histological classification of tumours of the exocrine pancreas

Epithelial tumours

Benign	
Serous cystadenoma	8441/0[1]
Mucinous cystadenoma	8470/0
Intraductal papillary-mucinous adenoma	8453/0
Mature teratoma	9080/0
Borderline (uncertain malignant potential)	
Mucinous cystic neoplasm with moderate dysplasia	8470/1
Intraductal papillary-mucinous neoplasm with moderate dysplasia	8453/1
Solid-pseudopapillary neoplasm	8452/1
Malignant	
Ductal adenocarcinoma ***The most common of all***	8500/3
Mucinous noncystic carcinoma	8480/3
Signet ring cell carcinoma	8490/3
Adenosquamous carcinoma	8560/3
Undifferentiated (anaplastic) carcinoma	8020/3
Undifferentiated carcinoma with osteoclast-like giant cells	8035/3
Mixed ductal-endocrine carcinoma	8154/3
Serous cystadenocarcinoma	8441/3
Mucinous cystadenocarcinoma	8470/3
– non-invasive	8470/2
– invasive	8470/3
Intraductal papillary-mucinous carcinoma ***(IPMN) Important entity***	3/3
– non-invasive	8453/2
– invasive (papillary-mucinous carcinoma)	8453/3
Acinar cell carcinoma	8550/3
Acinar cell cystadenocarcinoma	8551/3
Mixed acinar-endocrine carcinoma	8154/3
Pancreatoblastoma	8971/3
Solid-pseudopapillary carcinoma	8452/3
Others	

Non-epithelial tumours

Secondary tumours

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, (/2 for in situ carcinomas) and /3 for malignant tumours.

Endocrine Tumors

Pancreatic Neuro-Endocrine Tumors (PanNETs, PETs, or PNETs) = islet cell tumors = pancreatic endocrine tumors:

- are neuroendocrine neoplasms that arise from cells of the endocrine and nervous system within the pancreas.

Only 1 - 2% of clinically significant pancreas neoplasms are PanNETs.

Endocrine Tumors

Most types of Pan NET are malignant (except Insulinoma).

Generally, Pan NET (benign & malignant) can also be classified as **functional** or **non-functional**.

Generally, **non-functional PanNET are more common** than functional.

Functional PanNET (**insulinomas ”most common”,** gastrinomas, Vasoactive Intestinal Peptide (VIP)omas, glucagonomas, and somatostatinomas).

Non-functional PanNET are not associated with a clinical syndrome, but can still produce symptoms related to the presence of the tumor or its metastases.

Immunohistochemistry can help identify the type of NET, as well as serve as a biomarker for diagnosis. For example, there is a unique occurrence of psammoma bodies in somatostatinomas (functioning PanNET) localized within the duodenum.

Endocrine Tumors

Pan NETs are a type of neuroendocrine tumor (NET), representing about one third of GastroEnteroPancreatic NeuroEndocrine Tumors (GEP-NETs).

Aggressive PanNET tumors have traditionally been termed "islet cell carcinoma“,

While others termed “islet cell tumors”.

