2021 Cancers - Upper GI Tract: Diagnosis, Workup, Staging, Treatment

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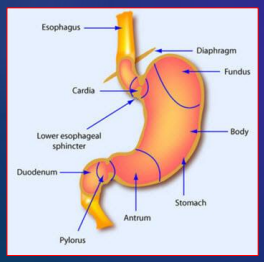
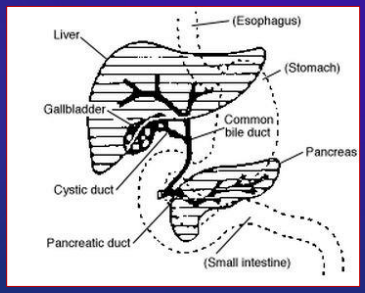
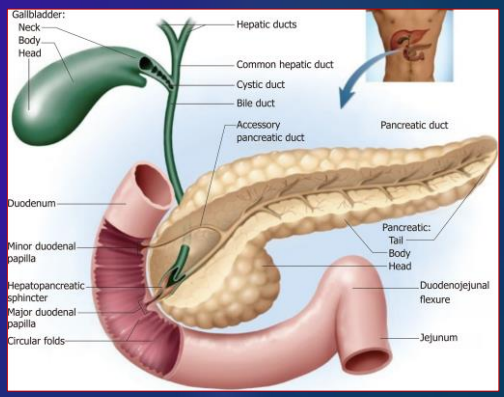
2020-2021 FCDS ANNUAL WEBCAST SERIES

FEBRUARY 18, 2021

STEVEN PEACE, CTR







CDC & Florida DOH Attribution

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FLccSC LMS – CEU Quiz –FCDS IDEA

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- Attendees must take and pass a 3-5 question CEU Quiz to get CEUs
- CEU Awards are Restricted to Attendees with a FLccSC LMS Account
- The CEU Quiz will be posted to FLccSC 1-2 hours after the webcast ends

- Only registered FLccSC Users will be given access to the CEU Quiz
- Florida attendees must have a Florida FLccSC Account to take the Quiz
- South Carolina attendees must have a South Carolina FLccSC Account
- New FLccSC States will follow similar instructions for the CEU Quiz

- Attendees can attend any of the live webcasts without receiving CEUs
- Recorded Sessions are also available for non-FLccSC Users – No CEUs

Presentation Outline

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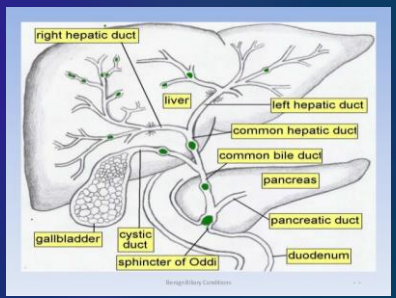
- Introduction to the Upper GI Tract
- Introduction to the Biliary System and Biliary Tree
- Introduction to the Physiology of the Upper GI Tract and Biliary System
- Incidence and Mortality – Increasing Rates Gallbladder and Liver Cancers
- Latest Advances and Use of Endoscopic Ultrasound (EUS)
- Each Section Will Cover: Anatomy/Physiology/Risk Factors/Symptoms/Classification/ Diagnosis/ Staging/Treatment for;
  - Esophagus (including GE Junction)
  - Stomach (including GE Junction)
  - Biliary System (Biliary Tree)
    - Pancreas (Pancreatic Duct)
    - Gallbladder (Intrahepatic Bile Ducts & Common Bile Duct)
    - Liver (Hepatic Ducts)
  - Upper Duodenum
- Tumor Markers and Genetic Testing
- References
- Questions



Introduction to the Upper GI Tract

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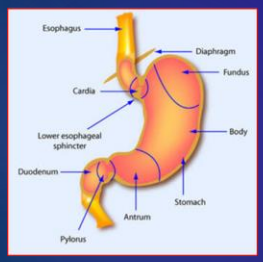
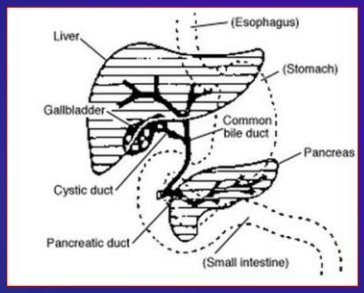
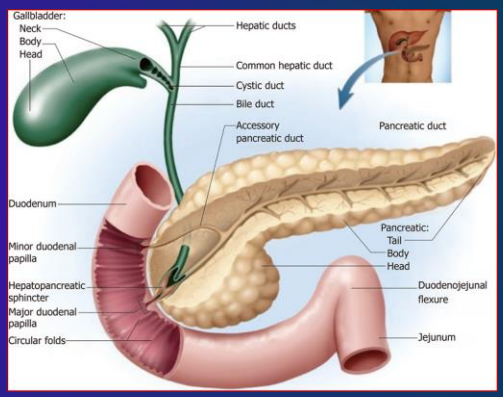
Cancers from these sites account for approximately 10% of all incident cancers – but, make up nearly 20% of all cancer deaths.







Introduction to the Upper GI Tract

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What is upper gastrointestinal (upper GI) cancer?

- Seven main types of upper gastrointestinal (Upper GI) cancer: esophageal, stomach, pancreatic, duodenal, gall bladder and bile duct, liver and small bowel cancers.
- **Esophageal cancer** - This can develop anywhere along the length of the esophagus (gullet/'food pipe'). Two common types are adenocarcinoma of the esophagus, and squamous cell carcinoma. These are named after the type of cells they originate from.
- **Stomach cancer** - Most stomach cancers develop in cells lining the stomach. This type of cancer is called an adenocarcinoma of the stomach. This usually develops slowly. Other stomach cancers include gastrointestinal stromal tumors (GISTs) or neuroendocrine tumors (NETs). These are relatively rare and can occur anywhere in the gastrointestinal tract (digestive system).
- **Pancreatic cancer** - The pancreas produces insulin and digestive enzymes. It sits below the stomach and has a duct which allows the enzymes which it produces to enter the duodenum (the first part of the small bowel). The pancreas is divided into head, neck, body and tail which all have different roles. Cancer can occur in any area.

Introduction to the Upper GI Tract

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What is upper gastrointestinal (upper GI) cancer?

- Seven main types of upper gastrointestinal (Upper GI) cancer: esophageal, stomach, pancreatic, duodenal, gall bladder and bile duct, liver and small bowel cancers.
- **Duodenal cancer** - The duodenum is the first part of the small intestine (bowel) below the stomach. Foods which have been mixed with stomach acid in the stomach are then released into the duodenum where they are mixed with bile (made in the liver and stored in the gall bladder) and with digestive juices from the pancreas. Duodenal cancer is relatively rare compared to stomach (gastric) cancer and colorectal cancer.
- **Biliary tract or gallbladder cancer** - This develops either in the gall bladder itself, or in the system of tubes which bring the bile ('gall') which the gallbladder stores, to the duodenum where it is used in the digestive process.
- **Liver cancer** – Primary liver cancer develops from liver cells that have become malignant. It is also possible to get secondary liver cancer, which is where cancers in other organs then spread (metastasis) to the liver. These are called by the name of the original ('primary') cancer - e.g. 'pancreatic cancer metastases in the liver'.

Introduction to Biliary System/Tree

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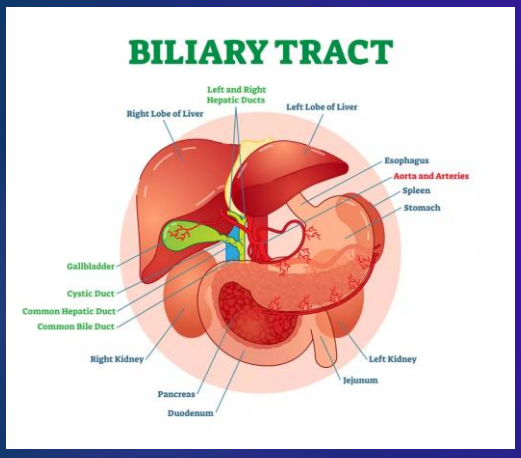

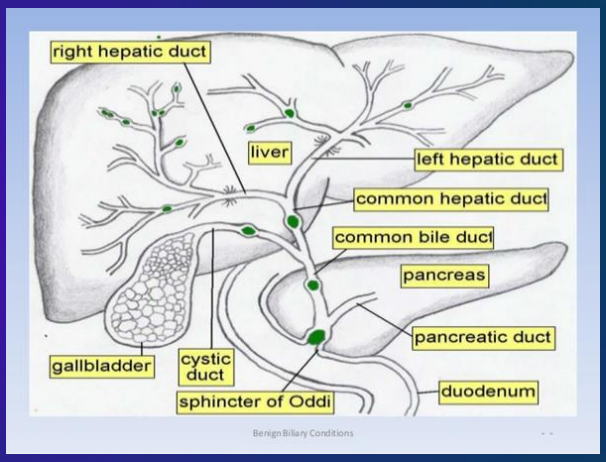

Physiology of Upper GI Tract & Biliary System

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Function of the Biliary System

- There are three important functions of the biliary system, these include:
  - Draining the waste products from the liver (into the duodenum)
  - Secreting bile in a controlled release manner
  - Transporting bile and pancreatic juices (to be used to help breakdown food in the small intestine

2021 Incidence & Mortality Estimates

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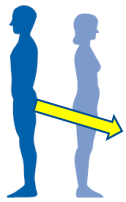
Figure 3. Leading Sites of New Cancer Cases and Deaths – 2021 Estimates

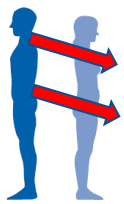
Estimated New Cases

Male			Female		
Prostate	248,530	26%	Breast	281,550	30%
Lung & bronchus	119,100	12%	Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%	Colon & rectum	69,980	8%
Urinary bladder	64,280	7%	Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%	Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%	Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%	Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%	Pancreas	28,480	3%
Leukemia	35,530	4%	Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%	Leukemia	25,560	3%
All sites	**970,250**		**All sites**	**927,910**	



