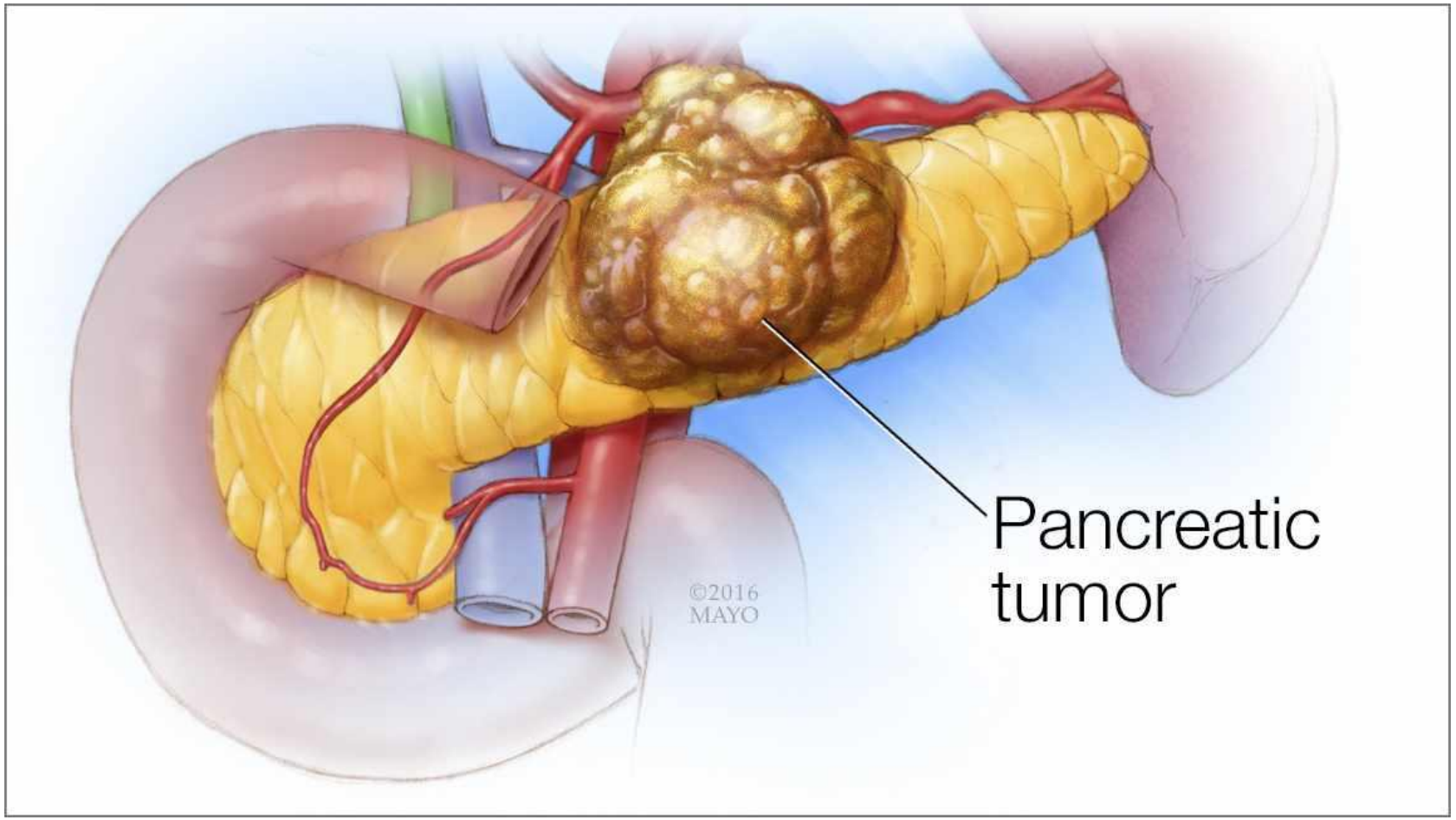
Pancreatic Cancer



Bible Class 15.12.2021 R.Sarraj / I.Kapoglou

Pancreatic Cancer: Epidemiology

2014

Estimated New Cases*

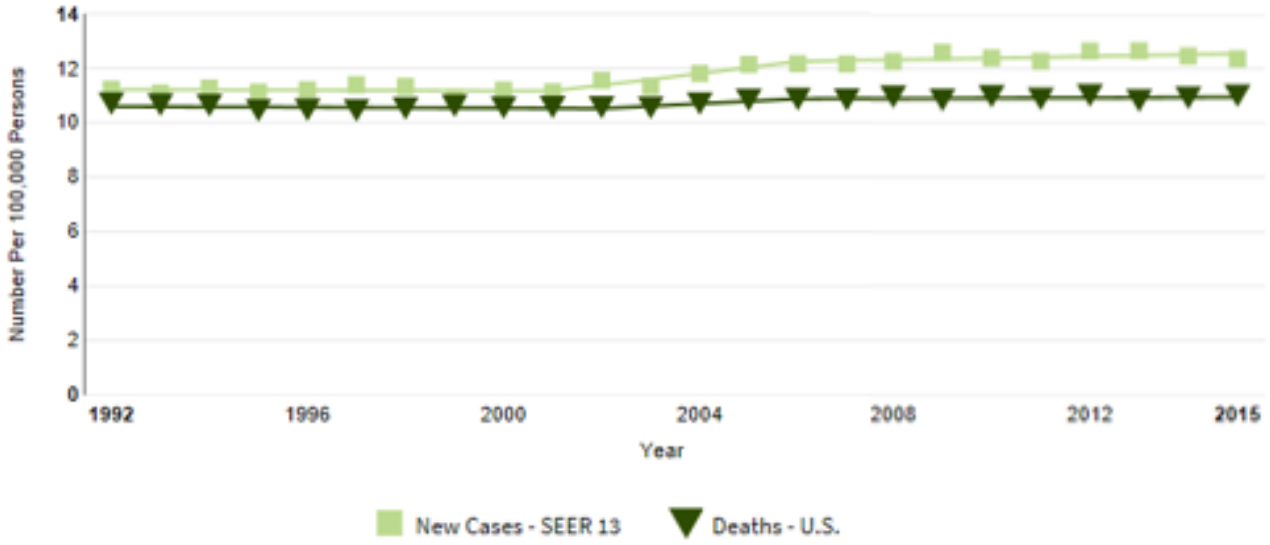
			Males	Females			
Prostate	241,740	29%			Breast	226,870	29%
Lung & bronchus	116,470	14%			Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%			Colon & rectum	70,040	9%
Urinary bladder	55,600	7%			Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%			Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%			Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%			Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%			Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%			Ovary	22,280	3%
Pancreas	22,090	3%			Pancreas	21,830	3%
All Sites	**848,170**	**100%**			**All Sites**	**790,740**	**100%**

Estimated Deaths

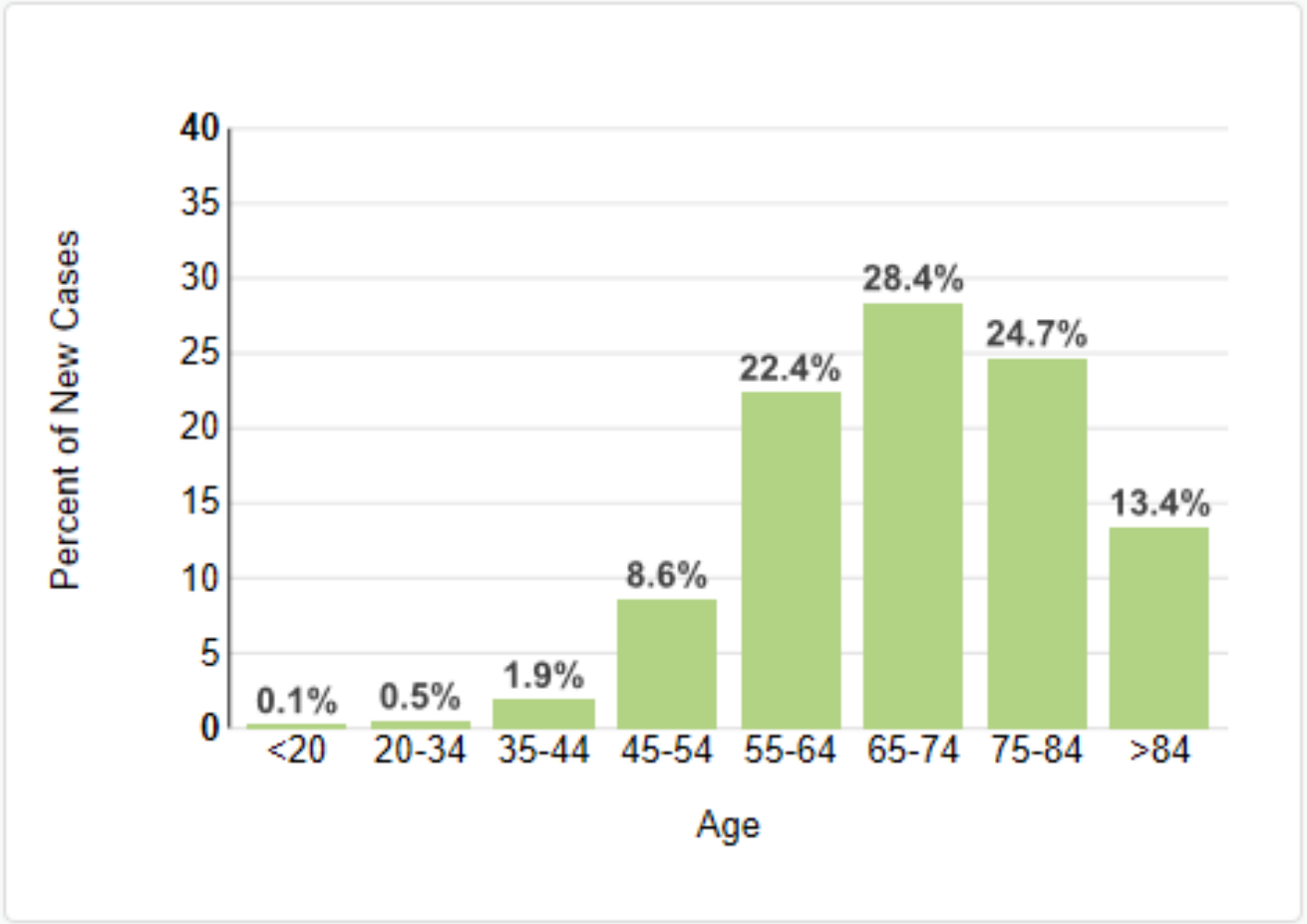
			Males	Females			
Lung & bronchus	87,750	29%			Lung & bronchus	72,590	26%
Prostate	28,170	9%			Breast	39,510	14%
Colon & rectum	26,470	9%			Colon & rectum	25,220	9%
Pancreas	18,850	6%			Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%			Ovary	15,500	6%
Leukemia	13,500	4%			Leukemia	10,040	4%
Esophagus	12,040	4%			Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%			Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%			Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%			Brain & other nervous system	5,980	2%
All Sites	**301,820**	**100%**			**All Sites**	**275,370**	**100%**