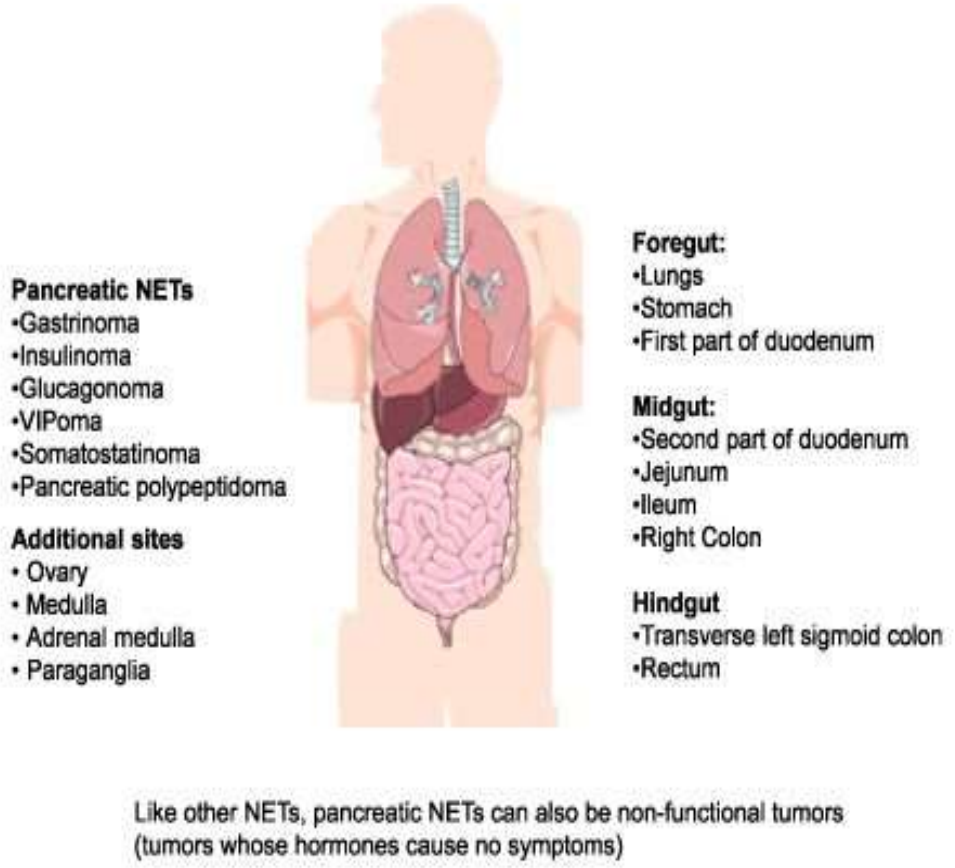


Table 1 Cellular classifications of pancreatic neuroendocrine tumors (islet cell tumors)

	Secreted peptide hormone(s)	Pancreatic NET	Clinical manifestation/syndrome
Islet Cell			
Alpha (α)	Glucagon	Glucagonoma	Diabetes, dermatitis, NME
Beta (β)	Insulin	Insulinoma	Fasting hypoglycemia, neuroglycopenia
Delta (δ)	Somatostatin	Somatostatinoma	Steatorrhea, cholelithiasis, mild diabetes
A→D	VIP, other 5-HT ACTH MSH		WDHA Carcinoid Cushing Syndrome Hyperpigmentation
Interacinar cell			
F	Pancreatic polypeptide (PP)	PPoma	Non-functional or various syndromes
EC	5-HT	Carcinoid	Carcinoid syndrome (facial flushing, secretory diarrhea, wheezing, right-sided heart valve abnormalities)

VIP, Vasoactive intestinal peptide; 5-HT, serotonin; ACH, andrenocarticotropin; MSH, melanocyte stimulating hormone; WDHA, watery diarrhea, hypokalemia, achlorhydria; EC, enterochromaffin; Modified from: national cancer institute at the national institutes of health, pancreatic neuroendocrine tumors (islet cell tumors) Treatment (PDQ®); Health professional version, last modified: 06/29/2012, http://www.cancer.gov/cancertopics/pdq/treatment/isletcell/HealthProfessional.

CLASSIFICATION OF FUNCTIONAL PANCREATIC ENDOCRINE TUMORS				
TUMOR (SYNDROME) *Arranged according to frequency*	*SOURCE*	*CLINICAL FEATURES*	*EXTRAPANCREATIC LOCATION*	*MALIGNANCY RATE*
Insulinoma	Beta cells	Whipple's Triad: **Hypoglycaemia, CNS dysfunction** & **Reversal by glucose.**	Rare	**10%**
Gastrinoma (Zollinger-Ellison)	G cells	Peptic ulcer Diarrhea	Frequent	50%
VIPoma (Verner-Morrison; WDHA; pancreatic cholera)		WDHA syndrome: **Watery Diarrhea, Hypokalemia,** & either **Achlorhydria** or **Acidosis.**	10%	Most
Glucagonoma	Alpha cells	Diabetes, Dermatitis (necrolytic migratory erythema)	Rare	Most
Somatostatinoma	Delta/S cells	Diabetes, Steatorrhea, Gallstones	Rare	Most

Endocrine Tumors

Insulinomas is the **most common type** of **Functional PanNET.**

90% of insulinomas are solitary, **90%** are sporadic, and **90%** are benign with location evenly distributed throughout the pancreas.

75% of gastrinomas are sporadic (25% are associated with Multiple Endocrine Neoplasia type 1 MEN-1 syndrome), and all should be considered to be of malignant potential.

Most gastrinomas are located in the *gastrinoma triangle* and may be intrapancreatic, within the wall of the duodenum, or in a peripancreatic lymph node, and in most cases local resection (enucleation) may be adequate therapy.

Glucagonomas usually present with a characteristic severe dermatitis (termed *necrolytic migratory erythema*) and are typically large and bulky and often with metastatic disease.

Pancreatic Cancer

Pancreatic cancer is the fourth leading cause of cancer death in USA, but in Jordan it is not one of the top five cancers.

Currently, only 15-20% of patients diagnosed with pancreatic adenocarcinoma are candidates for pancreatic resection.

5-year survival is 15-20% for patients with resected disease and only 3% for all stages combined.

The nonspecific symptoms associated with early pancreatic cancer, the inaccessibility of the pancreas to examination, the aggressiveness of the tumors, and the technical difficulties associated with pancreatic surgery make pancreatic cancer one of the most challenging diseases treated by general surgeons.