Estimated Deaths

Male			Female		
Lung & bronchus	69,410	22%	Lung & bronchus	62,470	22%
Prostate	34,130	11%	Breast	43,600	15%
Colon & rectum	28,520	9%	Colon & rectum	24,460	8%
Pancreas	25,270	8%	Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%	Ovary	13,770	5%
Leukemia	13,900	4%	Uterine corpus	12,940	4%
Esophagus	12,410	4%	Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%	Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%	Brain & other nervous system	8,100	3%
All sites	**319,420**		**All sites**	**289,150**	



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

2021 Cancer Facts and Figures – American Cancer Society

Observing Rising Trends in Mortality

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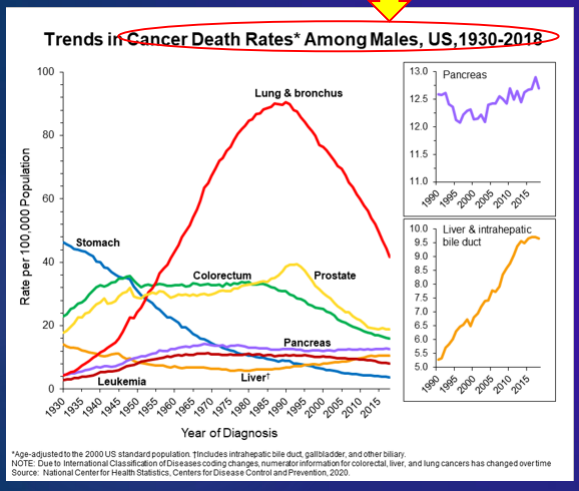

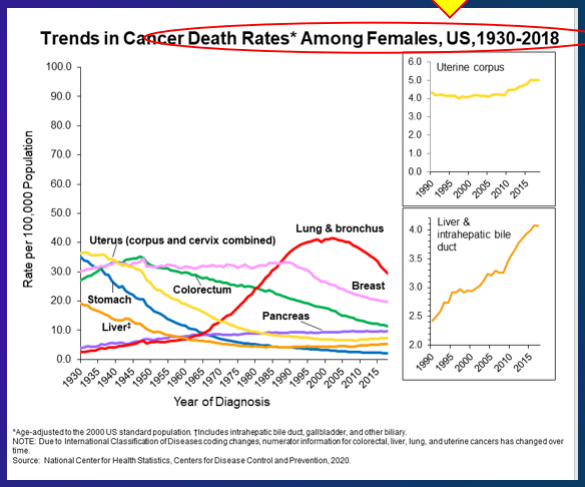

2021 Cancer Facts and Figures – American Cancer Society

Endoscopic Ultrasound (EUS)

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- Endoscopy refers to the procedure of inserting a long flexible tube via the mouth or the rectum to visualize the digestive tract (for further information, please visit the Colonoscopy and Flexible Sigmoidoscopy articles), whereas ultrasound uses high-frequency sound waves to produce images of the organs and structures inside the body such as ovaries, uterus, liver, gallbladder, pancreas, or aorta.
- Endoscopic Ultrasound (EUS) combines endoscopy and ultrasound in order to obtain images and information about the digestive tract and the surrounding tissue and organs.
- In EUS a small ultrasound transducer is installed on the tip of the endoscope. By inserting the endoscope into the upper or the lower digestive tract one can obtain high quality ultrasound images of the organs inside the body. Placing the transducer on the tip of an endoscope allows the transducer to get close to the organs inside the body. Because of the proximity of the EUS transducer to the organ(s) of interest, the images obtained are frequently more accurate and more detailed than the ones obtained by traditional ultrasound. The EUS also can obtain information about the layers of the intestinal wall as well as adjacent areas such as lymph nodes and the blood vessels.
- EUS plays an important role in the diagnosis of pancreatic cancer, including FNA with cytological or histological confirmation. Staging of pancreatic cancer is crucial and CT and EUS are the cornerstones of staging, currently providing the more accurate results. Furthermore, EUS also has a therapeutic role, providing biliary drainage when it is not feasible with ERCP and pain relief. EUS can also have future applications on pancreatic cancer management.

Endoscopic Ultrasound (EUS)

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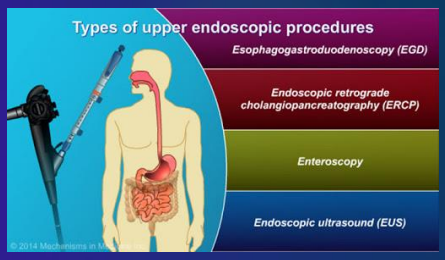
Prospective/retrospective studies on diagnostic performance of EUS versus CT for detection of pancreatic malignancy

Kamata *et al*[18]	2014	35	100 vs 56*	100 vs 100	NA
Kitano *et al*[19]	2012	277	91 vs 71*	94 vs 92	NA
Sakamoto *et al*[20]	2008	156	94 vs 50*	NA	NA
Jemma *et al*[21]	2008	42	100 vs 88*	89 vs 83	NA
Kitano *et al*[22]	2004	65	95 vs 68*	NA	NA
Agarwal *et al*[23]	2004	81	100 vs 75*	NA	94 vs 74*
DeWitt *et al*[9]	2004	120	98 vs 86*	NA	NA
Rivadeneira *et al*[24]	2003	48	100 vs 68*	75 vs 50*	98 vs 67*
Mertz *et al*[25]	2000	35	93 vs 53*	NA	86 vs 49*
Gress *et al*[26]	1999	151	100 vs 74	NA	NA
Harrison *et al*[27]	1999	19	100 vs 50*	NA	98 vs 63*
Midwinter *et al*[28]	1999	48	97 vs 76	NA	NA
Legmann *et al*[29]	1998	30	100 vs 92	NA	93 vs 93
Sugiyama *et al*[30]	1997	54	96 vs 89*	NA	NA
Howard *et al*[31]	1997	21	75 vs 63†	77 vs 100†	76 vs 86†
Melzer *et al*[32]	1996	12	100 vs 83	NA	100 vs 76
Nakaizumi *et al*[33]	1995	232	94 vs 65*	97 vs 94	96 vs 88*
Marty *et al*[34]	1995	37	92 vs 63	NA	NA
Müller *et al*[35]	1994	49	94 vs 69†	100 vs 64	96 vs 67
Palazzo *et al*[37]	1993	64	96 vs 69†	73 vs 53	91 vs 66*
Yasuda *et al*[38]	1993	29	100 vs 72†	NA	Duodenal Invasion: 83 vs 33 Gastric invasion: 79 vs 38
Rösch *et al*[39]	1991	102	99 vs 77	100 vs 53	NA

*Statistically significant data.

†Statistics are not available.



Endoscopic Ultrasound (EUS)

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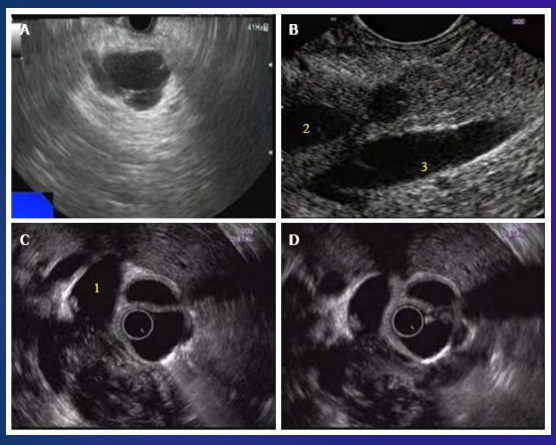

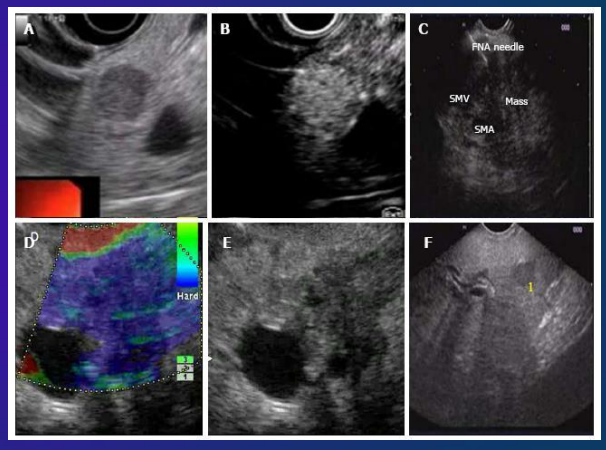

Endoscopic Ultrasound (EUS)

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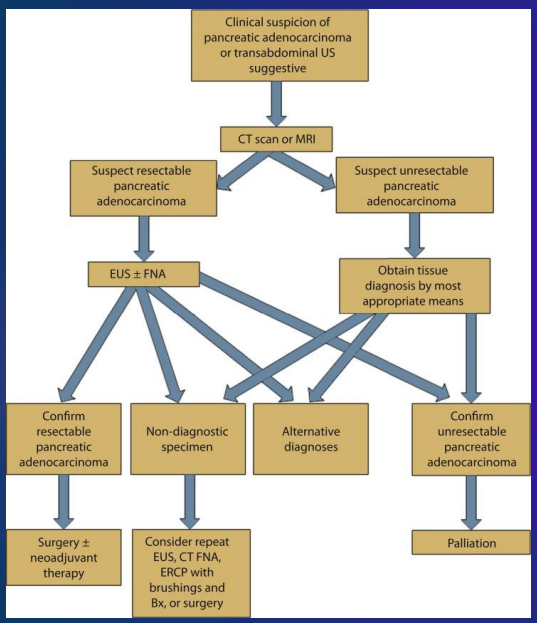

RCT comparing EUS-FNA and EUS-FNB for diagnosis of pancreatic cancers

Study	Year of study	Total no of patients	Accuracy/diagnostic yield, FNA versus FNB (%)	Sensitivity, FNA versus FNB (%)	Specificity, FNA versus FNB (%)
Cheng *et al*[80]	2018	408	80 vs 91.4*	NA	NA
Van Riet *et al*[82]	2019	608	87 vs 78*	90 vs 82*	96 vs 91
Wang *et al*[83]	2016	408	80 vs 93	NA	NA
Vanbiervliet *et al*[81]	2014	80	92.5 vs 90	NA	NA
Lee *et al*[84]	2014	118	94.8 vs 98.3	94.6 vs 98.2	100 vs 100
Strand *et al*[85]	2014	32	93.8 vs 28.1*	NA	NA

*Statistically significant data.