Estimated New Cases in 2018	55,440
% of All New Cancer Cases	3.2%

Estimated Deaths in 2018	44,330
% of All Cancer Deaths	7.3%



Percent of New Cases by Age Group: Pancreatic Cancer



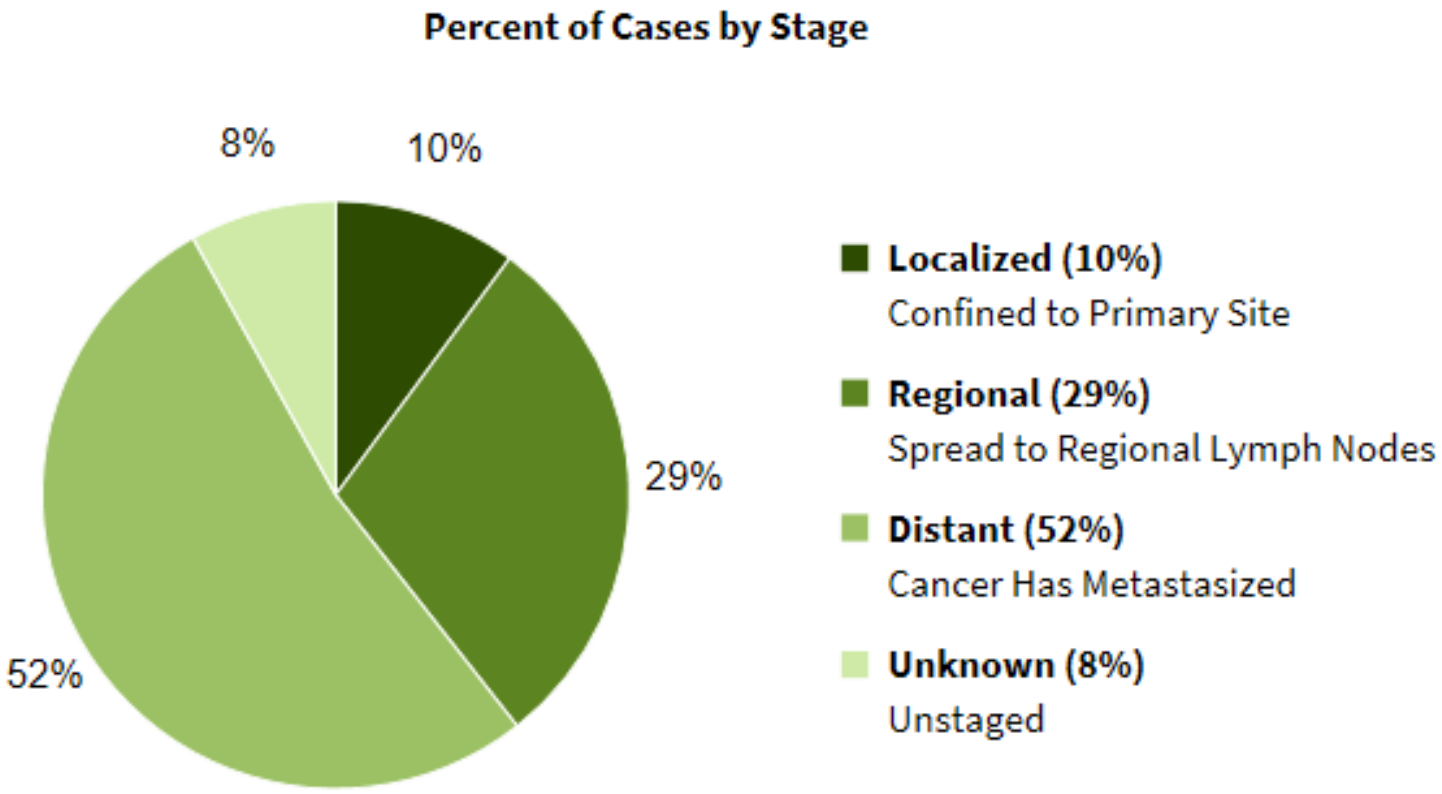
Pancreatic cancer is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis