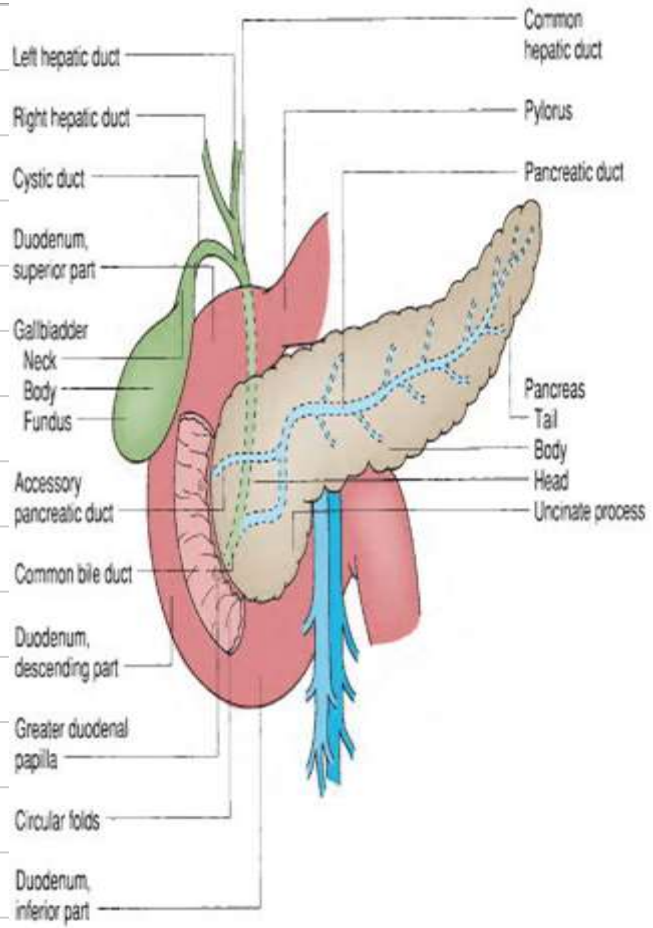
In recent years, significant advances have been made in our understanding of the pathogenesis and clinical management of pancreatic cancer.

RISK FACTORS FOR PANCREATIC CANCER			
	INCREASED RISK	*POSSIBLE RISK*	*UNPROVED RISK*
Demographic factors	Advancing age Male sex Black race	Geography	Socioeconomic status Migrant status
Host factors	Hereditary Non-Polyposis Colorectal Cancer (HNPCC) Familial breast cancer Peutz-Jeghers syndrome Ataxia-telangiectasia Familial Atypical Multiple Mole Melanoma (FAMMM) Hereditary pancreatitis		Peptic ulcer surgery
Environmental factors	**Tobacco**	Diet Occupation	Alcohol Coffee Radiation
Modified from Gold EB, Goldin SB. Epidemiology of and risk factors for pancreatic cancer. *Surg Oncol Clin North Am* 1998;7:67.			

GENETIC ALTERATIONS IN PANCREATIC ADENOCARCINOMAS		
GENE	*CHROMOSOME LOCUS*	*FREQUENCY (%)*
ONCOGENES		
K-*ras*	12	90
TUMOR-SUPPRESSOR GENES		
p16	9p	95
p53	17p	50-75
DPC4	18q	55
BRCA2	13q	7
LKB1	17p	4
MKK4	19p	5
ALK4	12q	2
Genome maintenance 4 genes *bMSH2*, *hMLH1*	2P, 3P	
Reproduced with permission from Hruban RH. Pancreatic cancer: from genes to patient care. *J Gastrointest Surg* 2001;5:583.		

GENETIC SYNDROMES ASSOCIATED WITH HEREDITARY PANCREATIC CANCER				
SYNDROME	*MODE OF INHERITANCE*	*GENE*	*FOLD INCREASE IN RISK*	*MANIFESTATION OF PANCREATIC CANCER*
Peutz-Jeghers	AD	*STKlI*	140×	Hamartomatous polyps of the gastrointestinal tract; mucocutaneous melanin macules
Hereditary pancreatitis	AD	*PRSSI*	60×	Recurrent episodes of severe pancreatitis starting at a young age
Familial pancreatic cancer	Unknown	Unknown	18×	At least one pair of first-degree relatives with pancreatic cancer
FAMMM	AD	p16	20×	Multiple nevi, atypical nevi, melanomas
Familial breast cancer 2	AD	*BRCA2*	10×	Breast, ovarian, and pancreatic cancer
HNPCC	AD	*MSH2HLHI*	Unknown	Colonic, endometrial, and gastric cancers; mutator phenotype
AD, autosomal dominant; FAMMM, familial atypical multiple mole melanoma; HNPCC, hereditary nonpolyposis colorectal cancer.				