EUS, endoscopic ultrasound; FNA, fine-needle aspiration; FNB, fine-needle biopsy; NA, not applicable; RCT, randomised control trial.

Diagnostic Confirmation Review

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Code	Description	Definition
1	Positive histology	Histologic confirmation (tissue microscopically examined).
2	Positive cytology	Cytologic confirmation (no tissue microscopically examined; fluid cells microscopically examined).
4	Positive microscopic confirmation, method not specified	Microscopic confirmation is all that is known. It is unknown if the cells were from histology or cytology.
5	Positive laboratory test/marker study	A clinical diagnosis of cancer is based on laboratory tests/marker studies which are clinically diagnostic for cancer. Examples include alpha-fetoprotein for liver cancer and abnormal electrophoretic spike for multiple myeloma. Elevated PSA is not diagnostic of cancer. If the physician uses the PSA as a basis for diagnosing prostate cancer with no other workup, record as code 5.
6	Direct visualization without microscopic confirmation	The tumor was visualized during a surgical or endoscopic procedure only with no tissue resected for microscopic examination.
7	Radiography and other imaging techniques without microscopic confirmation	The malignancy was reported by the physician from an imaging technique report only.
8	Clinical diagnosis only, other than 5, 6 or 7	The malignancy was reported by the physician in the medical record.
9	Unknown whether or not microscopically confirmed	A statement of malignancy was reported in the medical record, but there is no statement of how the cancer was diagnosed (usually nonanalytic).

Behavior of Tumor on EUS

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Reportable	ICD-O-3	Description
Yes	****/2	All Histologies with Behavior Code of /2 (in-situ)
Yes	****/3	All Histologies with Behavior Code of /3 (invasive)
Yes	8440/3	Cystadenocarcinoma of the pancreas
Yes	8150/3	Cystic Pancreatic Endocrine Neoplasm (CPEN)
Yes	8500/3	Infiltrating Duct Carcinoma of the pancreas
Yes	8503/2	Intraductal Oncocytic Papillary Neoplasm (IOPN) of the pancreas
Yes	8453/2	Intraductal Papillary Mucinous Neoplasms (IPMN) of the pancreas
Yes	8453/3	Intraductal Papillary Mucinous Neoplasm (IPMN) with invasive carcinoma
Yes	8503/2	Intraductal Tubule-Papillary Neoplasm (ITPN) of the pancreas
Yes	8503/3	Intraductal Tubule-Papillary Neoplasm (ITPN) with invasive carcinoma
Yes	8470/2	Mucinous Cystic Neoplasm (MCN) of the pancreas with high-grade dysplasia
Yes	8470/2	Non-invasive Mucinous Cystic Neoplasm (MCN) of the pancreas with high-grade dysplasia
Yes	8470/2	Mucinous Cystadenocarcinoma, non-invasive (MCN)
Yes	8470/3	Mucinous Cystadenocarcinoma of the pancreas
Yes	8470/3	Mucinous Cystic Neoplasm (MCN) of the pancreas with invasive carcinoma
Yes	8246/3	Neuroendocrine Carcinoma of the pancreas
Yes	8240/3	Neuroendocrine Tumor, Grade 1 (NET GR1) of the pancreas
Yes	8249/3	Neuroendocrine Tumor, Grade 2 (NET GR2) of the pancreas
Yes	8471/3	Papillary Mucinous Cystadenocarcinoma of the pancreas
Yes	8452/3	Solid Pseudo-Papillary Neoplasm (SPN) of the pancreas
Yes	8552/3*	Mixed acinar-ductal carcinoma
Yes	8163/2*	Papillary neoplasm, pancreatobiliary-type, with high grade intraepithelial neoplasia
Yes	8163/3*	Pancreatobiliary-type carcinoma
No	n/a	Histologies with Behavior Code of /0 (benign)
No	n/a	Histologies with Behavior Code of /1 (borderline)
No	n/a	Serous cystadenomas, solid and cystic papillary (Hamoudi) tumors, lympho-epithelial cysts and simple cysts are all benign and not reportable

* New histology codes not yet implemented in the U.S. are still reportable – use histology 8500 or 8140

References: 2010 WHO Classification of Tumours of the Pancreas; Pathologe. 2011 Nov;32 Suppl 2:332-6. doi: 10.1007/s00292-011-1515-2; Ann Surg. 2004 May; 239(5): 651–659), 2011 ICD-O-3 Updates, 2015 SEER Program Coding and Staging Manual, and NCI SEER Ask A SEER Registrar.

Upper GI Tract & Biliary System

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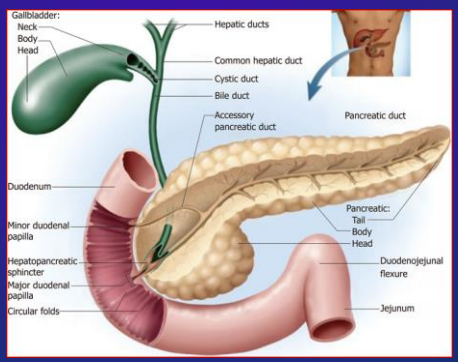
Anatomy/Physiology
Risk Factors/Symptoms
Classification of Neoplasms – WHO 5th ed.
Diagnosis & Staging
Genetic Testing
Treatment



Esophagus (including GE Junction) Anatomy/Physiology

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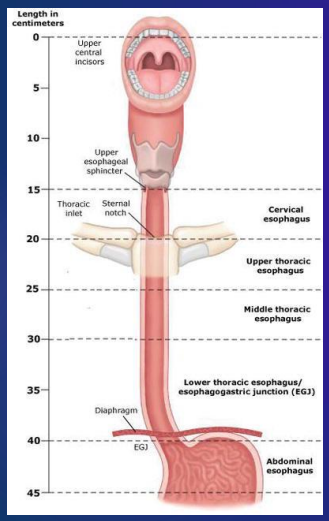

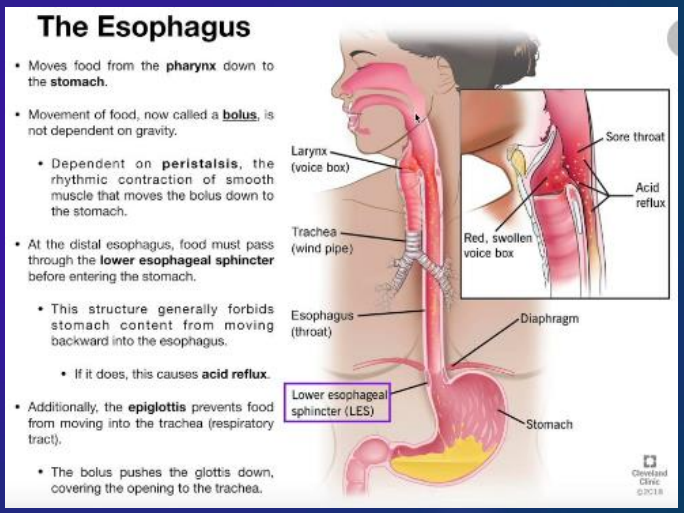

Esophagus (including GE Junction) Anatomy/Physiology

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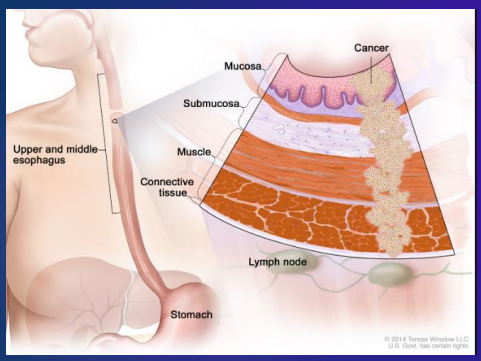

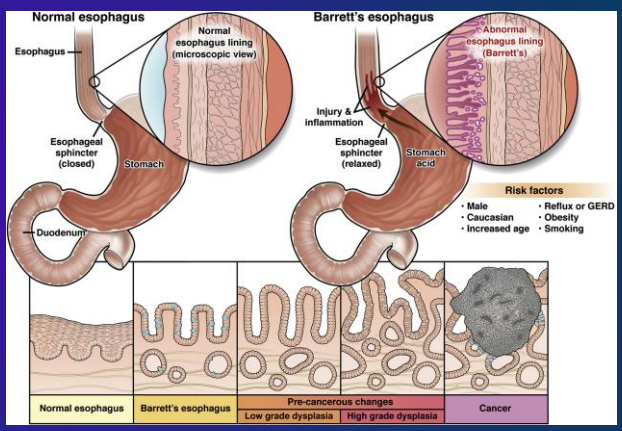

Esophagus (including GE Junction) Risk Factors/Symptoms

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Risk Factors Include:

- Age > 55
- Male
- Tobacco and Alcohol Use – risk for both squamous and adenocarcinoma of the esophagus
- Gastroesophageal Reflux Disease – GERD
- Barrett's Esophagus
- Obesity
- Diet
- Physical Activity
- Injury to Esophagus – for example exposure to lye in cleaning products or drinking toxic chemicals
- HPV infection
- Acquired Gene Mutations – from one of the other conditions above
- Inherited Gene Mutations – Tylosis (Howel-Evans Syndrome), Bloom Syndrome, Fanconi Anemia, Familial Barrett's Esophagus

Symptoms Include:

- Trouble swallowing
- Chest pain
- Weight loss
- Hoarseness
- Chronic cough
- Vomiting
- Bone pain (if cancer has spread to the bone)
- Bleeding into the esophagus.