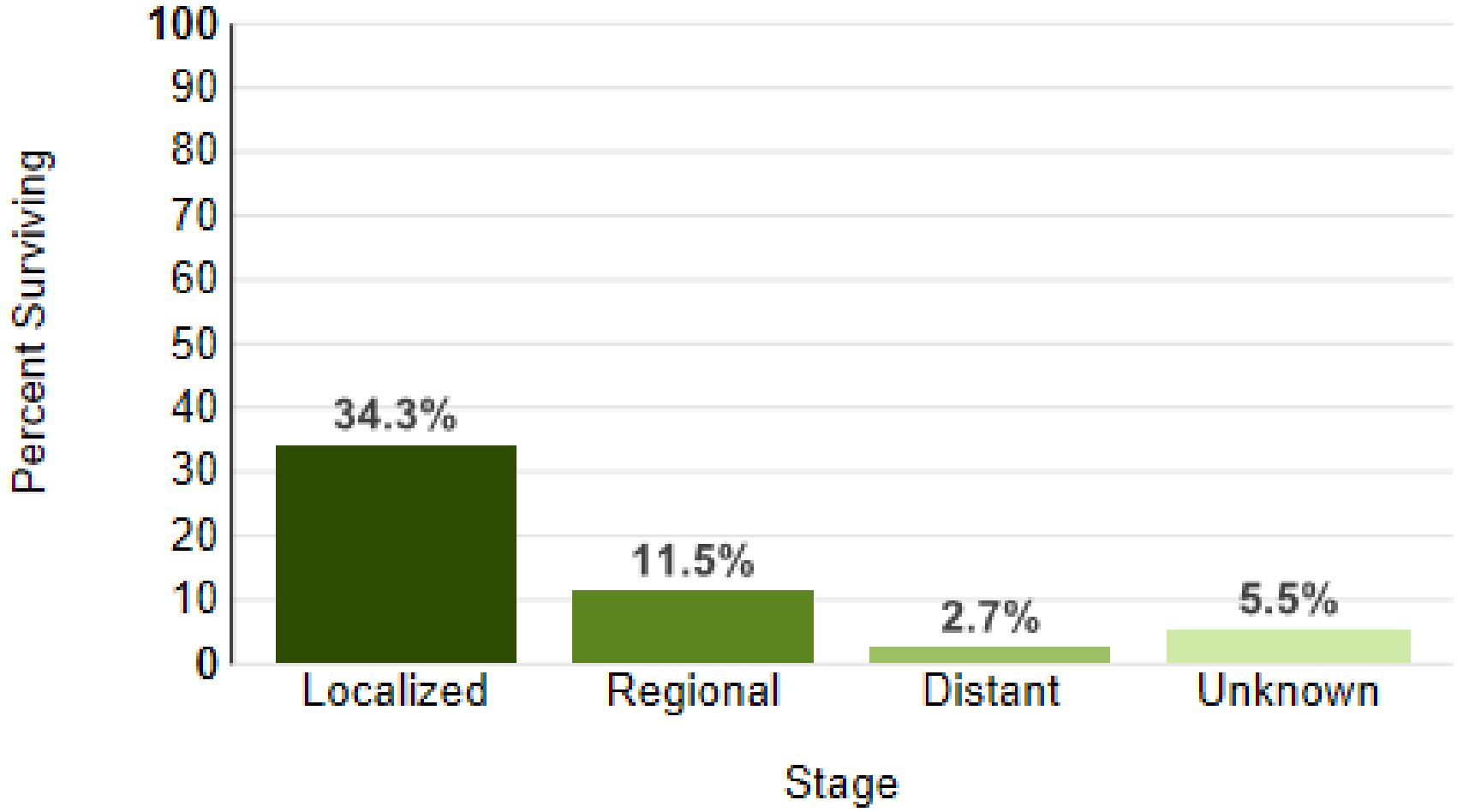
70

SEER 18 2011-2015, All Races, Both Sexes

Stage at Diagnosis: Pancreatic Cancer

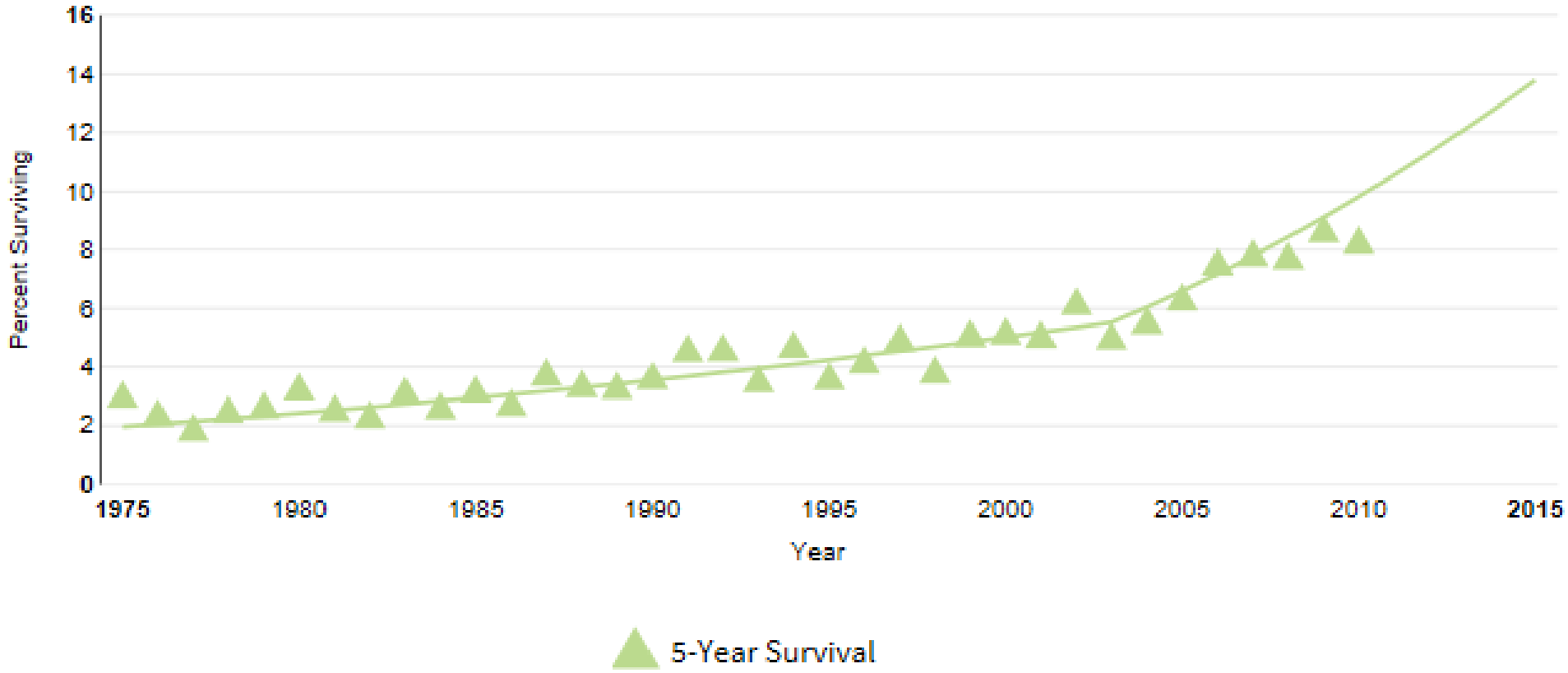


5-Year survival rate



Percent Surviving 5 Years
8.5%
2008-2014

5-Year survival rate



SEER 9 5-Year Relative Survival Percent from 1975-2010, All Races, Both Sexes.

Genetic risk factors

- 80% of pancreatic carcinomas are due to sporadically occurring mutations.

- <10% are due to inherited germline mutations
  - BRCA2
  - P16
  - ATM
  - STK11
  - PRSS1/PRSS2
  - SPINK1
  - PALB2
  - DNA mismatch repair genes

Familial syndromes linked to pancreatic cancer

Familial Syndrome	Genetic abnormality	Increased RR
Peutz-Jaegers	STK11/LKB1	30-40
Familial pancreatitis	PRSS1, SPINK1	50
FAMM	CDKN2A	10-20
HNPCC	hMLH1, hMSH2	4
Hereditary breast-ovarian syndrome	BRCA1, BRCA2, PALB2	1-2
Cystic fibrosis	CFTR	
FAP	APC	
Ataxia-telangiectasia	ATM	unknown
Li-Fraumeni	p53	unknown
Familial pancreatic cancer	unknown	

It is important to take a thorough family history in new patients with PC, in particular with regard to:

- Pancreatitis
- Melanoma
- Cancers of the colorectum, pancreas, breast and ovaries.

Genetic predisposition (familial pancreatic cancer)

- **PC has familial component in approximately 10 %** of cases **but** in most cases (80%) **the genetic basis** of this predisposition is **not known.**

- **Definition: Familial pancreatic cancer**
  - at least two first-degree relatives with PC

- **Familial excess of PC is associated with high risk**
  - number of first-degree relatives with PC raises the risk for PC

Number of FDRs	Increased risk of developing PC	Cumulative risk by age of 70 y	Lifetime risk
1	4.6-fold		
2	6.4-fold	3 %	8-12 %
3 or more	32-fold	7-16 %	40 %

- **Risk is even higher in families with young-onset of PC** (age <50 years)

Screening

Population-based screening is not recommended because of the low incidence of PC in the general population (lifetime risk 1.3 %)

Questions

1. **Who should be screened ?**

2. **How should high-risk individuals be screened and followed up ?**

Screening

Recommendations of the International Cancer of the Pancreas Screening **(CAPS) Consortium for** the management of **patients with increased risk** for familial pancreatic cancer

Who should be screened ?

Syndrome	Gene	Estimated cumulative risk of pancreatic cancer	Estimated increased risk compared to general population
Peutz-Jeghers Syndrome	*STK11*	11%–36% by age 65–70 years[59]	132-fold[58]
Familial Pancreatitis	*PRSS1, SPINK1, CFTR*	40%–53% by age 70–75 years[63-65]	26-fold to 87-fold[29,63-65]
Melanoma-Pancreatic Cancer Syndrome	*CDKN2A*	17% by age 75 years[68]	20-fold to 47-fold[67,68]
Lynch Syndrome	*MLH1, MSH2 (MSH6)*	4% by age 70 years[77]	9-fold to 11-fold[77,78]
Hereditary Breast-Ovarian Cancer Syndrome	*BRCA1, BRCA2*	1.4%–1.5% (women) and 2.1%–4.1% (men) by age 70[79,84]	2.4-fold to 6-fold[79,83,84]
Familial Pancreatic Cancer	Unknown in most families (family X is an exception)*	≥3 first-degree relatives with pancreatic cancer: 7%–16% by age 70[51] 2 first-degree relatives with pancreatic cancer: 3% by age 70[51]	≥3 first-degree relatives with pancreatic cancer: 32-fold[90] 2 first-degree relatives with pancreatic cancer: 6.4-fold[90] 1 first-degree relative with pancreatic cancer: 4.6-fold[90]

Screening

- **How should high-risk individuals be screened ?**
  - **Initial screening** should include **EUS and/or MRI/MRCP**
  - **CT should not be a routine screening test**
    - EUS/MRI are superior with regard to small, predominantly cystic lesions
    - radiation exposure
  - **Transabdominal ultrasound and ERCP are not recommended**
    - their low diagnosic sensitivity and risk of pancreatitis
- **Surveillance after baseline screening ?**
  - **No consensus with regard to screening intervall, 73.5% of participants suggested a 12-month interval (EUS and/or MRI)**

Screening using biomarkers

- Methylation patterns in cell-free plasma DNA can differentiate between pancreatitis and pancreatic cancer with a sensitivity of 91.2% and specificity of 90.8%.

Liggett T, Melnikov A, Yi QL, et al. Cancer 2010;116:1674-1680.

- CA19-9 levels may be elevated in patients up to 2 years before a pancreatic cancer diagnosis

O'Brien DP et al. Clin Cancer Res 2014.

- CAVE: **low positive predictive value**

Non-genetic risk factors

Factor	Relative risk	Attributable fraction
Tobacco	2	11%–32%
Helicobacter pylori infection	1.5	4%–25%
Non-O-blood group	1.4	13%–19%
Diabetes mellitus	1.4–2.2	1%–16%
Obesity	1.2–1.5	3%–16%
Red meat intake	1.1–1.5	2%–9%
Heavy alcohol intake	1.1–1.5	9%
Low fruit and folate intake	0.5–1.0	<12%

A Systematic Review of Intra-pancreatic Fat Deposition and Pancreatic Carcinogenesis

13 studies (2178 individuals) → The presence of PC was associated with a significantly increased risk of intra-pancreatic fat deposition (relative risk 2.78 (95% CI, 1.56-4.94, $p < 0.001$).

Sreedhar UL,J Gastrointest Surg. 2020 Nov;24(11):2560-2569.

Location and pathology of pancreatic carcinoma

- **90-95% within the exocrine portion**

  Ductal epithelium, acinar cells, connective tissue

  80% ductal adenocarcinoma

Other variants:

- Acinar cell PC
- Adenosquamous carcinoma
- Undifferentiated carcinomas

Cystic neoplasms:

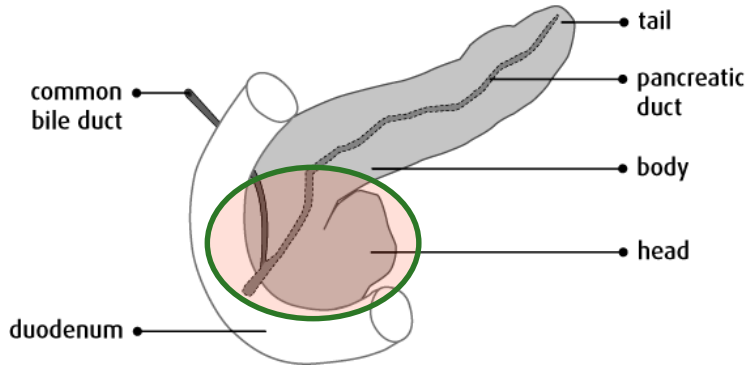
- Serous cystadenocarcinoma
- intraductal papillary mucinous neoplasm (IPMN)
- Mucinous cystadenocarcinoma

Tumour location

Head of the pancreas :60-70 %

Body and tail: 20-25 %

10-20% diffusely involve the pancreas



- **5-10% neuroendocrine**
  - Gastrinoma (Zollinger-Ellison Syndrome), Glucagonoma, Insulinoma, Somatostatinoma, VIPoma (Verner-Morrison Syndrome), non-functional Islet Cell Tumor

Molecular biology (mutations)