SYMPTOMS *OF PANCREATIC CANCER*			
SYMPTOM	*PATIENTS (%)*	*SYMPTOM*	*PATIENTS (%)*
HEAD		**BODY AND TAIL**	
Weight loss	92	Weight loss	100
Jaundice	82	Pain	87
Pain	72	Weakness	43
Anorexia	64	Nausea	43
Dark urine	63	Vomiting	37
Light stools	62	Anorexia	33
Nausea	45	Constipation	27
Vomiting	37	Hematemesis	17
Weakness	35	Melena	17
Pruritus	24	Jaundice	7
Diarrhea	18	Fever	7
Melena	12	Diarrhea	3
Constipation	11		
Fever	11		
Hematemesis	8		



SIGNS *OF PANCREATIC CANCER*			
SIGN	*PATIENTS (%)*	*SIGN*	*PATIENTS (%)*
HEAD		**BODY AND TAIL**	
Jaundice	87	Palpable liver	33
Palpable liver	83	Tenderness	27
Palpable gallbladder	29	Abdominal mass	23
Tenderness	26	Ascites	20
Ascites	14	Jaundice	13
Abdominal mass	13	Diarrhea	3

Presenting Signs and Symptoms of Pancreatic Tumours

Pancreatic cancer can occur anywhere in the pancreas, but it occurs in the pancreatic head in approximately 75% of cases.

Patients with cancer in the head of the pancreas often present with obstructive jaundice secondary to occlusion of the intrapancreatic bile duct.

Patients with cancer in the body and tail of the pancreas often present with abdominal pain and other vague abdominal symptoms as these tumors do not obstruct the bile duct and lead to obvious clinical signs. As a result, tumors in the pancreatic head are often picked up at an earlier stage.

Similarly, in benign pancreatic diseases such as chronic pancreatitis, disease in the pancreatic head may cause benign biliary strictures and jaundice, whereas disease in the body and tail more often presents with abdominal pain.

Patients with cancer in the pancreatic head often have invasion of the adjacent duodenum. They may present with or develop signs and symptoms of duodenal or gastric outlet obstruction requiring gastrojejunostomy.

In addition, as pancreatic cancer progresses, the nervous plexuses along the celiac axis in the retroperitoneum can be invaded by tumor, causing the characteristic intractable back pain. Celiac ganglion blockade (sympathectomy) or neurolysis using alcohol can provide significant pain relief by interrupting these somatic fibers.

Investigations

The best imaging technique for a pancreatic neoplasm is Computed Tomography **(CT) scan -** pancreatic protocol.

MRCP offers no significant advantages over CT. MRI can be considered an alternative in patients with allergies to iodinated contrast agents and in patients with renal insufficiency.

MRCP with **secretin stimulation** provides a clearer view of the ductal system and of its relations with cystic lesion of the pancreas, thus allowing better diagnostic classification of the IPMN.