Esophagus (including GE Junction)

WHO 5th edition Classification of Neoplasms of Pancreas

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Epithelial Tumors

- Benign epithelial tumors and precursors
  - Esophageal squamous papilloma
  - Barrett dysplasia
  - Esophageal squamous dysplasia
- Malignant epithelial tumors
  - Adenocarcinoma of the esophagus and esophagogastric junction NOS
  - Esophageal adenoid cystic carcinoma
  - Esophageal adenosquamous and mucoepidermoid carcinomas
  - Esophageal squamous cell carcinoma NOS
  - Esophageal undifferentiated carcinoma
  - Esophageal neuroendocrine neoplasms

Esophagus (including GE Junction) Diagnosis/Staging

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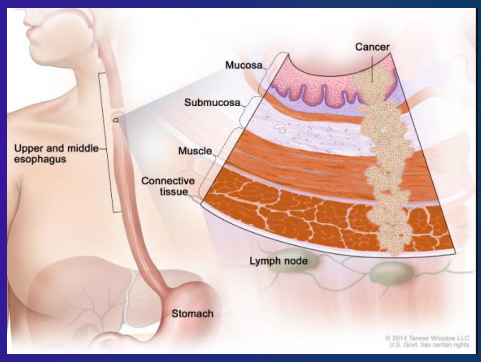
- Screening of High Risk Groups
- Screening in High Risk Geographic Areas
- Diagnostic Imaging
- Barium Swallow
- Upper Endoscopy
- Endoscopic Ultrasound
- Bronchoscopy
- Thoracoscopy and Laparoscopy
- Labs: CBC, Liver Enzymes, HER2, PD-L!, MMR, MSI



Esophagus (including GE Junction) Treatment

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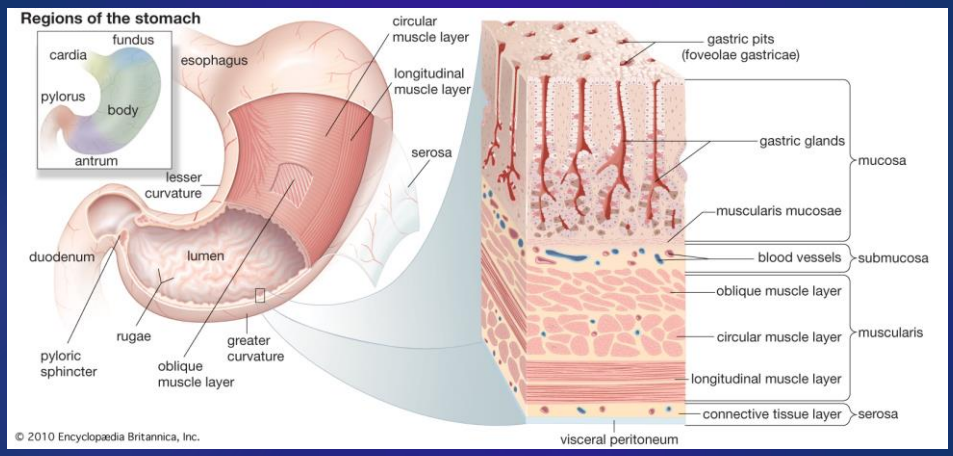
- Treating for Barrett's Esophagus to find early disease
- Endoscopic Treatments
  - Endoscopic mucosal resection
  - Photodynamic therapy
  - Radiofrequency ablation
- Surgery – esophagectomy (depends on location of primary), nodes
- Palliative Surgery – to relieve symptoms
- Radiation – External Beam (IMRT) or Brachytherapy (high or low dose)
- Chemotherapy – neoadjuvant (pre-surgical), adjuvant (post-surgical)
- Targeted Therapies
- Immunotherapy
- Combination therapy

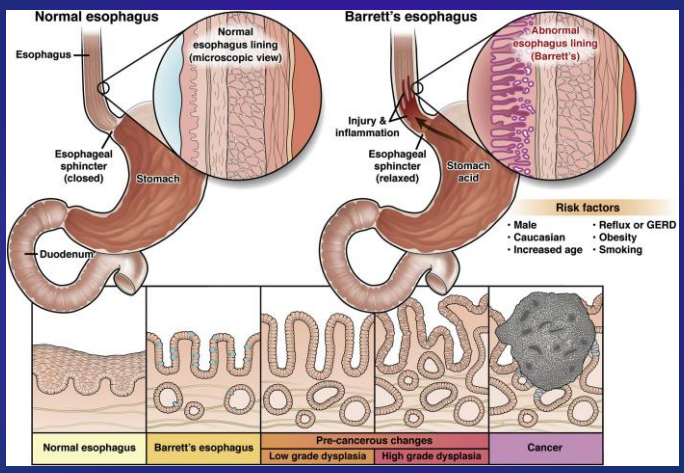
Stomach (including GE Junction) Anatomy/Physiology

25



Stomach (including GE Junction) Anatomy/Physiology

26



Stomach (including GE Junction) Risk Factors/Symptoms

27

- Gender – more common in men than women
- Age – sharp increase in rates over age 50 but most diagnosed in late 60's-80's
- Ethnicity – more common in Hispanic Americans, African Americans, Native Americans, and Asian/Pacific Islanders than it is in non-Hispanic whites.
- Geography - more common in Japan, China, Southern and Eastern Europe, and South and Central America. This disease is less common in Northern and Western Africa, South Central Asia, and North America
- Helicobacter pylori infection - Infection with Helicobacter pylori (H pylori) bacteria seems to be a major cause of stomach cancer, especially cancers in the lower (distal) part of the stomach. Long-term infection of the stomach with this germ may lead to inflammation (called chronic atrophic gastritis) and pre-cancerous changes of the inner lining of the stomach. People with stomach cancer have a higher rate of H pylori infection than people without this cancer. H pylori infection is also linked to some types of lymphoma of the stomach.
- Stomach Lymphoma – Persons with MALT lymphoma have an increased risk of getting adenocarcinoma of the stomach. This is probably because MALT lymphoma of the stomach is caused by infection with H pylori bacteria.
- EBV Infection - Epstein-Barr virus causes infectious mononucleosis (also called mono). EBV has been linked to some forms of lymphoma8. It is also found in the cancer cells of about 5% to 10% of people with stomach cancer. These people tend to have a slower growing, less aggressive cancer with a lower tendency to spread.
- Diet/Obesity/Overweight/Inactivity – large amounts of smoked foods, salted fish and meat, and pickled vegetables
- Type A Blood
- Menetrier Disease – hypertrophic gastropathy)
- Pernicious Anemia – vitamin B12 deficiency
- Occupation – coal, metal and rubber industries at risk
- Familial Syndromes – Li-Fraumeni, Peutz-Jeghers, Lynch Syndrome (HNPCC), family history of stomach cancer
- FAP/BRCA1/BRCA2
- Tobacco Use

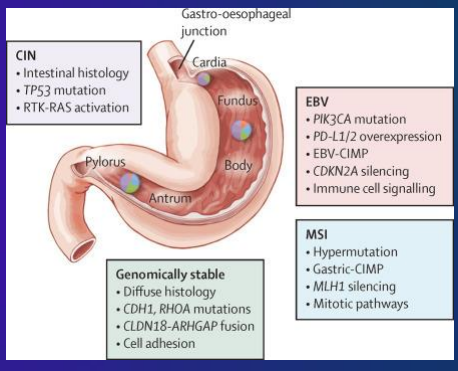
Stomach (including GE Junction)

WHO 5th edition Classification of Neoplasms of Pancreas

28

Tumors of the stomach

- Epithelial tumors
  - Benign epithelial tumors and precursors
    - Fundic gland polyps
    - Gastric hyperplastic polyps
    - Gastric dysplasia
    - Intestinal-type gastric adenoma
    - Foveolar-type adenoma
    - Gastric pyloric gland adenoma
    - Oxyntic gland adenoma
  - Malignant epithelial tumors
    - Gastric adenocarcinoma
    - Gastric squamous cell carcinoma
    - Gastric adenosquamous carcinoma
    - Gastric undifferentiated carcinoma
    - Gastroblastoma
    - Gastric neuroendocrine neoplasms
- Mesenchymal tumors
  - Gastrointestinal Stromal Tumor (GIST)
- MALT Lymphoma and Leiomyosarcoma



Stomach (including GE Junction) Diagnosis/Staging

29

- Medical History and Physical Exam – pain, bloating, acid stomach
- Test for Helicobacter Pylori Infection
- Upper Endoscopy – for Screening and for Diagnosis
- Endoscopic Ultrasound
- Diagnostic Imaging
- Upper GI Series – barium swallow uses x-rays – single or double contrast
- Biopsy (includes testing of biopsy material by IHC and FISH for HER2, PD-L1, etc)
- Sentinel Node Mapping
- Laparoscopy

SEER stage	5-year relative survival rate
Localized	69%
Regional	31%
Distant	5%

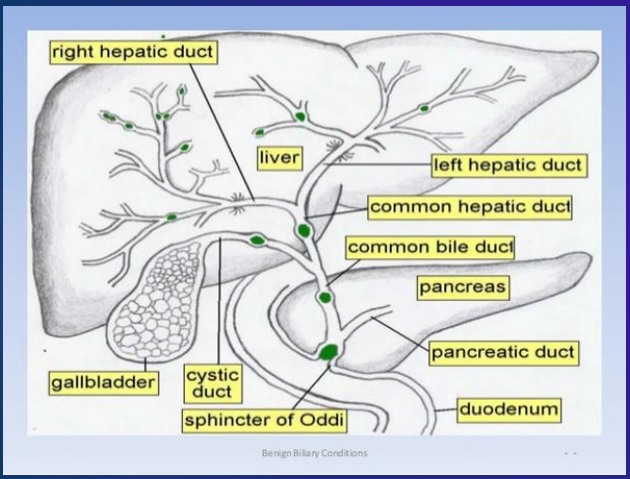
Stomach (including GE Junction) Treatment

