DIAGNOSIS AND TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER (LAPC)

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DISCLOSURES

- Participant in multiple clinical research protocols, all US-based.
- Medical expert for legal requests

OBJECTIVES

- Epidemiology and incidence
- Risk factors and associations
- Clinical presentations
- Outcomes
- Diagnosis and screenings
- Treatment options

PANCREATIC CANCER: INCIDENCE

- Pancreatic cancer : 14th most common cancer
- 7th highest cause of cancer mortality world-wide
- Estimates: 460,000 diagnoses, 435,000 deaths globally in 2018.
- Highest incidence in Europe and North America
- Lowest incidence in Africa and South Central Asia
- Higher rates: developed versus developing countries

GRAPH ON INCIDENCE

RISK FACTORS AND ASSOCIATIONS

-Mostly investigated using case-control studies

Weakness include selection bias and recall bias

Risks are divided into non-modifiable and modifiable risk factors

MODIFIABLE RISK FACTORS:

- Smoking
- Alcohol
- Obesity
- Dietary factors
- *Helicobacter pylori*

NON MODIFIABLE RISK FACTORS

- Age
- Sex
- Ethnicity
- Blood group, gut microbiota, family history
- Diabetes- type 1, and new onset diabetes mellitus.

PATHOLOGY OF PANCREATIC CANCER

- Pancreatic adenocarcinoma accounts for 90% of all pancreatic cancers.
- 60%-70% develop in the head of pancreas
- 15% in body and tail respectively
- TYPES: PanIN, IPMN, mucinous cyst neoplasms

DIAGNOSIS OF PANCREATIC CANCER:

Diagnosis is a challenge

Screening protocols are in development

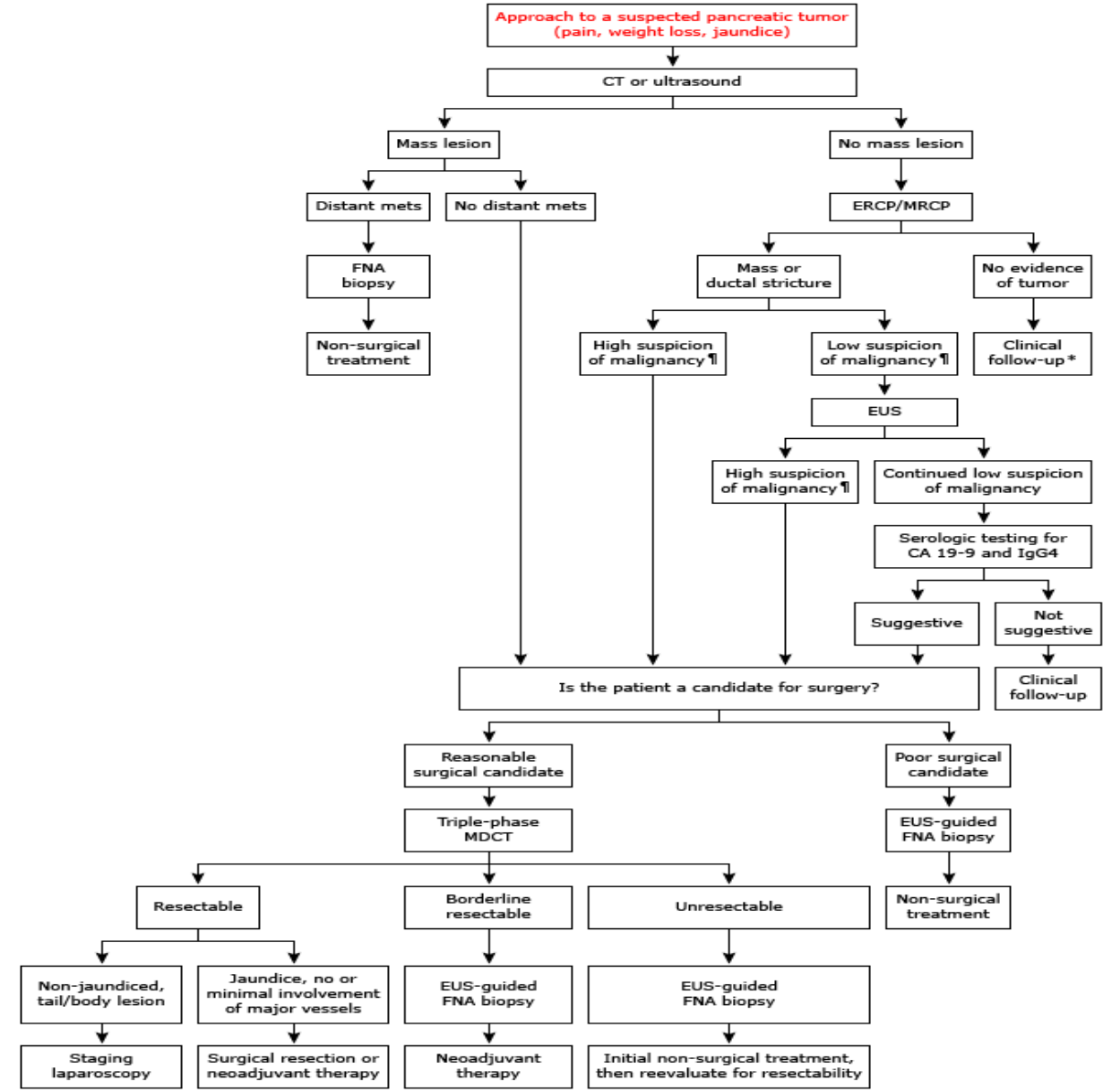
Presenting symptoms can be present for months.