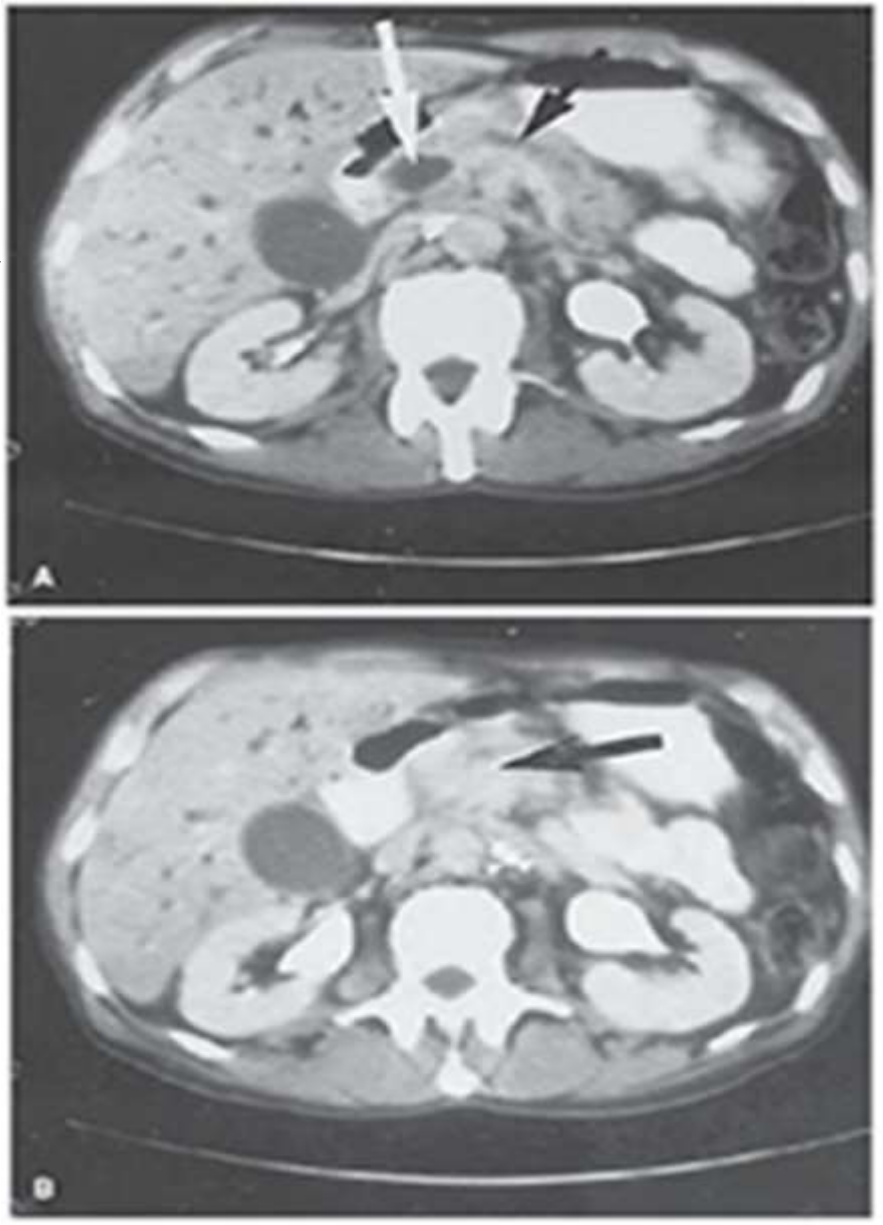
Endoscopic ultrasonography (+/- biopsy) is particularly useful in localizing tumors in patients with gastrinoma and insulinoma.

ERCP may add brush cytology in some cases, but very little yeald.

ERCP may be useful for palliative biliary stent insertion.

Investigations

Computed tomography scan is the preferred non-invasive imaging test for the diagnosis and staging of pancreatic cancer demonstrating the primary lesion and its relationship to adjacent visceral vessels as well as metastatic disease to the liver and peritoneum.