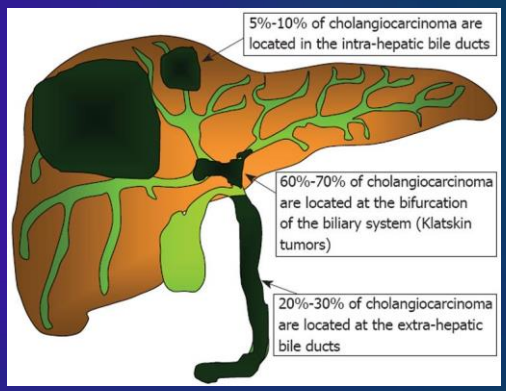
30

- Antibiotics to prevent cancer in patients with H pylori
- NSAIDS – not proven but suggestion that these may help prevent cancer
- Screening Tests to identify early disease and treat it before it becomes cancer
- Endoscopic Resection
- Open Surgery – depends on primary tumor location and imaging results
- Open Surgery – total gastrectomy, subtotal gastrectomy, esosphagogastrectomy
- Palliative Surgery for Unresectable Cancer – Gastric Bypass, Tumor Ablation, Stent
- Chemotherapy – neoadjuvant, adjuvant
- Targeted Therapies – HER2 (Trastuzumab/Herceptin, EGFR (Panitumumab)
- Immunotherapy – Pembrolizumab/Keytruda – targets PD-L1 – checkpoint inhibitor
- Radiation Therapy – External Beam

Introduction
Pancreato-Hepato-Biliary System

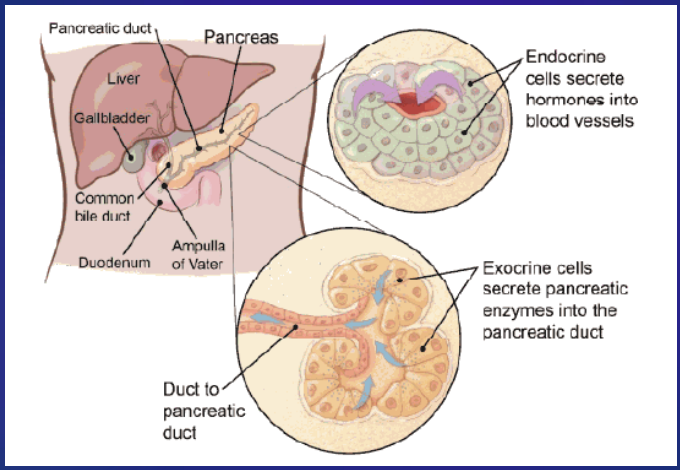
31





Pancreas (Pancreatic Duct)
Anatomy/Physiology

32



Pancreas (Pancreatic Duct) Risk Factors/Symptoms

33

Risk Factors

- Tobacco Use
- Obesity/Overweight/Inactivity
- Type 2 Diabetes
- Chronic Pancreatitis – long term inflammation of pancreas seen in folks with heavy smoking and/or heavy drinking history or current use
- Workplace Chemical Exposures – dry cleaning and metal working
- Age >65
- Male
- African American – may be due to other risk factors
- Family History & Inherited Genetic Syndromes
- Acquired Gene Mutations due to exposures above

Symptoms

Jaundice – yellowing of eyes and skin

Acute pancreatitis symptoms include:
- Upper abdominal pain
- Abdominal pain that radiates to your back
- Abdominal pain that feels worse after eating
- Fever
- Rapid pulse
- Nausea
- Vomiting
- Tenderness when touching the abdomen

Chronic pancreatitis symptoms include:
- Upper abdominal pain
- Losing weight without trying
- Oily, smelly stools (steatorrhea)

Pancreas (Pancreatic Duct)

WHO 5th edition Classification of Neoplasms of Pancreas

34

Epithelial Tumors

- **Benign epithelial tumors and precursors**
  - **Acinar cystic transformation of the pancreas**
  - **Serous neoplasms of the pancreas**
  - **Pancreatic intraepithelial neoplasia**
  - **Pancreatic intraductal papillary mucinous neoplasm**
  - **Pancreatic intraductal oncocytic papillary neoplasm**
  - **Pancreatic intraductal tubulopapillary neoplasm**
  - **Pancreatic mucinous cystic neoplasm**
- **Malignant epithelial tumors**
  - **Pancreatic ductal adenocarcinoma**
  - **Pancreatic acinar cell carcinoma**
  - **Pancreatoblastoma**
  - **Solid pseudopapillary neoplasm of the pancreas**

Precursor Lesions

- Serous cystic neoplasms (SCNs) (also known as serous cystadenomas) are tumors that have sacs (cysts) filled with fluid. SCNs are almost always benign, and most don't need to be treated.
- Mucinous cystic neoplasms (MCNs) (also known as mucinous cystadenomas) are slow-growing tumors that have cysts filled with a jelly-like substance called mucin. These tumors can progress to cancer over time if not treated, so these tumors are typically removed with surgery.
- Intraductal papillary mucinous neoplasms (IPMNs) are benign tumors that grow in the pancreatic ducts. Like MCNs, these tumors make mucin, and over time they sometimes become cancer if not treated.
- Solid pseudopapillary neoplasms (SPNs) are rare, slow-growing tumors that develop in young women. Even though these tumors tend to grow slowly, they can sometimes spread to other parts of the body, so they are best treated with surgery.

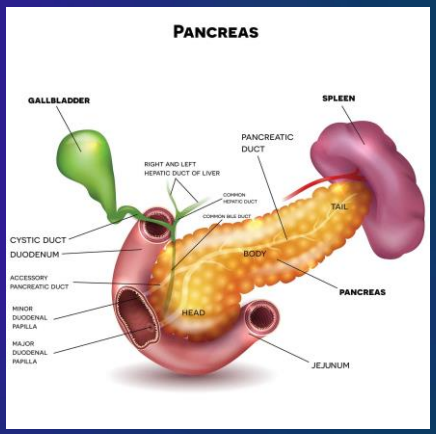
Pancreas (Pancreatic Duct)

35

WHO 5th edition Classification of Neoplasms of Pancreas

Pancreatic Neuroendocrine Neoplasms

- Pancreatic neuroendocrine neoplasms: Introduction
- Non-functioning pancreatic neuroendocrine tumors
- Functioning pancreatic neuroendocrine tumors
  - Insulinoma
  - Gastrinoma
  - VIPoma
  - Glucagonoma
  - Somatostatinoma
  - ACTH-producing neuroendocrine tumor
  - Serotonin-producing neuroendocrine tumor
- Pancreatic neuroendocrine carcinoma
- Pancreatic MiNENs



Pancreas (Pancreatic Duct) Diagnosis/Staging

36

- Medical History and Physical Exam
- Diagnostic Imaging – typical (CT, MRI, PET, Ultrasound)
- Cholangiopancreatography – a specialized imaging test
- Magnetic resonance cholangiopancreatography (MRCP)
- Percutaneous transhepatic cholangiography (PTC)
- Liver Function Tests
- Tumor Markers – CA19-9 and CEA – neither are every diagnostic – alone
- Biopsy – percutaneous, endoscopic, surgical
- Genetic Testing – BRCA1, BRCA2, NTRK – targeted drugs available

SEER Stage	5-year Relative Survival Rate
Localized	37%
Regional	12%
Distant	3%
All SEER stages combined	9%

Pancreas (Pancreatic Duct) Treatment

37

- Staging Laparoscopy
- Tumor Ablation or Embolization of Primary Tumor or Metastasis
- Surgery – Distal Pancreatectomy – removes tail of pancreas and some of body
- Surgery – Total Pancreatectomy – removes entire pancreas and gallbladder, part of stomach and small intestine and the spleen
- Surgery – Whipple Procedure – Pancreaticoduodenectomy – most common
- Surgery – palliative to reduce symptoms – less extensive or bypass surgery
- Radiation Therapy – External Beam Radiation
- Chemotherapy – neoadjuvant, adjuvant, palliative
- Targeted Therapy – Erlotinib/Tarceva (EGFR Inhibitor), Olaparib/Lynparza (PARP Inhibitor), Larotrectinib/Vitrakvi and Entrectinib/Rozyltrek (NTRK proteins/gene mutations)
- Immunotherapy – Immune Checkpoint Inhibitors (Keytruda/Pembrolizumab – PD-1 Inhibitor)
- Pain Control Only – opioids including morphine

Liver (Hepatic Ducts) Anatomy/Physiology

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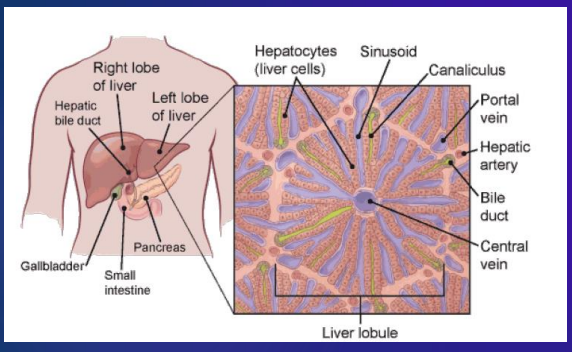