The most frequent precursors are microscopic PanIN followed by IPMN and MCN

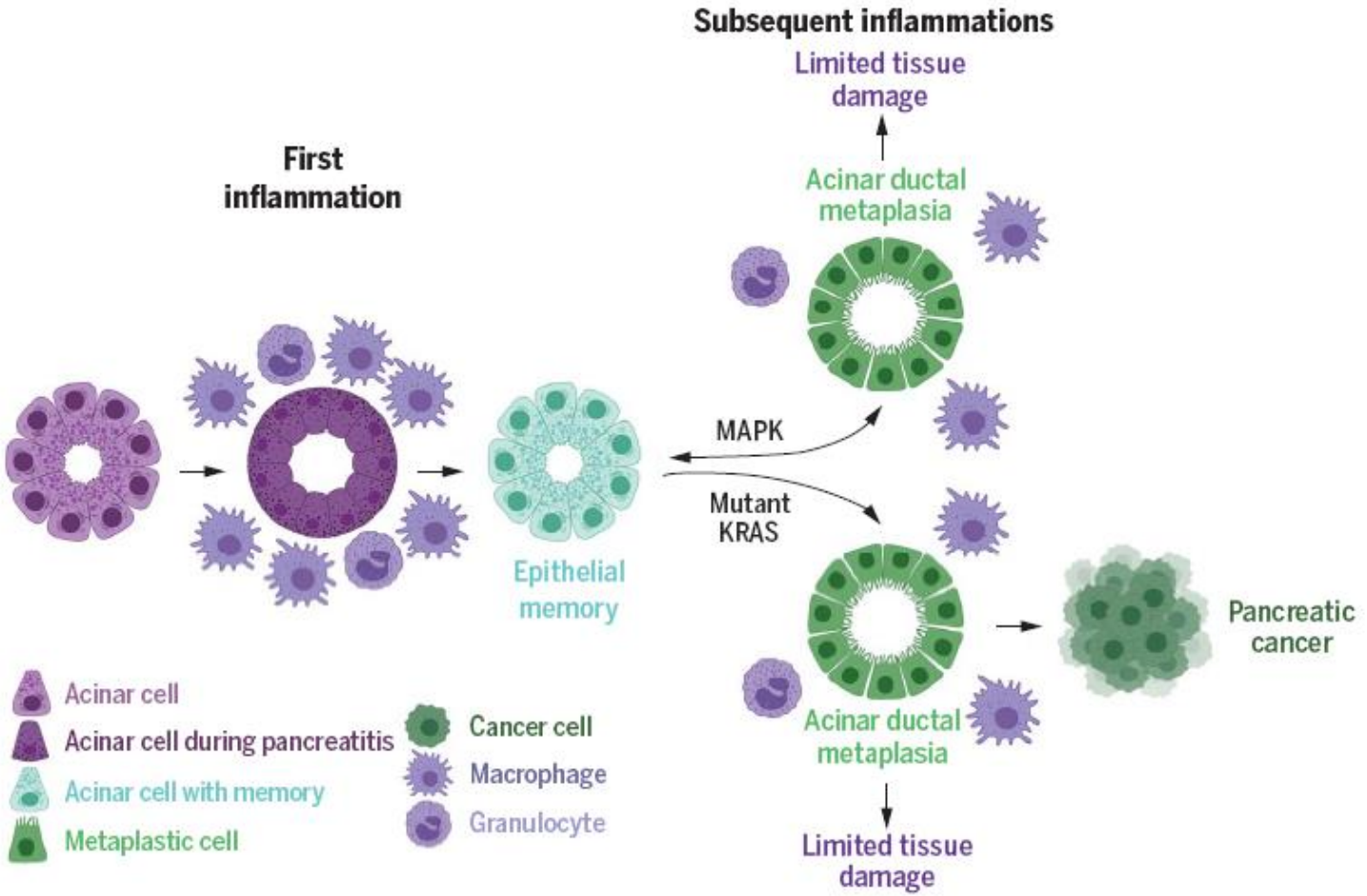
- KRAS mutations[1]
  - Very common (> 90%)
  - Early genetic event in pancreatic carcinogenesis, considered to be a “signature” of pancreatic cancer
- BRAF mutations[2]
  - Observed in 30% of the pancreatic cancers with WT KRAS gene

- Inactivation of tumour suppressor genes (TP53, p16/CDKN2A and SMAD4).

- Inactivation of genome maintenance genes (hMLH1 and MSH2)

1. Almoguera C, et al. *Cell*. 1988;53:549-54;
2. Kanda M, et al. *Gastroenterology.* 2012;142:730-3;

Epithelial memory of inflammation limits tissue damage while promoting pancreatic tumorigenesis



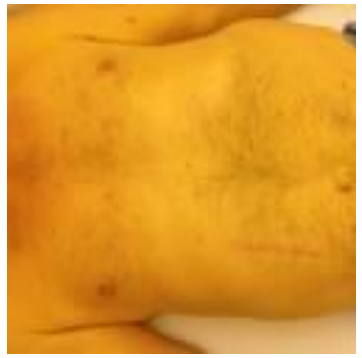
Del Poggetto et al., Science 373, 1326 (2021) 17 September 2021

Symptoms

- Early symptoms of pancreatic cancer result from a mass effect.

- Tumours located in the body and the tail are likely to be diagnosed at a more advanced stage than tumours located in the head

- (painless) jaundice, pruritus
- abdominal pain
- weight loss
- steatorrhoea
- new-onset diabetes
- upper gastroduodenal obstruction



Diagnostic tools for pancreatic cancer

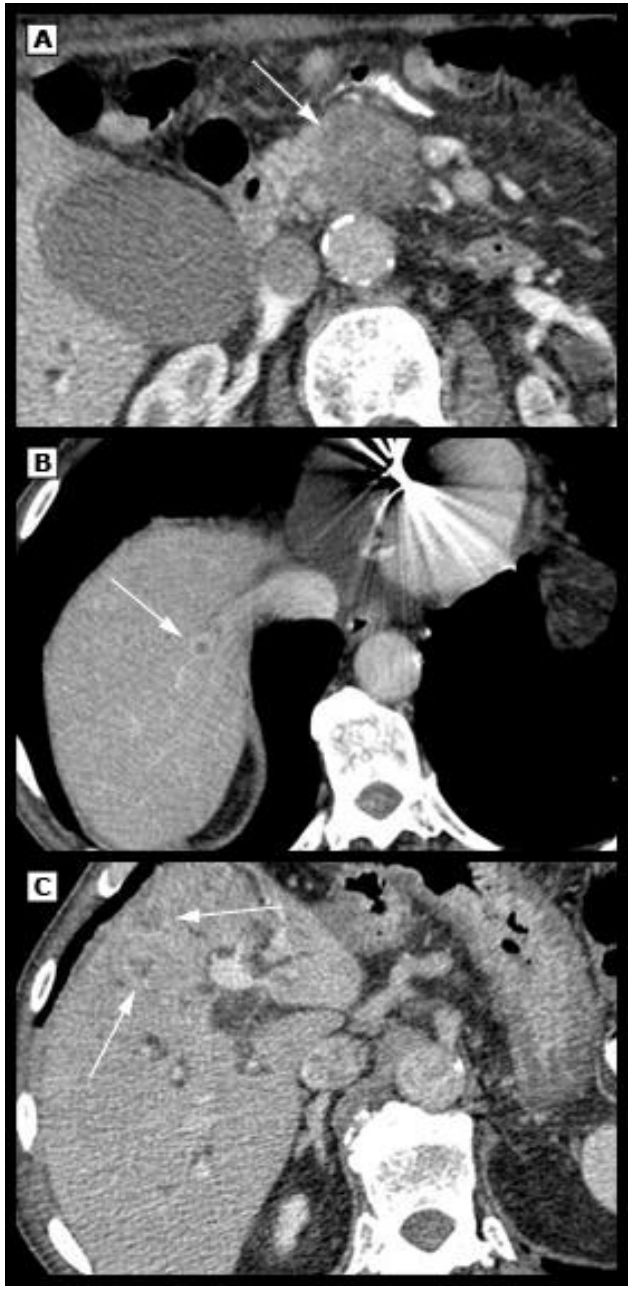
- Imaging modalities
  - Transabdominal US
  - CT scan
  - EUS
  - ERCP
  - MRI/MRCP
  - PET scanning
  - Staging laparoscopy

- Lab studies
  - Tumor markers i.e. CA19-9

Imaging Evaluations

– Abdominal CT

- Triple-phase, multidetector row CT
- Sensitivity:
  - 100 % for tumors > 2 cm
  - 77 % for tumors < 2 cm
- **Hypodense lesion** (contrast enhancement is highest during the late arterial phase)
- **Secondary signs:**
  - Pancreatic duct cut-off
  - Dilatation of the pancreatic and/or common bile duct
  - Double duct sign present in 62-77% of cases
  - Parenchymal atrophy
  - Contour abnormalities



Imaging Evaluations

- **Abdominal CT**
  - **Triple-phase CT assess vascular invasion (prediction of resectability)** and allows selective visualisation of
    - **Arterial** (celiac axis, superior mesenteric artery, peripancreatic arteries)
    - **Venous structures** (superior mesenteric vein, splenic vein, portal vein)

Imaging Evaluations (MRI/EUS)

– MRI

- Can be helpful for characterization of CT-indeterminate liver lesions
- when suspected pancreatic tumors are not visible
- in cases of contrast allergy

– Endoscopic Ultrasound

- **Not** recommended as a **routine staging tool**
- May provide additional information for patients when initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes
- **EUS can be used**
  - »to evaluate periampullary masses (invasive vs. noninvasive)
  - »to better characterize cystic pancreatic lesions (ability of FNA)

Imaging Evaluations

–ERCP

- **In general ERCP is limited to therapeutic interventions**
  - »**Palliative drainage**
  - »**Delayed surgery**

- **Duct brushing cytology** is recommended for patients without a mass in the pancreas and without metastatic disease who require biliary drainage and who undergo additional imaging with EUS

Biliary drainage

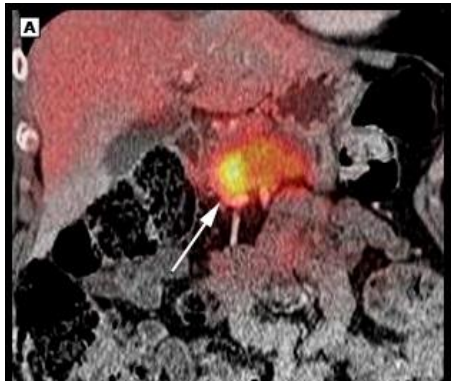
- nearly 2-fold increase in the rate of serious complications in the stented group

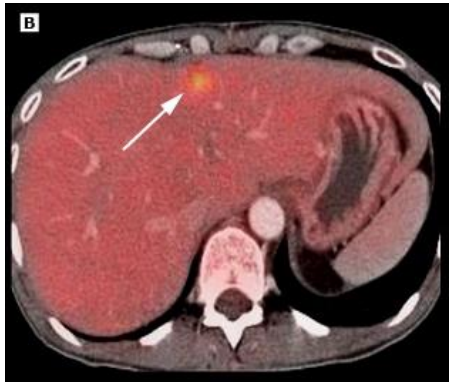
N Engl J Med 2010;362:129-37.