Average patient has visited a health care provider at least **4-7** times before the diagnosis is established.

DIAGNOSTIC MODALITIES:

- CT scans
- MRI
- EUS
- Sonography
- Biomarkers for early detection

Pancreatic cancer diagnosis algorithm



CT: computed tomography; mets: metastases; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; FNA: fine-needle aspiration; EUS: endoscopic ultrasound; CA 19-9: carbohydrate antigen 19-9; IgG4: immunoglobulin G4; MDCT: multidetector row computed tomography.

* If the clinical suspicion for malignancy is high, obtaining an EUS is reasonable to exclude a small pancreatic cancer.

¶ Based on symptomatology and the appearance of the mass or stricture.

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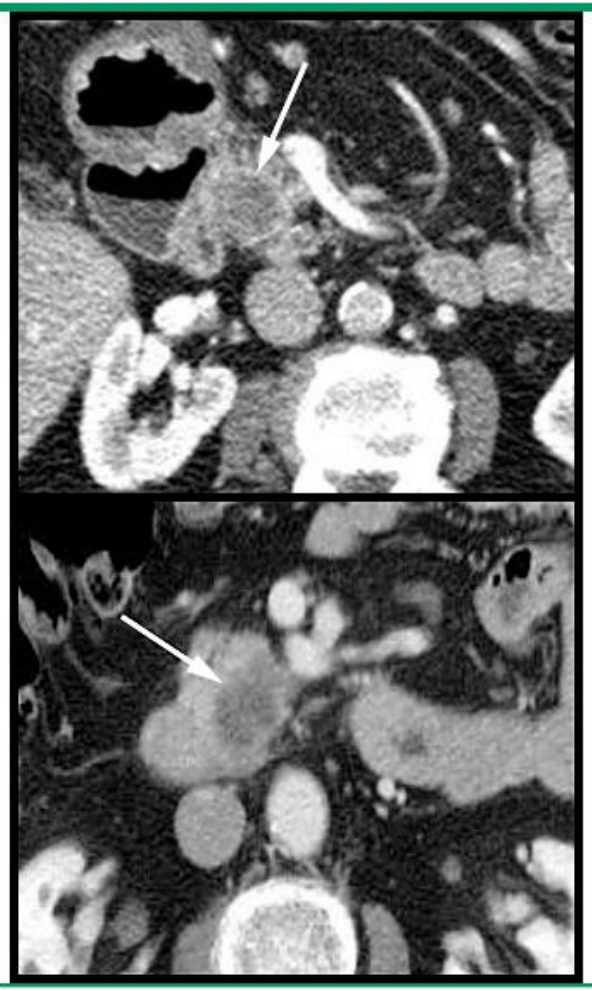
STAGING OF PANCREATIC CANCER:

Typical appearance of pancreatic adenocarcinoma



Multidetector enhanced CT of two different patients, in which ill-defined hypodense, solid tumors are present in the head and uncinate process of the pancreas (arrows). Typically, normal pancreatic tissue enhances to a greater extent than do pancreatic adenocarcinomas.

CT: computed tomography.

Courtesy of Rocio Perez-Johnston.

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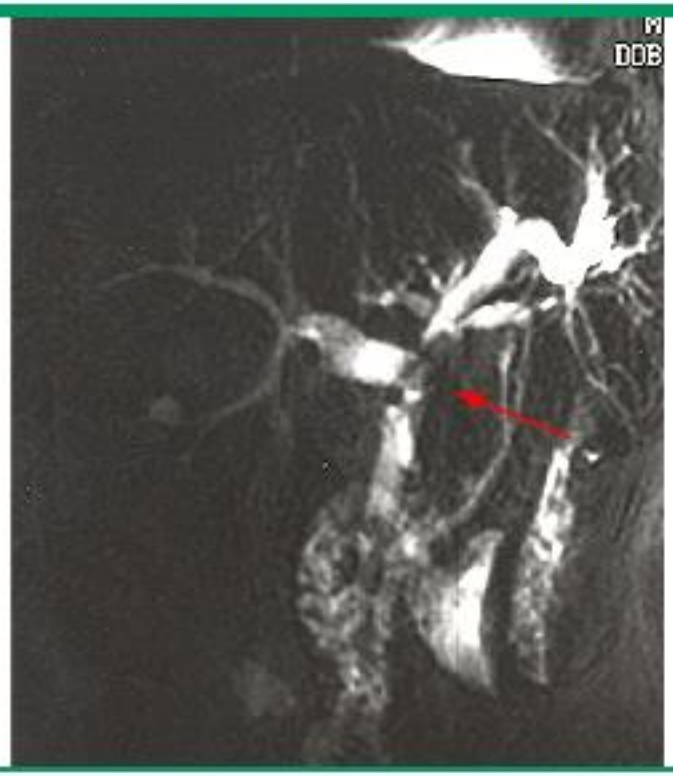
Hilar cholangiocarcinoma as seen on MRCP



This magnetic resonance cholangiopancreatography (MRCP) image depicts an intrabiliary filling defect (arrow) due to a hilar papillary cholangiocarcinoma.