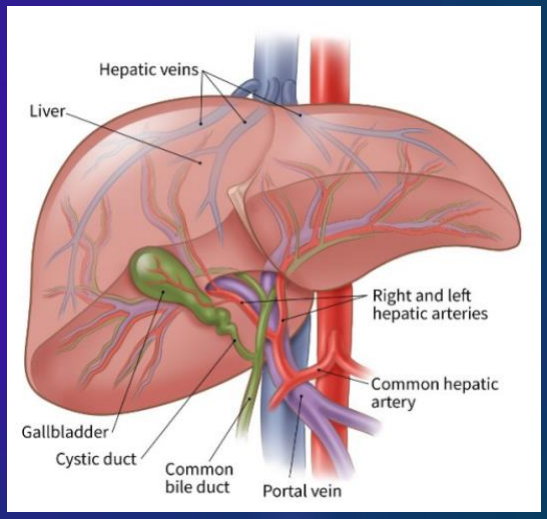

Liver (Hepatic Ducts) Risk Factors/Symptoms

39

- Male
- Asian Americans and Pacific Islanders
- Hispanics/Latinos, American Indians/Alaska Natives
- African Americans and Whites
- Chronic Viral Hepatitis (HBV or HCV)
- Cirrhosis
- Non-Alcoholic Fatty Liver Disease
- Primary Biliary Cirrhosis
- Heavy Alcohol Use & Tobacco Use
- Obesity
- Type 2 Diabetes
- Exposure to Aflatoxins – fungus that contaminates peanuts, wheat, soybeans, ground nuts, corn and rice from poor storage practices
- Exposure to Vinyl Chloride / Thorium Dioxide (Thorotrast)
- Long-Term Anabolic Steroid Use

- Weight loss (without trying)
- Loss of appetite
- Feeling very full after a small meal
- Nausea or vomiting
- An enlarged liver, felt as fullness under the ribs on the right side
- An enlarged spleen, felt as fullness under the ribs on the left side
- Pain in the abdomen (belly) or near the right shoulder blade
- Swelling or fluid build-up in the abdomen (belly)
- Itching
- Yellowing of the skin and eyes (jaundice)

Liver (Hepatic Ducts)

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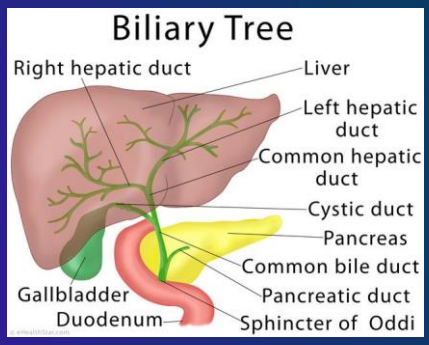
WHO 5th edition Classification of Neoplasms of Pancreas

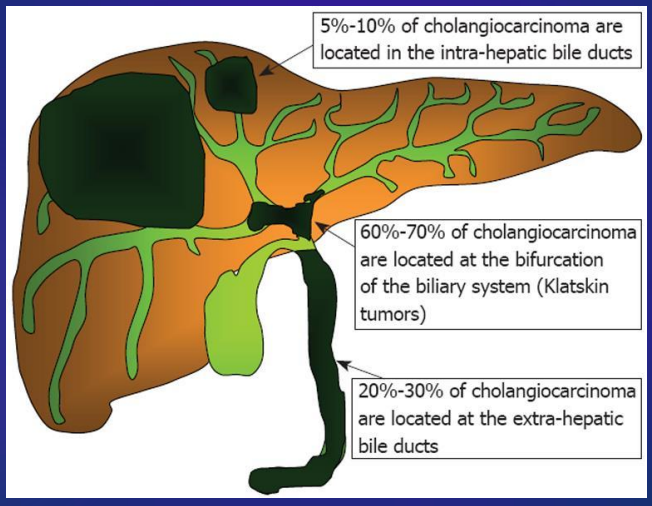
Epithelial Tumors

- Benign hepatocellular tumors
  - Focal nodular hyperplasia of the liver
  - Hepatocellular adenoma
- Malignant hepatocellular tumors and precursors
  - Hepatocellular carcinoma
  - Hepatoblastoma
- Benign biliary tumor's and precursors
  - Bile duct adenoma
  - Biliary adenofibroma
  - Biliary intraepithelial neoplasia (See chapter 9)
  - Intraductal papillary neoplasm of the bile ducts (See chapter 9)
  - Mucinous cystic neoplasm of the liver and biliary system
- Malignant biliary tumors
  - Intrahepatic cholangiocarcinoma
- Combined hepatocellular-cholangiocarcinoma and undifferentiated primary liver carcinoma
- Hepatic neuroendocrine neoplasms



"Cholangiocarcinoma" A loosely used term…

41



Liver (Hepatic Ducts) Diagnosis/Staging

42

- Prevention
- Medical History and Physical Exam
- Screening for Hepatitis B and Hepatitis C
- Lab Tests with AFP and other proteins in the blood
- Liver Function Tests & Kidney Function Tests
- Ultrasound
- Imaging – CT/MRI/PET/Bone Scan/Angiography
- Fibrosis Score – indicates whether or not transplant is an option to treat
- Biopsy – FNA, Laparoscopic, Surgical Biopsy

Cancer Staging Systems

- UICC/AJCC TNM Staging System
- The Barcelona Clinic Liver Cancer (BCLC) system
- The Cancer of the Liver Italian Program (CLIP) system
- The Okuda system
- Child-Pugh Score – cirrhosis staging

Liver (Hepatic Ducts) Treatment

43

- Surgery - resectable, transplantable, unresectable, inoperable
- Surgery – partial hepatectomy
- Surgery - liver transplant
- Chemoembolization/Radioembolization – infuse chemo/xrt beads and seal them off with embolization
- Chemotherapy – Gemcitabine, Oxaliplatin, Cisplastin, Doxorubicin, 5-FU, Capecitabine, Mitroxantrone
- Ablation Therapy – RFA, MWA, Cryoablation, Ethanol Ablation
- Trans-arterial embolization (TAE)
- Trans-arterial chemoembolization (TACE)
- Drug-eluting Bead Chemoembolization (DEB-TACE)
- Radioembolization
- Targeted Therapy – Nexavar/sorafenib – Kinase Inhibitor - inhibits blood vessel growth
- Targeted Therapy – Cyramza/ramucirumab – Monoclonal Antibody – same as above
- Targeted Therapy – Monoclonal Antibodies – Beevacizumab/Avastin
- Virus Therapy – JX-594 – same virus used to make smallpox vaccine
- Immunotherapy – PD-1 and PD-L1 Inhibitors and CTLA-4 Inhibitor - Yervoy

Gallbladder (Intrahepatic Bile Ducts & Common Bile Duct) Anatomy/Physiology

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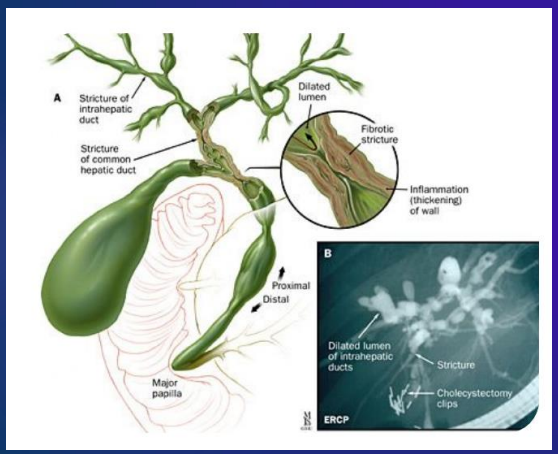

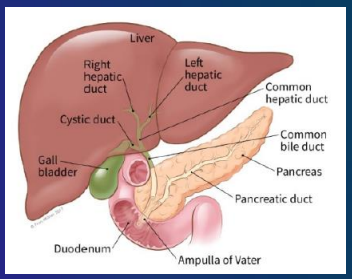

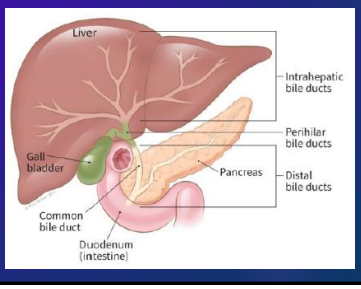

Gallbladder (Intrahepatic Bile Ducts & Common Bile Duct) Risk Factors/Symptoms

45

- Medical History of Chronic Infection and Inflammation
  - Primary Sclerosing Cholangitis (PSC)
  - Bile Duct Stones
  - Choledochal Cyst Disease
  - Liver Fluke Infections
  - Cirrhosis
  - Abnormalities Involving Junction of Bile Duct and Pancreatic Duct Anatomy
  - Infection with Hepatitis B and/or Hepatitis B
  - HIV Infection
- Chronic Pancreatitis and History of Gallstones
- Inflammatory Bowel Disease – ulcerative colitis, Crohn's disease
- Hispanic Americans, Southeast Asia and China residents (liver flukes)
- Non-alcoholic Fatty Liver Disease
- Age > 60
- Obesity
- Diabetes
- Alcohol & Tobacco Abuse
- Exposure to asbestos, radon, PCBs, nitrosamines, chemicals used in rubber and textile industry

- Jaundice
- Itching
- Light-colored/Greasy Stools
- Dark Urine
- Abdominal Pain
- Loss of Appetite / Weight Loss
- Fever
- Nausea & Vomiting

Gallbladder (Intrahepatic Bile Ducts & Common Bile Duct)

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WHO 5th edition Classification of Neoplasms of Pancreas

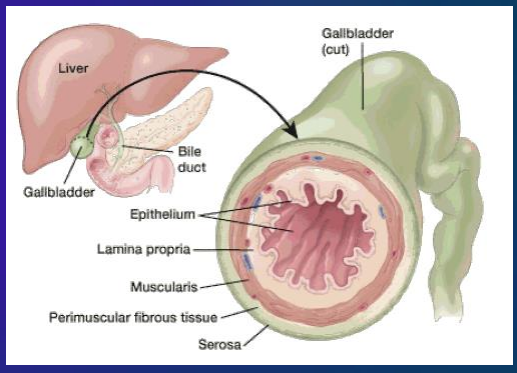
Epithelial Tumors

- Benign epithelial tumors and precursors
  - Pyloric gland adenoma of the gallbladder
  - Biliary intraepithelial neoplasia
  - Intracholecystic papillary neoplasm
    - formerly Intracystic / intraductal papillary neoplasm
  - Intraductal papillary neoplasm of the bile ducts
- Malignant epithelial tumors
  - Carcinoma of the gallbladder
  - Carcinoma of the extrahepatic bile ducts
  - Neuroendocrine neoplasms of the gallbladder and bile ducts