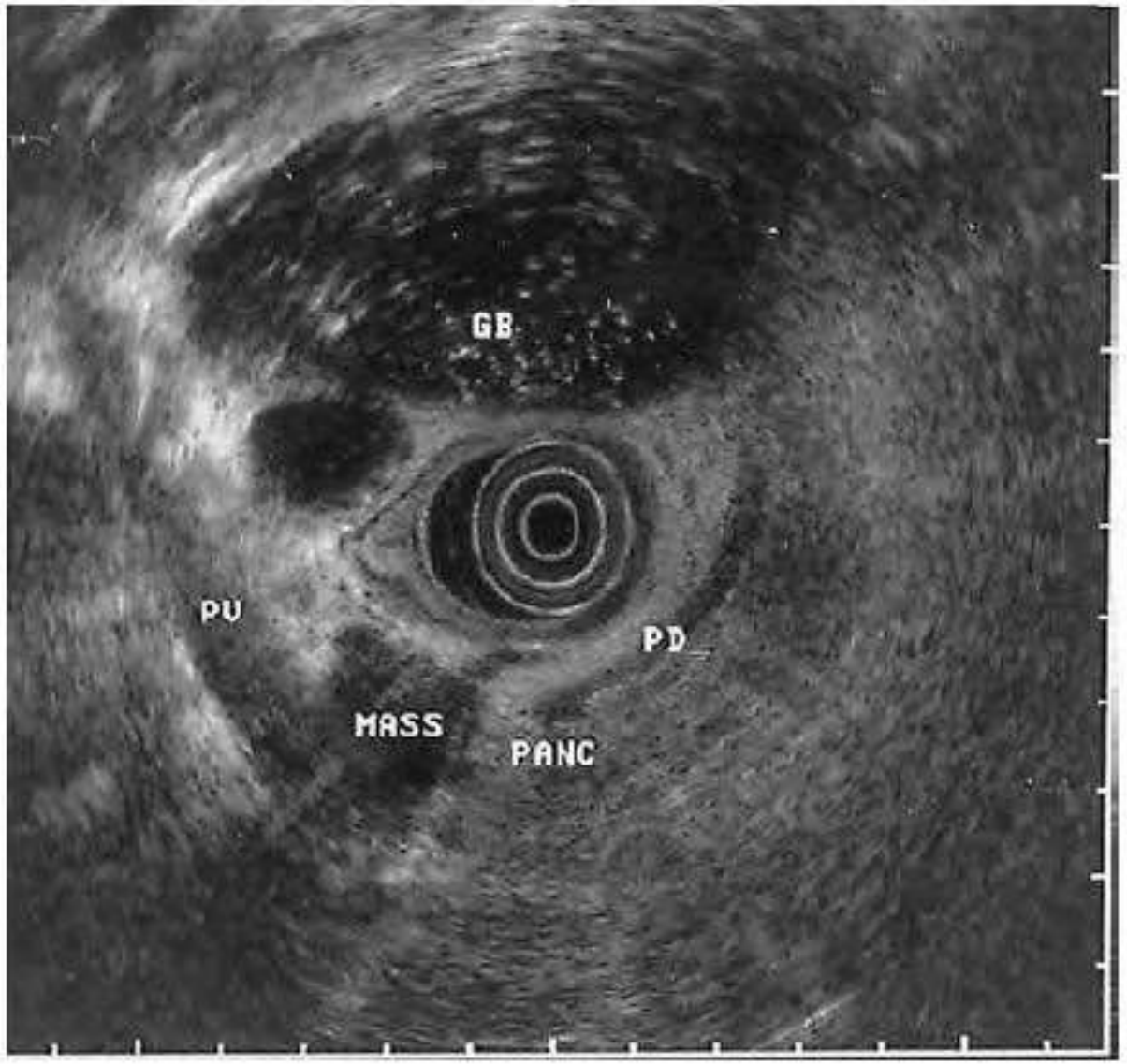


CT-scan abdomen of a patient with adenocarcinoma of the pancreas.
A: The obstructed and dilated common bile duct (light arrow) and pancreatic duct (dark arrow) can be seen.
In the adjacent cross section **(B)**, a large mass is present in the head of the pancreas (arrow).

Investigations

The strengths of Endoscopic ultrasonogram (EUS):
Clarification of small lesions (<2 cm) when CT findings are questionable or negative,
Detection of malignant lymphadenopathy,
Detection of vascular involvement, and
Ability to perform EUS-guided fine-needle aspiration (FNA) for definitive diagnosis and staging.

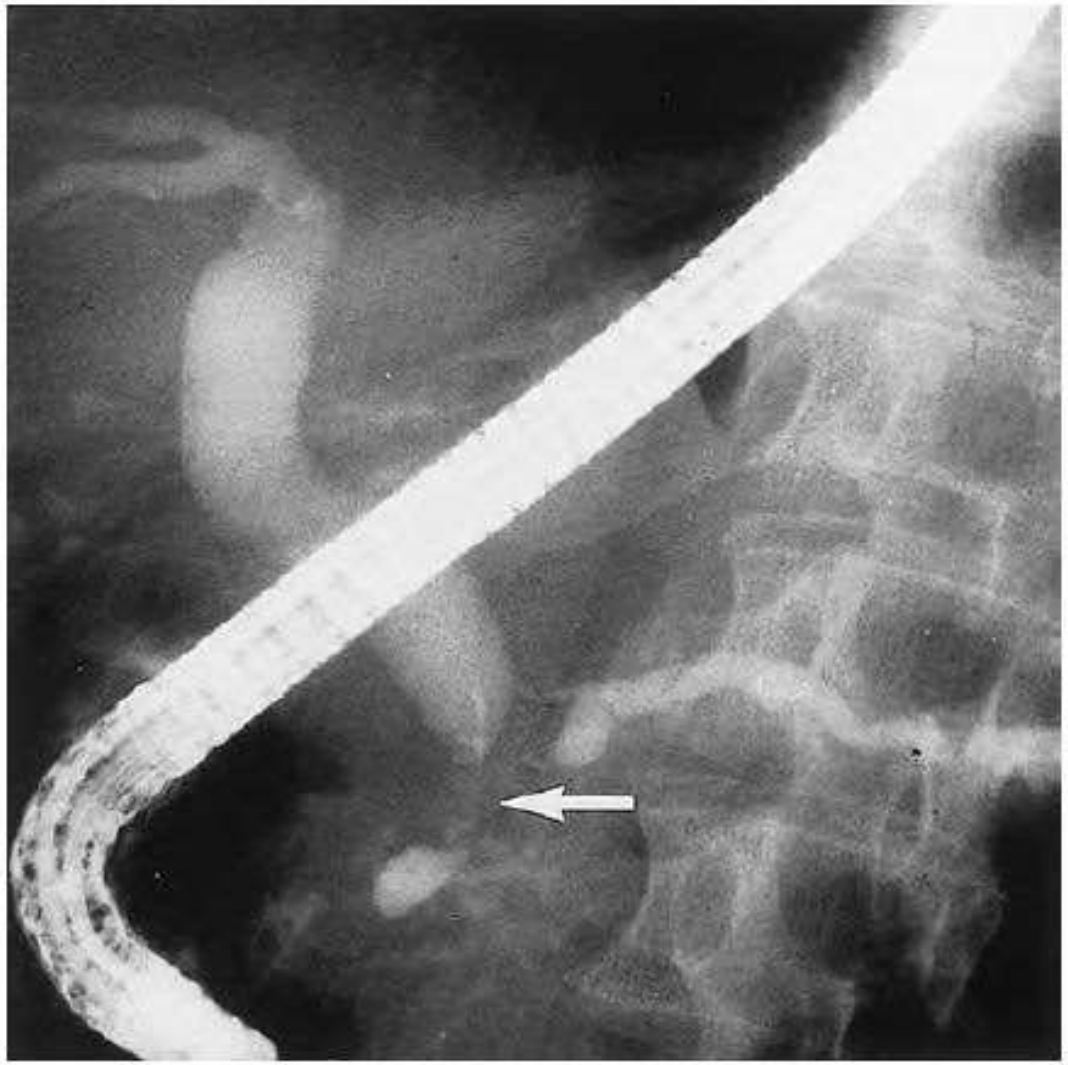
EUS is not effective in assessing metastatic disease to the liver.