- Consider preoperatively only if patient:
  - Symptomatic
  - Septic (cholangitis)
  - Coagulopathic
  - renal insufficiency
  - in whom surgical resection is significantly delayed (>1-2w)

- Placement of a stent is required prior to administration of neoadjuvant therapy for patients with jaundice

Imaging Evaluations





–PET/CT and laparoscopy

- **Can be diagnostic tools** for staging in **high risk pat.**
- **High risk patients**
  - » Borderline resectable disease
  - » Large primary tumors
  - » Large regional lymph nodes
  - » Markedly elevated CA 19-9
  - » highly symptomatic patients

- **PET/CT:**

  Can be used in addition to CT in high risk patients to increase sensitivity for the detection of metastatic disease.

- **Laparoscopy:**

  can identify peritoneal, capsular or serosal implants or studding of metastatic tumor on the liver in high risk patients

Biopsy

- **Pathologic diagnosis not required before surgery, but necessary**
  - –before administration of neoadjuvant therapy
  - –for patients staged with locally advanced, unresectable PC or metastatic disease

- Diagnostic tools:
  - –**EUS/FNA**
  - –Other methods
    - »CT-directed FNA (additional risks: greater bleeding and infection)
    - »ERCP with ductal brushings

–Biomarkers

- **CA 19-9**
  - –Best validated and most clinical useful biomarker
  - –Preoperative levels correlate with staging and resectability

  - –Ca19-9 may be **falsely positive** in cases of
    - »Biliary infection
    - »Inflammation
    - »Biliary obstruction
  - –**Measurement** should be performed **after biliary decompression**

  - –CA 19-9 requires the presence of the Lewis blood group antigen to be expressed (**Lewis-negative phenotype: 5-10% of the population**)

  - –**Recommendation: Serum CA 19-9 levels should be measured**
    - »**Prior to surgery**
    - »**Following surgery prior to administration of adjuvant therapy**
    - »**For surveillance**

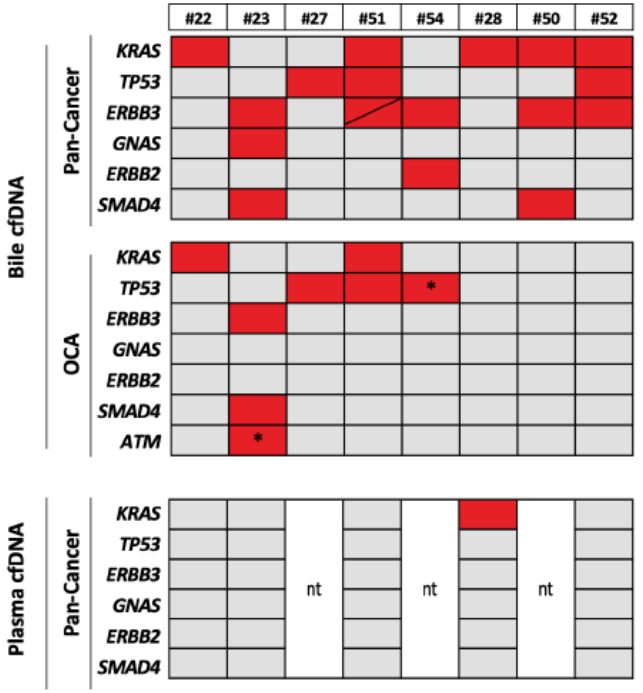
NGS of bile cell-free DNA for the early detection of patients with malignant biliary strictures

Advantages

- It does not entail any additional risk for patients undergoing ERCP.
- It is based on an NGS platform open to clinical laboratory implementation.
- Its high sensitivity for malignancy can hasten diagnosis, avoiding additional and unnecessary diagnostic interventions and their associated complications.
- It provides more comprehensive mutational information than tissue analysis.
- It may guide patient selection for targeted therapies, particularly in unoperable cases needing systemic treatment from which no tissue is available for mutational profiling.

Limitations

- It can be only applied to patients undergoing ERCP or other diagnostic procedures in which bile can be obtained.
- The mutation analysis is limited to a defined panel of genes.
- False positives may occur, although these should be interpreted with caution.



Differential Diagnosis

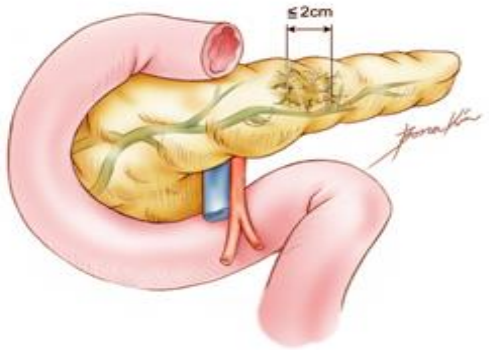
- Chronic pancreatitis
- Autoimmune pancreatitis
  - IgG4 levels of >1.0 g/L combined with CA 19-9 levels of <74 U/mL distinguishes patients with autoimmune pancreatitis from those with adenocarcinoma with 94% sensitivity and 100% specificity

van Heerde MJ et al. Dig Dis Sci 2014;59:1322-1329.

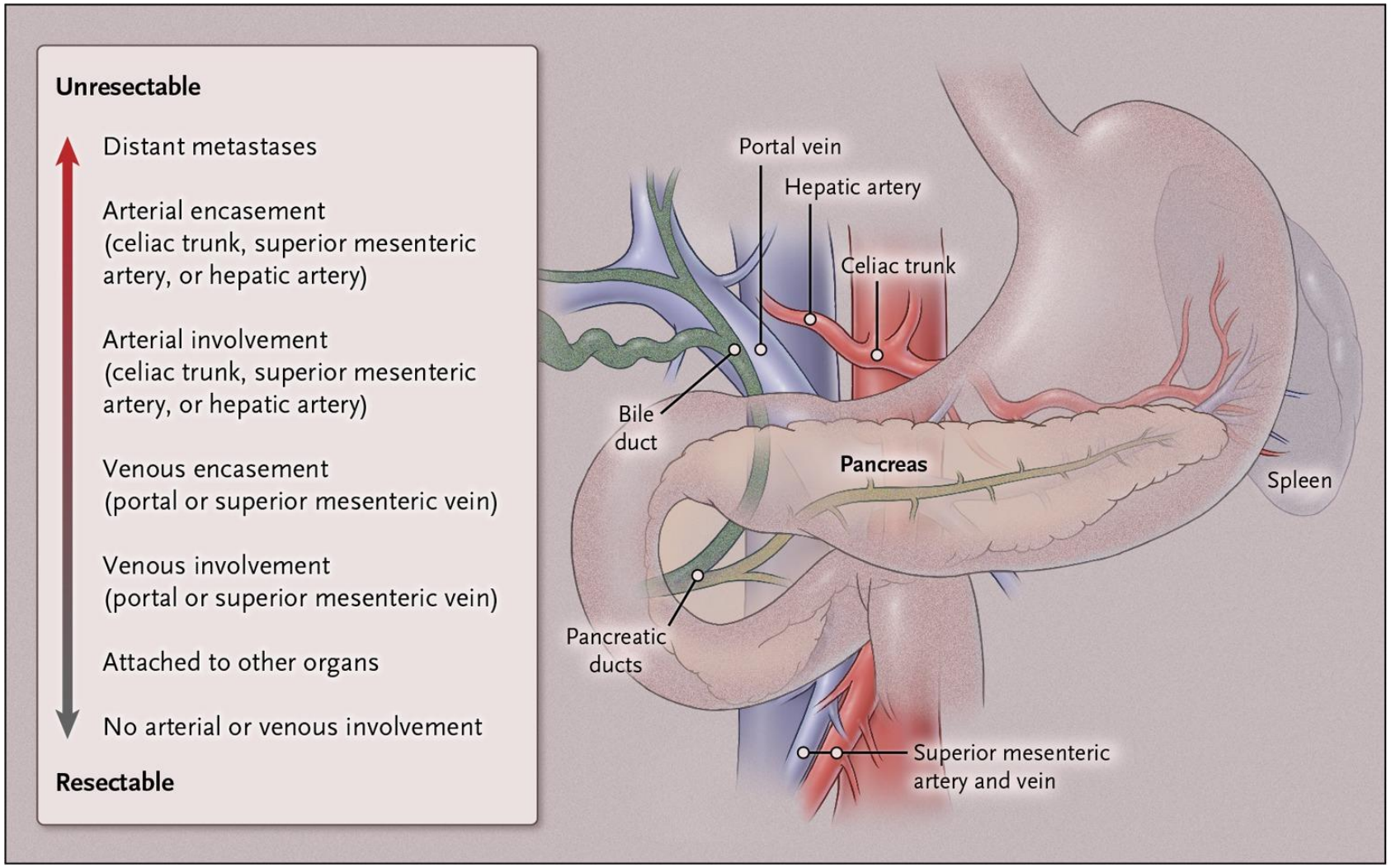
Major clinical stages

- **Resectable**

- **Borderline resectable**
  - tumors that are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable with a high chance of an R1 resection
- **Locally advanced**
  - tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease
- **Metastatic**