Gallbladder (Intrahepatic Bile Ducts & Common Bile Duct) Diagnosis/Staging

47

- Screening High Risk Populations
- Medical History and Physical Exam
- Lab Tests of liver and gallbladder function
- Tumor Markers – CEA, CA19-9 (not diagnostic confirmation = 5)
- Imaging – Ultrasound, EUS, Laparoscopic, CT, MRI, Cholangiography, MRI Cholangiopancreatography (MRCP), Endoscopic Retrograde Cholangiopancreatography (ERCP), Percutaneous Transhepatic Cholangiography (PTC), Angiography
- Biopsy – various types and approaches
- Assess Resectable or Unresectable Disease



Gallbladder (Intrahepatic Bile Ducts & Common Bile Duct) Treatment

48

- Pre-Surgical Laparoscopy to plan for surgery
- Surgery – curative or palliative/resectable or unresectable
  - Simple Cholecystectomy
  - Laparoscopic Cholecystectomy
  - Open Cholecystectomy
  - Extended Cholecystectomy/Radical Cystectomy
- Liver Transplant or Tumor Ablation (RFA or Cryo), Photodynamic Therapy and Embolization
- Radiation Therapy – External Beam (IMRT), 3D Conformal, Stereotactic XRT, Brachytherapy
- Chemotherapy – adjuvant chemo, primary treatment chemo, palliative chemo, chemoradiation
- Chemotherapy – Hepatic Artery Infusion (HAI)
- Targeted Therapy – Pemigatinib (Pemazyre) – FGFR2 inhibitor for bile duct cancers only
- Immunotherapy – not available
- Palliative Therapy – code it if it is first course treatment – bypass surgery, stents, chemo, etc.

Upper Duodenum Anatomy/Physiology

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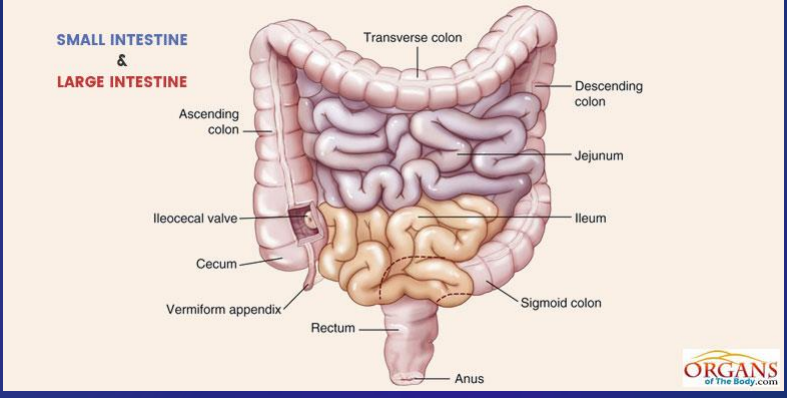


Upper Duodenum Risk Factors/Symptoms

50

- Male
- Age>60
- African American
- Smoking & Alcohol
- Diet – red meat, salted or smoked foods
- Celiac Disease
- Colon Cancer
- Crohn's Disease
- Inherited Syndromes
  - Familial Adenomatous Polyposis (FAP)
  - Lynch Syndrome (hereditary nonpolyposis colorectal cancer or HNPCC)
  - Peutz-Jeghers Syndrome
  - MUTYH-Associated Polyposis
  - Cystic Fibrosis

- Pain in the belly (abdomen)
- Nausea and vomiting
- Weight loss (without trying)
- Weakness and feeling tired (fatigue)
- Dark-colored stools (bleeding in the intestine)
- Low red blood cell counts (anemia)
- Yellowing of the skin and eyes (jaundice)

Upper Duodenum

WHO 5th edition Classification of Neoplasms of Duodenum

51

Epithelial Tumors

- Benign epithelial tumors and precursors
  - Non-ampullary adenoma
  - Ampullary adenoma
- Malignant epithelial tumors
  - Non-ampullary adenocarcinoma
  - Ampullary adenocarcinoma
  - Small intestinal and ampullary neuroendocrine neoplasms

Range of hematolymphoid tumors including but not limited to:

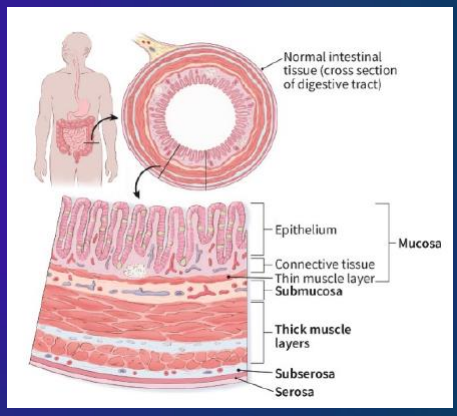
- Extranodal MALT lymphoma of digestive tract
- Duodenal-type follicular lymphoma
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Intestinal T-cell lymphoma NOS
- Indolent T-cell lymphoproliferative disorder of the GI tract

Upper Duodenum Diagnosis/Staging

52

- Medical History and Physical Exam
- Screening for individuals at high risk due to inherited genetic syndromes
- Imaging – CT, MRI, PET
- Upper GI Series
- Enterocylisis/CT Enterocylisis/MRI Enterocyclisis – Detailed Upper GI Series
- Barium Enema
- CT-Guided Needle Biopsy
- Endoscopy – Capsule Endoscopy, Double-Balloon Enteroscopy
- Biopsy
- Labs for Mismatch Repair (MMR) and Microsatellite Instability (MSI)

Staging



Upper Duodenum Treatment

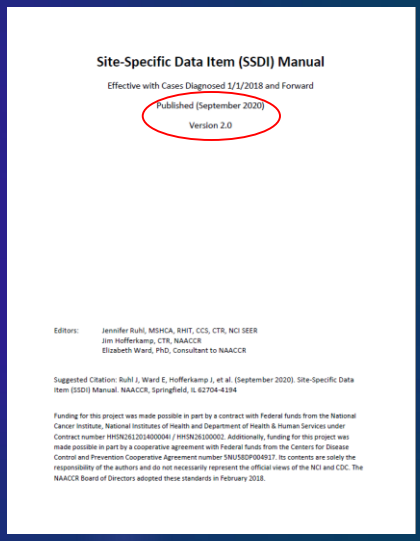
53

- Surgery – depends on resectable or unresectable cancer
- Surgery – segmental resection
- Surgery – Whipple Procedure (pancreaticoduodenectomy)
- Surgery – Palliative for pain control includes bypass surgery
- Chemotherapy – Capecitabine, 5-FU, Oxaliplatin, Irinotecan
- Chemotherapy – multi-agent
  - Capecitabine and oxaliplatin (called CAPOX)
  - 5-FU and leucovorin with oxaliplatin (FOLFOX)
  - 5-FU and leucovorin with irinotecan (FOLFIRI)
- Radiation Therapy – External Beam

SSDIs for Hepatopancreatobiliary

54

- FCDS only Requires 1 SSDIs for these neoplasms – Fibrosis Score
- Fibrosis Score – liver and intrahepatic bile ducts
- Gallbladder – Schema Discriminator 1 – which staging criteria
  - Gallbladder (primary site C240 only)
  - Perihilar Bile Ducts
  - Distal Bile Ducts
- Stomach & Esophagus – Schema Discriminator 1
  - Location Relative to GE Junction
  - Undifferentiated Carcinoma, NOS
- CoC Required – NOT FCDS Required – SSDIs in addition to above:
  - Alpha-Fetoprotein – Value and Interpretation
  - Bilirubin – Value and Unit of Measure
  - Creatinine – Value and Unit of Measure
  - International Normalized Ratio for Prothrombin Time (PTT)
  - Primary Sclerosing Cholangitis
  - Tumor Growth Pattern
  - CA19-9 Value



Site-Specific Data Item (SSDI) Manual

Effective with Cases Diagnosed 1/1/2018 and Forward

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- CEA – not for upper GI Tract tumors – for lower GI Tract tumors
- CA19-9 – Pancreas, Gallbladder, Bile Duct, Stomach – blood – To assess whether treatment is working
- AFP – Liver – blood - To help diagnose liver cancer and follow response to treatment; to assess stage, prognosis, and response to treatment of germ cell tumors
- C-kit/CD117 – GIST – tissue, blood, bone marrow – To help in diagnosing and determining treatment
- Chromagranin A (CgA) – neuroendocrine tumors – blood – To help in diagnosis, assessment of treatment response, and evaluation of recurrence
- Des-gamma-carboxy prothrombin (DCP) – Hepatocellular – blood – To monitor effectiveness of treatment and detect recurrence
- DPD gene mutation – Pancreas, Stomach – tissue - To predict risk of toxic reaction to 5-fluorouracil therapy
- Gastrin – Gastrinoma – blood – To help in diagnosis, to monitor effectiveness of treatment, to detect recurrence

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- HER2/neu gene amplification or protein overexpression – pancreas, stomach – tissue – pancreas, stomach – tissue – to determine whether treatment with certain targeted therapies is appropriate
- 5-HIAA – carcinoid tumors – urine – to help in diagnosis and to monitor disease
- Programmed death ligand 1 (PD-L1) – stomach, liver, ge junction – tissue – to determine whether treatment with a particular type of targeted therapy is appropriate
- Somatostatin receptor – neuroendocrine tumors affecting pancreas or GI Tract (GEP-NETs) – tissue – to determine whether treatment with particular type of targeted therapy is appropriate
- Liquid Biopsy/Blood Test – assay testing hundreds of genetic mutations to define profile for this tumor
- FoundationOne® CDx (F1CDx) genomic test – see Jan 2021 FCDS Memo – any solid tumor – tissue – a companion diagnostic test to determine whether treatment with a particular type of targeted therapy is appropriate
- Guiardan360 CDx genomic test – see Jan 2021 FCDS Memo – any solid tumor – tissue – a companion diagnostic test to determine whether treatment with a particular type of targeted therapy is appropriate

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- FoundationOne CDx - FoundationOne CDx is the first FDA-approved tissue-based broad companion diagnostic (CDx) that has been clinically and analytically validated for all solid tumors. Test results include microsatellite instability (MSI) and tumor mutational burden (TMB) to help inform immunotherapy decisions, and loss of heterozygosity (LOH) for ovarian cancer patients.