EUS of a 2.2-cm mass in the head of the pancreas. The transducer tip is located in the duodenum. The dilated common bile duct and gallbladder (GB) can be seen at the top of the image. The pancreatic duct (PD) is also dilated. The mass involves the portal vein (PV).

Investigations

Although ERCP is reliable in confirming the presence of a clinically suspected pancreatic cancer, it should not be used routinely. Diagnostic ERCP should be reserved for patients with presumed pancreatic cancer and obstructive jaundice in whom no mass is demonstrated on CT, symptomatic but nonjaundiced patients without an obvious pancreatic mass, and patients with chronic pancreatitis who develop jaundice.



Endoscopic retrograde cholangiopancreatography in a patient with adenocarcinoma of the pancreas demonstrates a stricture of both the distal common bile duct and the pancreatic duct (arrow).

Laboratory Tests

In patients with cancer of the **head** of the pancreas, an increase in serum total bilirubin, alkaline phosphatase, and γ-glutamyl transferase, indicating **bile duct obstruction**.

In patients with localized cancer of the **body and tail** of the pancreas, laboratory values are frequently **normal** early in the course.

Patients with pancreatic cancer may also demonstrate a **normochromic anemia** and **hypoalbuminemia** secondary to the nutritional consequences of the disease.

In patients with jaundice, the **Prothrombin Time (PT)** can be abnormally prolonged. This usually is an indication of biliary obstruction, which prevents bile from entering the gastrointestinal tract and leads to malabsorption of **fat-soluble vitamins** and decreased hepatic production **of vitamin K-dependent clotting factors**. The prothrombin time can usually be normalized by the administration of **parenteral vitamin K.**

Serum amylase and lipase levels are usually normal in patients with pancreatic cancer

Laboratory Tests

The most extensively studied **tumor marker is CA 19-9**, a Lewis blood group-related mucin glycoprotein.

Approximately **5%** of the population lacks the Lewis gene and therefore cannot produce CA 19-9.

The accuracy of the CA 19-9 level in identifying patients with pancreatic adenocarcinoma is only about 80-85%.

The combined use of CA 19-9 and CT, EUS, or ERCP can improve the accuracy of the individual tests, so that the combined accuracy approaches 100% for the diagnosis of pancreatic cancer.

Levels of CA 19-9 correlates with prognosis and **tumor recurrence**.

Laboratory Tests

In general, higher CA 19-9 values before surgery indicate an increased size of the primary tumor and increased rate of **unresectability**.