Anatomy and Surgical Resectability of Pancreatic Cancer



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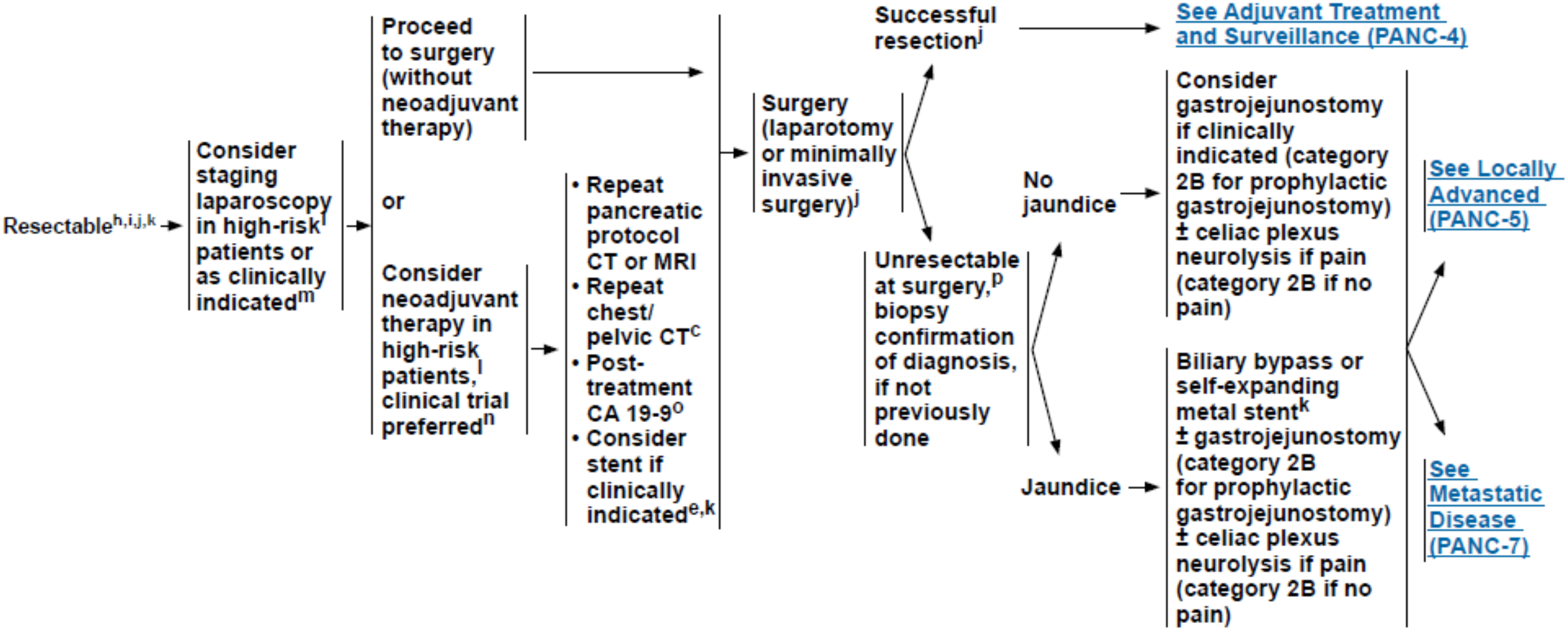
CRITERIA DEFINING RESECTABILITY STATUS

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	<u>Pancreatic head/uncinate process</u>: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. <u>Pancreatic body/tail</u>: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some panel members prefer these criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° 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 (IVC).
Unresectable[b]	• Distant metastasis (including non-regional lymph node metastasis) <u>Head/uncinate process</u>: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° <u>Body and tail</u>: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	<u>Head/uncinate process</u>: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV <u>Body and tail</u>: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

TNM Classification (8th edition)

	Bisherige Klassifikation [4]	Neue Klassifikation [5]
T1	Auf Pankreas begrenzt, ≤2 cm	a ≤0,5 cm b ≤1 cm c ≤2 cm
T2	Auf Pankreas begrenzt, >2 cm	
T3	Pankreas überschreitend, jedoch ohne Infiltration des Truncus coeliacus oder der A. mesenterica superior	>4 cm
T4	Tumorinfiltration von Truncus coeliacus oder A. mesenterica superior	Tumorinfiltration von Truncus coeliacus, A. hepatica oder A. mesenterica superior
N0	Keine positiven Lymphknoten	Keine positiven Lymphknoten von mindestens 12 exstirpierten
N1	Positive Lymphknoten nachgewiesen –	1–3/>12
N2		≥4/>12