- You can also order PD-L1 immunohistochemistry (IHC) testing* as an optional add-on test. The FoundationOne CDx test detects substitution, insertion and deletion genetic alterations, and genetic copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens.

  - FoundationOne CDx (324 DNA genes interrogated from a tissue sample)
  - FoundationOne Liquid CDx (324 DNA genes* interrogated from a simple blood draw)
  - FoundationOne Heme (406 DNA and 265 RNA genes interrogated from a variety of sample options)

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Current Gene List[2]

Genes with full coding exonic regions included in FoundationOne®CDx for the detection of substitutions, insertion-deletions (indels), and copy-number alterations (CNAs).

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	APC
AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2
BTK	C19orf20 (DMTF)	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	CDH1
CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHD4	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R	CTCF
CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1	DDR2
DIS3	DNMT3A	DOT1L	EED	EGFR	EP300	EPHA3	EPHB1	EPHB4
ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRFI1	ESR1	EZH2	FAM46C
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNAQ	GNAS	GRM3	GSK3B	H3F3A	HDAC1
HGF	HNF1A	HRAS	HSD3B1	IDH1	IDH2	IGF1R	IKBKE	IKZF1
INPPL1	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3	JUN	KDM5A
KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6	KMT2A (MLL)	KMT2D (MLL2)
KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4	MAP3K1	MAP3K13
MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MENT	MERTK	MET
MITF	MKNK1	MLH1	MPL	MRE11A	MSH2	MSH3	MSH6	MST1R
MTAP	MTOR	MUTYH	MYC	MYCL1 (MYCL2)	MYCN	MYD88	NBN	NF1
NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS
NTRK1	NTRK2	NTRK3	P2RY8	PALB2	PARK2	PARP1	PARP2	PARP3
PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)	PDGFRA	PDGFRB	PDK1	PIK3C2G	PIK3C3
PIK3CA	PIK3R1	PIM1	PMS2	POLD1	POLE	PPARG	PPP2R1A	PPP2R2A
PRDM1	PRKAR1A	PRKCI	PTCH1	PTEN	PTPN11	PTPRO	QKI	RAC1
RAD21	RAD50	RAD51B	RAD51C	RAD51D	RAD54L	RAF1	RARA	RB1
RBM10	REL	RET	RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB
SDHC	SDHD	SETD2	SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1
SMO	SNCAIP	SOCS1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2
STAT3	STAT1	SUFU	SYK	TBX3	TEK	TET2	TGFBR2	TNFAIP3
TNFRSF14	TNFRSF1A	TP53	TSC1	TSC2	TYRO3	UBA1	VEGFA	VHL
WISP3 (HMGT)	WNT3	WT1	XPO1	XRCC2	ZNF217	ZNF703		

Select Rearrangements[2,3]

Genes with select intronic regions for the detection of gene rearrangements, one gene with a promoter region and one non-coding RNA gene.

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV4
ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT	KMT2A (MLL)
MSI2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSPO2	SDC4	SLC34A2	TERC*	TERT promoter region**	
TMPRSS2								

*TERC is a non-coding RNA gene.
**TERT is gene with promoter region

Table 1: Companion diagnostic indications

INDICATIONS	BIOMARKER	FDA-APPROVED THERAPY
Non-Small Cell Lung Cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), Tagrisso® (osimertinib) or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa®(alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	Tabrecta® (capmatinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E or V600K	Mekinist® (trametinib) or Cotellic®(cobimetinib), in combination with Zelboraf®(vemurafenib)
Breast Cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
	PIK3CA alterations	Piqray® (alpelisib)
Colorectal Cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3 and 4)and *NRAS* wild-type (absence of mutations in exons 2, 3 and 4)	Vectibix® (panitumumab)
Ovarian Cancer	*BRCA1/2* alterations	Lynparza® (olaparib) or Rubraca® (rucaparib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre® (pemigatinib)
Prostate Cancer	Homologous Recombination Repair *(HRR) gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L)* alterations	Lynparza® (olaparib)
Solid tumors	TMB ≥ 10 mutations per megabase	Keytruda® (pembrolizumab)

The test is also used for detection of genomic loss of heterozygosity (LOH) from formalin-fixed, paraffin-embedded (FFPE) ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the Rubraca product label.

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- Guardant360 CDx - Guardant360® CDx is a qualitative next generation sequencing-based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels) in 55 genes, copy number amplifications (CNAs) in two (2) genes, and fusions in four (4) genes. Guardant360 CDx utilizes circulating cell-free DNA (cfDNA) from plasma of peripheral whole blood collected in Streck Cell-Free DNA Blood Collection Tubes (BCTs).

Table 3. Genes Containing Alterations Reported by Guardant360 CDx

Alteration Type	Genes
Single Nucleotide Variants (SNVs)	*AKT1, ALK, APC, AR, ARAF, ATM*, BRAF, BRCA1**, BRCA2**, CCND1, CDH1, CDK4, CDK6, CDK12*, CDKN2A, CTNNB1, EGFR, ERBB2, ESR1, FGFR1, FGFR2, FGFR3, GATA3, GNA11, GNAQ, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MAP2K2, MET, MLH1, MTOR, MYC, NF1, NFE2L2, NRAS, NTRK1, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, RHEB, ROS1, SMAD4, SMO, STK11, TERT, TSC1, VHL*
Indels	*AKT1, ALK, APC, ATM*, BRAF, BRCA1**, BRCA2**, CDH1, CDK12*, CDKN2A, EGFR, ERBB2, ESR1, FGFR2, GATA3, HNF1A, HRAS, KIT, KRAS, MET, MLH1, NF1, PDGFRA, PIK3CA, PTEN, RET, ROS1, STK11, TSC1, VHL*
Copy Number Amplifications (CNAs)	*ERBB2, MET*
Fusions	*ALK, NTRK1, RET, ROS1*

*Reporting is enabled for pathogenic germline alterations only. Somatic alterations will not be reported.
** Reporting is enabled for both germline and somatic alterations.

2021 Changes

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- Retire Flat File Format – will allow flat file submissions/data transmissions until 6/30/2021
- XML File Format – 7/1/2021 (tentative)/optional for submissions starting Jan 2021
- 2021 New Reportable Criteria – ALL GIST, ALL Thymoma, Evolving Melanoma
- 2021 Not Reportable Criteria – Need to remove NIFTP, EFVPTC, EFVPTC and other histologies from thyroid and review non-invasive histologies for pancreas – need to clarify removals
- Schema ID – changes to criteria and one new schema added
- 2021 Solid Tumors – 2 newly revised chapters (Melanoma/Other) and changes to all 8 other chapters
- Expecting to see GYN Solid Tumor Rules before September 2021 according to ETC Training Schedules
- Please participate in any 2021 Updates Webinars sponsored by NAACCR, FCDS, SEER, CoC
- FCDS will be sponsoring some webinars – but, other experts may do a better job of explaining

2021 Changes

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2021 New Data Items Required

- Name-Birth Surname – Replaces Maiden Name which will be Retired
- Medicare Beneficiary ID
- Grade Post Therapy Clinical (yc)
- Gleason Pattern Clinical
- Gleason Pattern Pathological
- Gleason Score Clinical
- Gleason Score Pathological
- Gleason Tertiary Pattern

Changed Data Items

- HER2 Overall Summary added to Esophagus and Stomach Schemas 00161, 00169, 00170
- Radiation Modality New Codes
- Changes to SSDIs
- FIGO Stage
- Grade – schema specific
- Grade Field Conversions
- Stage Conversions
- SSDI Conversions
- 2021 Retired Data Items – TNM 6 & 7, Maiden Name
- **2021 FCDS DAM Revision**
- **FCDSv21 EDITS Metafile**
- **FCDSv21 Updates to Abstractor Code Test & Review of Existing Q&A**
- 2021 Grade Manual
- 2021 SSDI Manual
- 2021 Heme Updates
- 2021 Solid Tumors – 2 newly revised chapters (Melanoma/Other) and changes to all 8 other chapters
- Expecting to see GYN Solid Tumor Rules before September 2021 according to ETC Training Schedules
- 2021 ICD-O-3 Updates
- 2021 STORE Manual

Resources

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- American Cancer Society – 2021 Cancer Facts and Figures and Cancer Statistics 2021 Presentation – www.cancer.org
- National Cancer Institute – PDQ for Cancers Noted in Presentation and Tumor Markers/Genetics – www.cancer.gov
- American Cancer Society Introduction to Cancer Series By Cancer Site/Type – www.cancer.org
- NCCN Guidelines Series by Cancer Site/Type – www.nccn.org
- Cancers in Series from NCI, ACS and NCCN Include:
  - Esophagus
  - Stomach
  - Pancreas
  - Liver
  - Bile Duct
  - Gallbladder
  - Small Bowel
- Mayo Clinic Website/Johns Hopkins Website/MD Anderson Website
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- Upper gastrointestinal tumours: diagnosis and staging, Cancer Imaging (2006) 6, 213–217 DOI: 10.1102/1470-7330.2006.0032, Gore, Mehta, Berlin
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- World J Gastrointest Oncol. 2014 Sep 15; 6(9): 360–368. Published online 2014 Sep 15. doi: 10.4251/wjgo.v6.i9.360 PMCID: PMC4163734 PMID: 25232461 Role of endoscopic ultrasound in the diagnosis of pancreatic cancer Juana Gonzalo-Marin, Juan Jose Vila, and Manuel Perez-Miranda
- FoundationOne CDx and Guiardan360 CDx Websites

Questions ……