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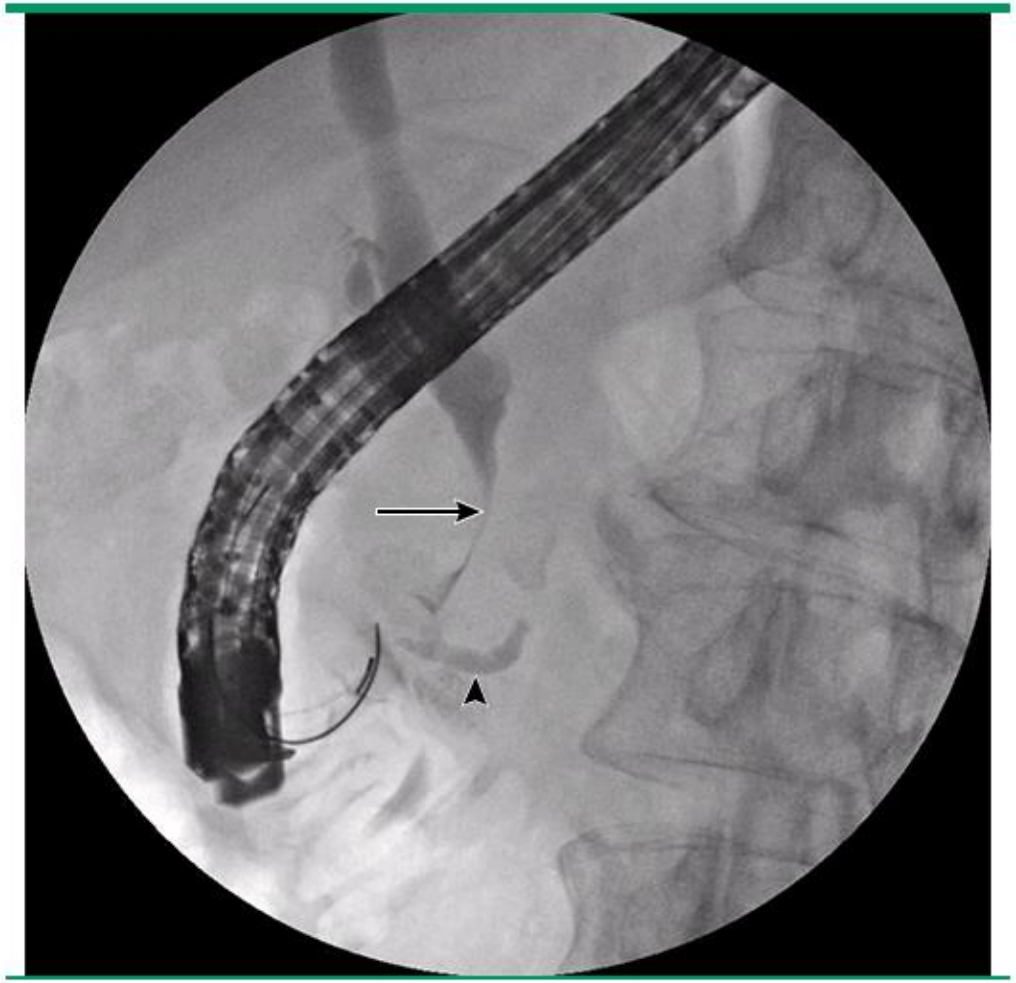
"Double duct" sign in a patient with pancreatic cancer



Endoscopic retrograde cholangiopancreatography (ERCP) in a patient with adenocarcinoma in the head of the pancreas. The common bile duct is dilated proximal to a stricture (arrow). In addition, the pancreatic duct is dilated (arrowhead) due to obstruction by the tumor. The dilation of both the common bile duct and the pancreatic duct is known as the "double duct" sign, a finding that is highly suggestive of a malignancy.