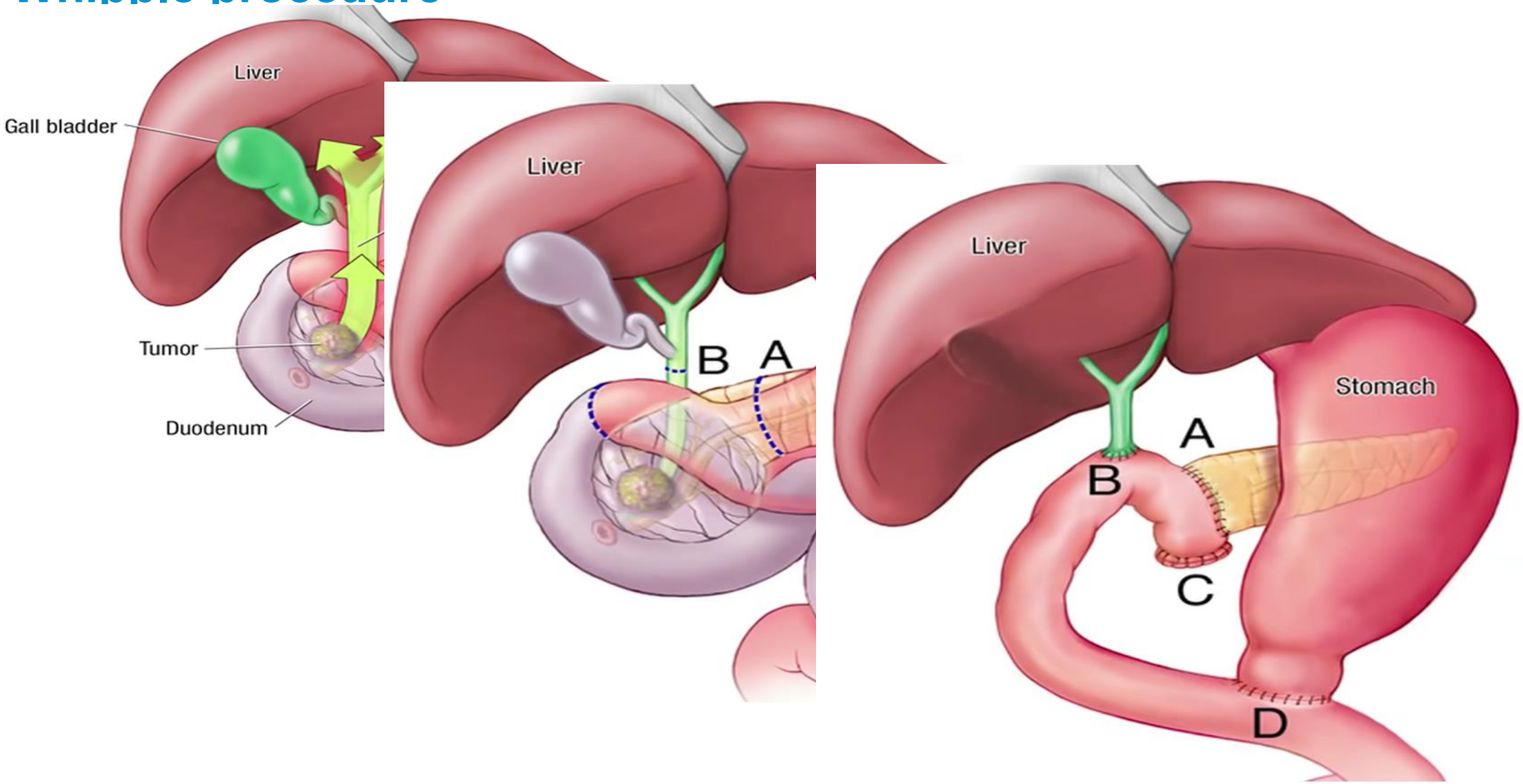
Treatment for resectable disease



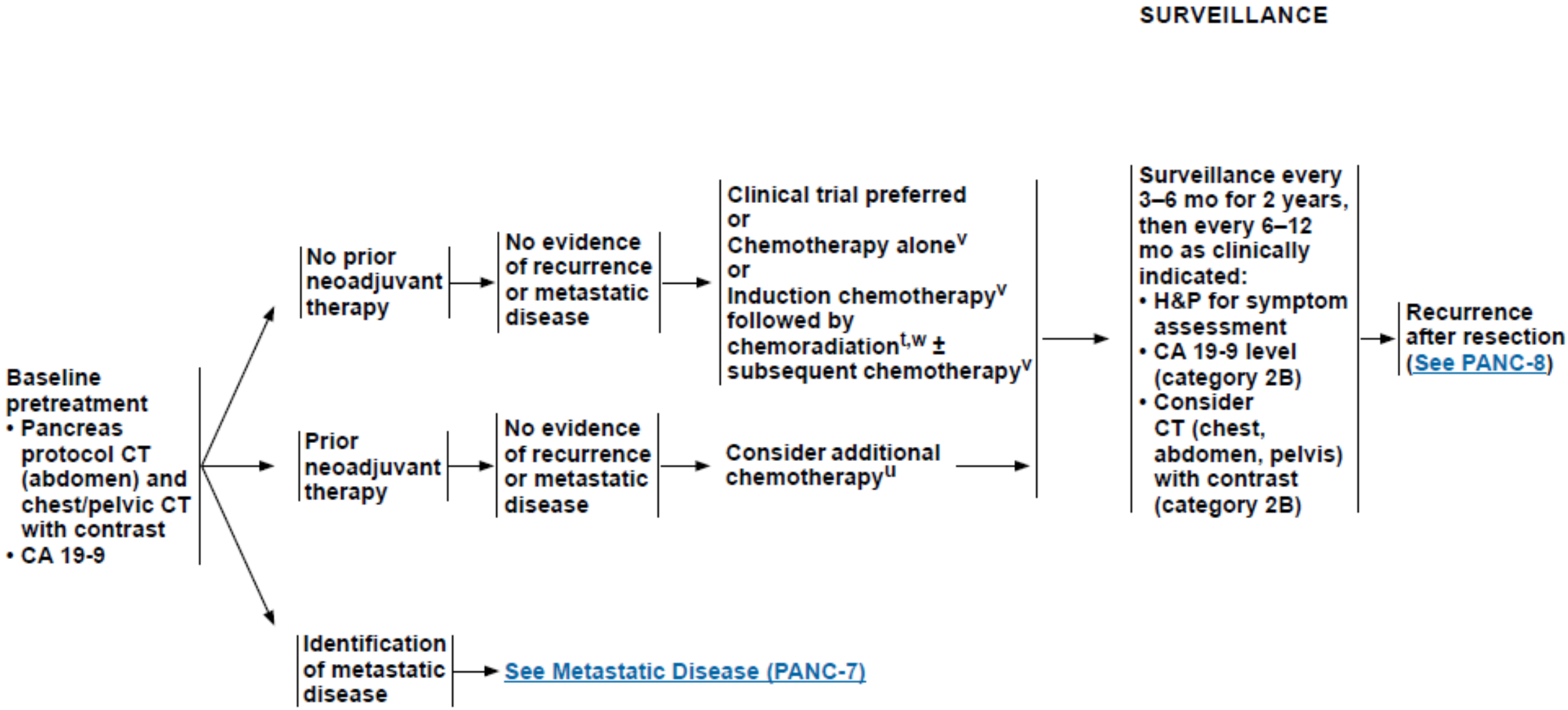
Pancreatic resection

- Whipple procedure (pancreaticoduodenal resection)
- Total pancreatectomy when necessary for adequate margins
- Distal pancreatectomy (including speen) for tumors of the body and tail of the pancreas