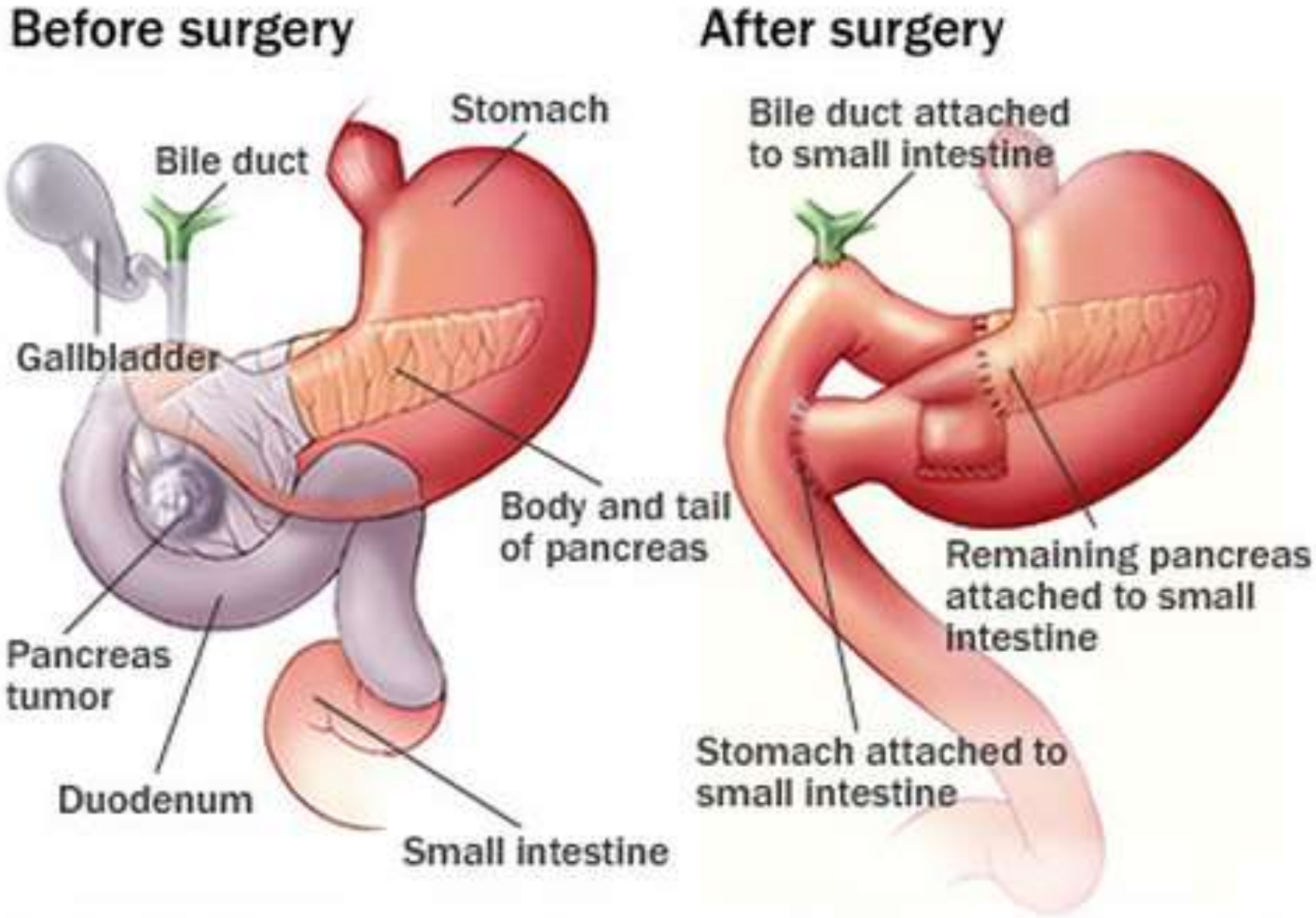
In addition, the CA 19-9 level has been used to **monitor** the results of neoadjuvant and adjuvant **chemoradiation** therapy in patients.

Increasing CA 19-9 levels usually indicate **recurrence** or **progression** of disease, whereas stable or declining levels indicate a stable tumor burden, absence of recurrence on imaging studies, and an improved prognosis.

Treatment

Pancreaticoduodenectomy (whipple's procedure or modified methods) for tumors in the Head, Neck, or Uncinate Process of pancreas.

Distal pancreatectomy for tumors in the body and tail of pancreas.



COMPLICATIONS AFTER PANCREATICODUODENECTOMY	
COMMON	**UNCOMMON**
Delayed gastric emptying Pancreatic fistula Intra-abdominal abscess Hemorrhage Wound infection Metabolic •Diabetes •Pancreatic exocrine insufficiency	Fistula •Biliary •Duodenal •Gastric Organ failure •Cardiac •Hepatic •Pulmonary •Renal Pancreatitis Marginal ulceration
From Yeo CJ, Cameron JL. Pancreatic cancer. *Curr Probl Surg* 1999;36:61, with permission.	

Treatment

Perioperative mortality rates following pancreaticoduodenectomy have fallen to the range of 2% to 5%, although perioperative complications occur in approximately 40% of patients.

The survival rate after pancreaticoduodenectomy for pancreatic cancer is approximately 20%, with factors influencing survival including tumor size, margin status, and node status.

Most data support the role for adjuvant therapy, either chemotherapy or chemoradiation, for patients following resection of pancreatic cancer.

Surgical palliation of patients with pancreatic cancer located in the head found to be unresectable at laparotomy includes biliary stents, biliary bypass, gastrojejunostomy, and chemical splanchnicectomy to palliate the symptoms of jaundice, duodenal obstruction, and pain, respectively.

THANK YOU