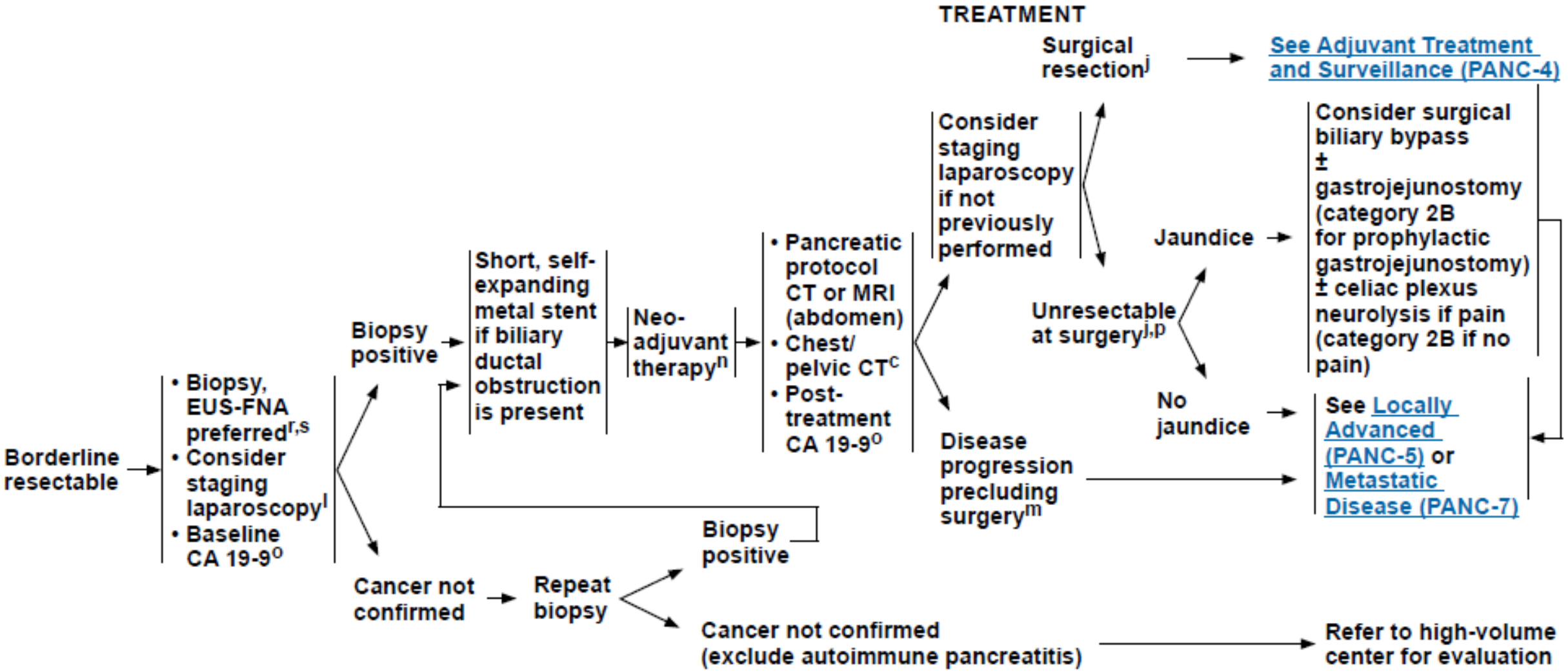
Whipple procedure



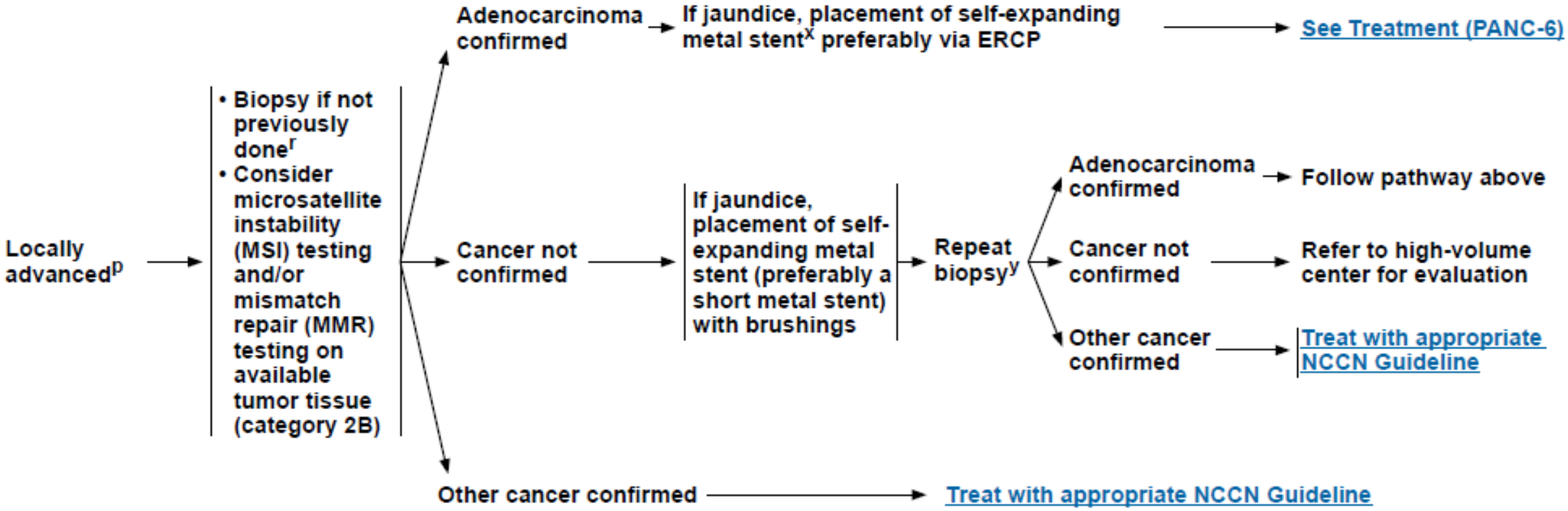
Postoperative adjuvant treatment



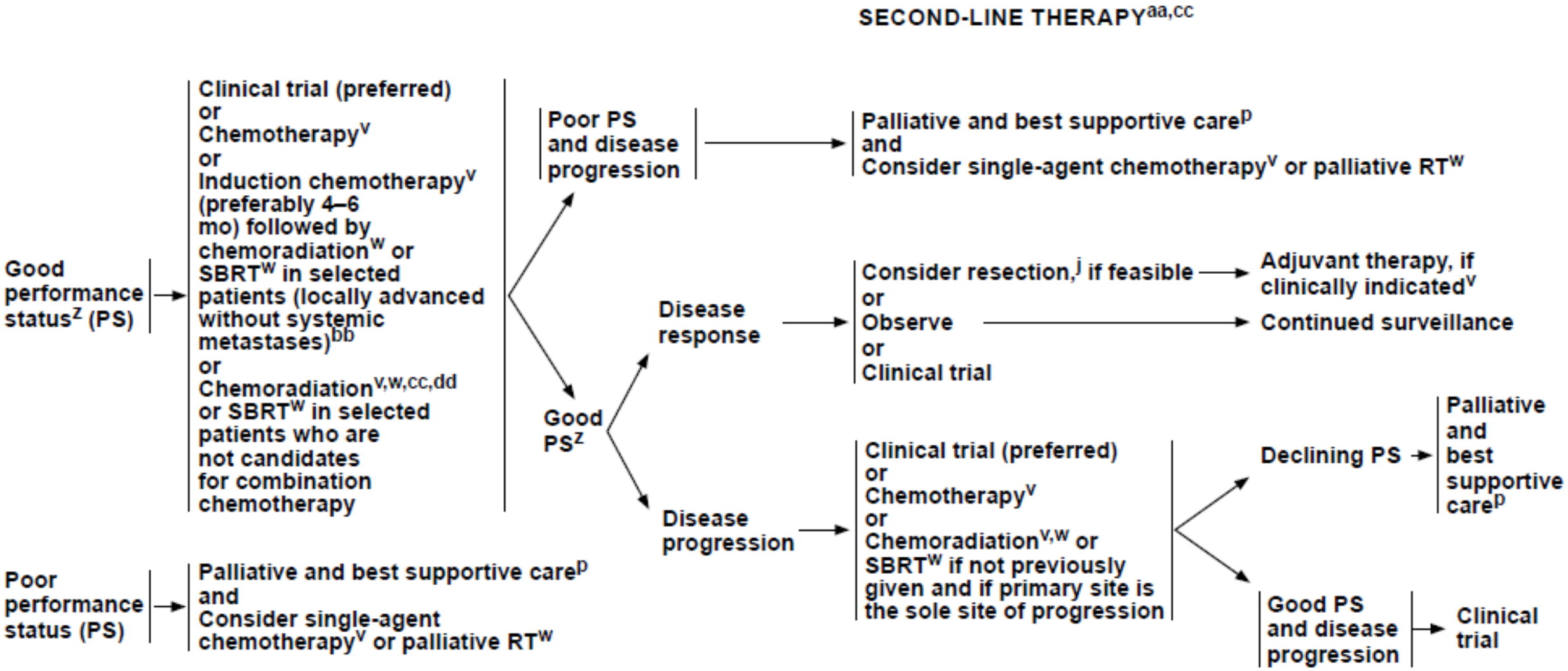
Treatment for borderline resectable (no metastasis)



Locally advanced workout (I)



Locally advanced workout (II)



Management of Locally Advanced Disease (IRE)

- Irreversible electroporation (IRE) is an ablative technique in which electric pulses are used to create nanopores that induce cell death similar to apoptosis

Table 1

Histologic effects of thermal ablation modalities (radio-frequency, microwave ablation, and cryo-ablation) and irreversible electroporation

Effect	Thermal ablation	Irreversible electroporation
Act of damage	Entire cell	Only cell membrane
Protein denaturation	Typical	Not present
Blood flow	Effects efficacy ablation	No effect
Connective tissue	Damaged	Spared
Region of damage	Gradual change	Better defined
IHC effects	Present	Not present

- Mainly used in patients with locally advanced tumor
- Margin accentuation for borderline resectable tumors
- Treatment of locally recurrent pancreatic adenocarcinoma

Metastatic disease

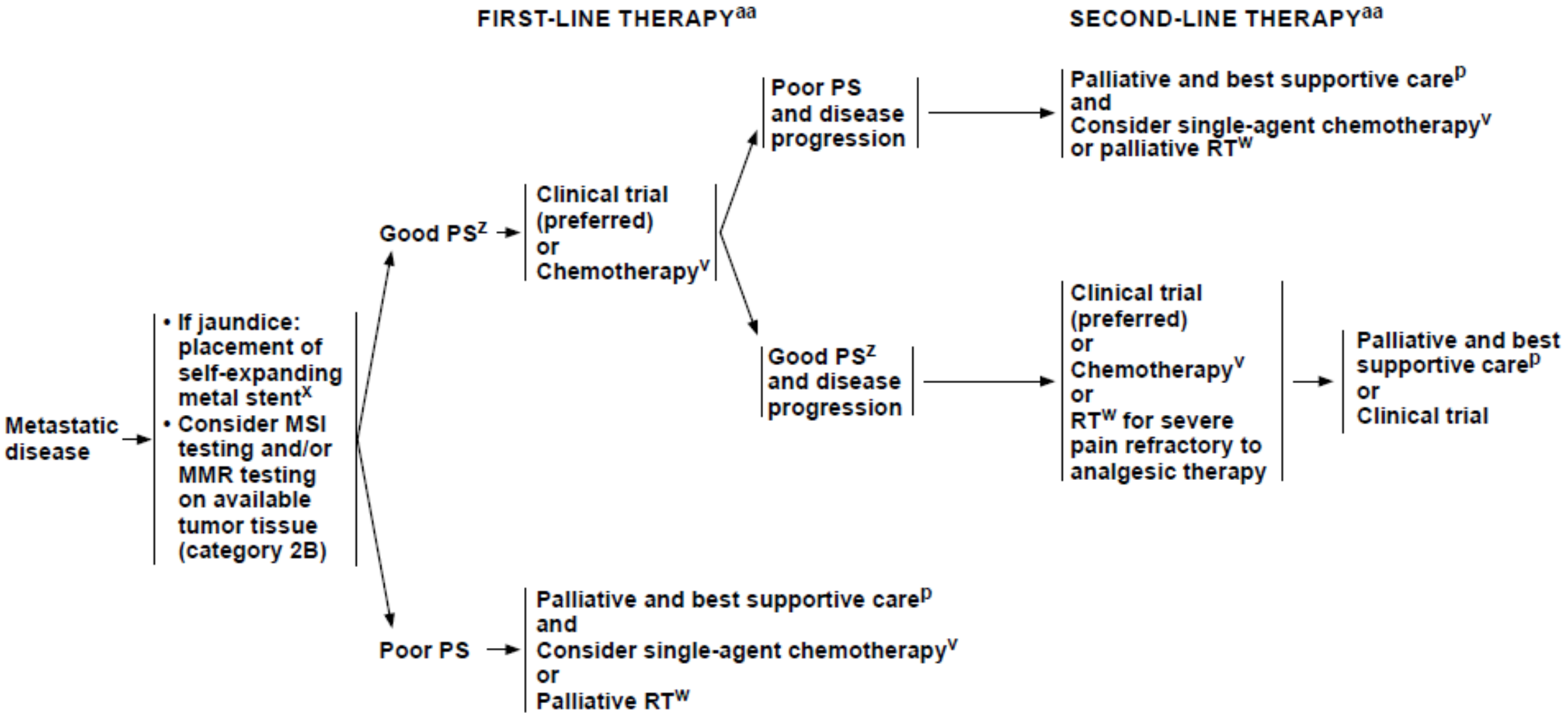


Table 2: Potential Indications for Various Therapies in the Treatment of Pancreatic Adenocarcinoma

Regimen	Resectable (adjuvant)	Borderline Resectable/ Resectable (neoadjuvant)	Locally Advanced (category recommendations for good performance status only unless otherwise noted)	Metastatic (category recommendations for good performance status only unless otherwise noted)	Second-Line Therapy (good performance status only unless otherwise noted)
Gemcitabine	√ (category 1)		√ (category 1 for poor performance status)	√ (category 1 for good and poor performance status)	√ (if previously treated with fluoropyrimidine-based therapy; or category 1 for poor performance status)
Gemcitabine/albumin-bound paclitaxel		√	√	√ (category 1; preferred)	√ (if previously treated with fluoropyrimidine-based therapy)
Gemcitabine/erlotinib			√	√ (category 1)	√ (if previously treated with fluoropyrimidine-based therapy)
Gemcitabine/cisplatin		√ (only for known *BRCA1/2* mutations)	√ (only for known *BRCA1/2* mutations)	√ (only for known *BRCA1/2* mutations)	√ (if previously treated with fluoropyrimidine-based therapy, only for known *BRCA1/2* mutations)
Gemcitabine/ capecitabine	√ (category 1)		√	√	
Fixed-dose-rate gemcitabine			√ (poor performance status only; category 2B)	√ (poor performance status only; category 2B)	√ (poor performance status only; category 2B)
GTX [fixed-dose-rate gemcitabine/docetaxel/ capecitabine]			√ (category 2B)	√ (category 2B)	

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5-FU/leucovorin	√ (category 1)				
5-FU/ leucovorin/liposomal irinotecan					√ (if previously treated with fluoropyrimidine-based therapy and no prior irinotecan; or category 1 if previously treated with gemcitabine-based therapy and metastatic disease)
5-FU/ leucovorin/irinotecan (FOLFIRI)					√ (if previously treated with gemcitabine-based therapy)
FOLFIRINOX		√	√	√ (category 1; preferred)	√ (if previously treated with gemcitabine-based therapy)
Capecitabine	√ (category 2B)		√ (good and poor performance status; category 2B)	√ (poor performance status only; category 2B)	√ (if previously treated with gemcitabine-based therapy; or category 2B for poor performance status)
Continuous infusion 5-FU	√		√ (category 2B)	√ (poor performance status only; category 2B)	√ (if previously treated with gemcitabine-based therapy; or category 2B for poor performance)
Fluoropyrimidine/ oxaliplatin (eg, OFF, FOLFOX, CapeOx)			√ (category 2B)	√ (category 2B)	√ (if previously treated with gemcitabine-based therapy)
Chemoradiation	√ (following induction chemotherapy, with or without subsequent chemotherapy)	√ (subsequent chemoradiation is sometimes included)	√ (in select patients who are not candidates for combination therapy, and following induction chemotherapy in select patients without systemic metastases)		√ (if locally advanced disease; if not previously given; and if primary site is the sole site of progression)
Pembrolizumab					√ (only for MSI-H or dMMR tumors)

Radiation and Chemoradiation Approaches

- In patients with pancreatic cancer, radiation is usually given concurrently with gemcitabine- or fluoropyrimidine-based chemotherapy.

- Chemotherapy is used as a radiosensitizer, increasing the toxicity of radiation to tumor cells.

- sometimes used in the resectable and adjuvant settings (although the majority of the data do not generally show an advantage to the addition of radiation)
  - Possible benefit for pat. with R1-resection

- Radiation without chemotherapy in metastatic setting as palliation for pain refractory to analgesic therapy.

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