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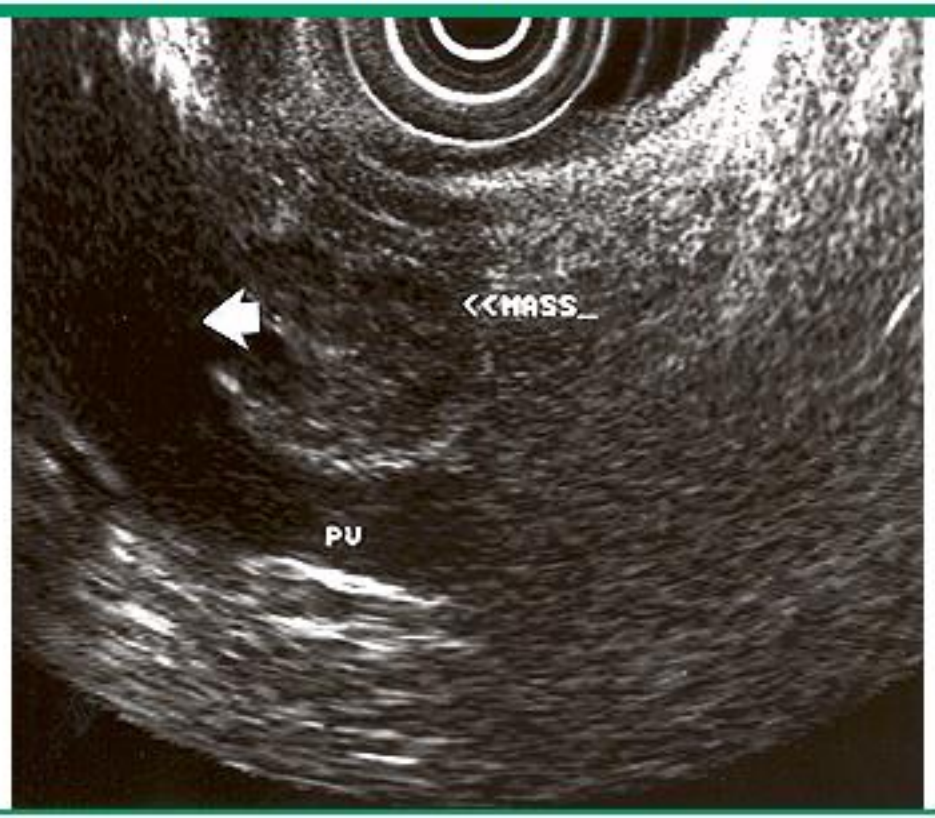
Pancreatic cancer staging with endoscopic ultrasound



Endoscopic ultrasound view of pancreatic cancer (MASS) that can be seen invading into the portal vein (PV) with loss of the vascular interface (arrow). This tumor is stage T4.

Courtesy of Frank G Gress, MD.

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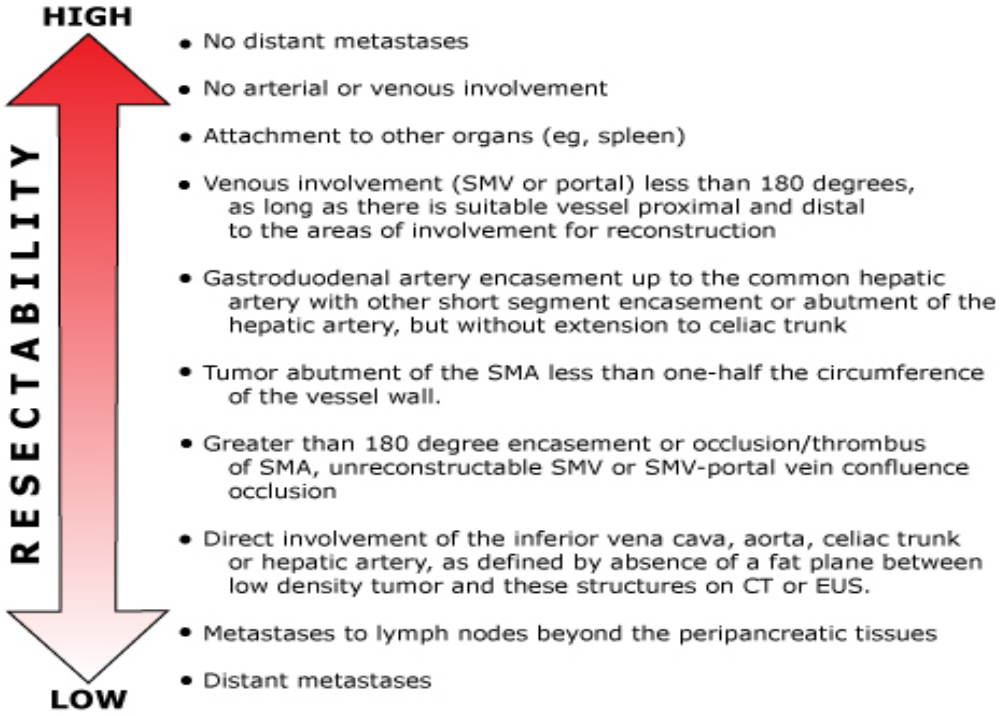
Continuum of resectability for pancreatic adenocarcinoma



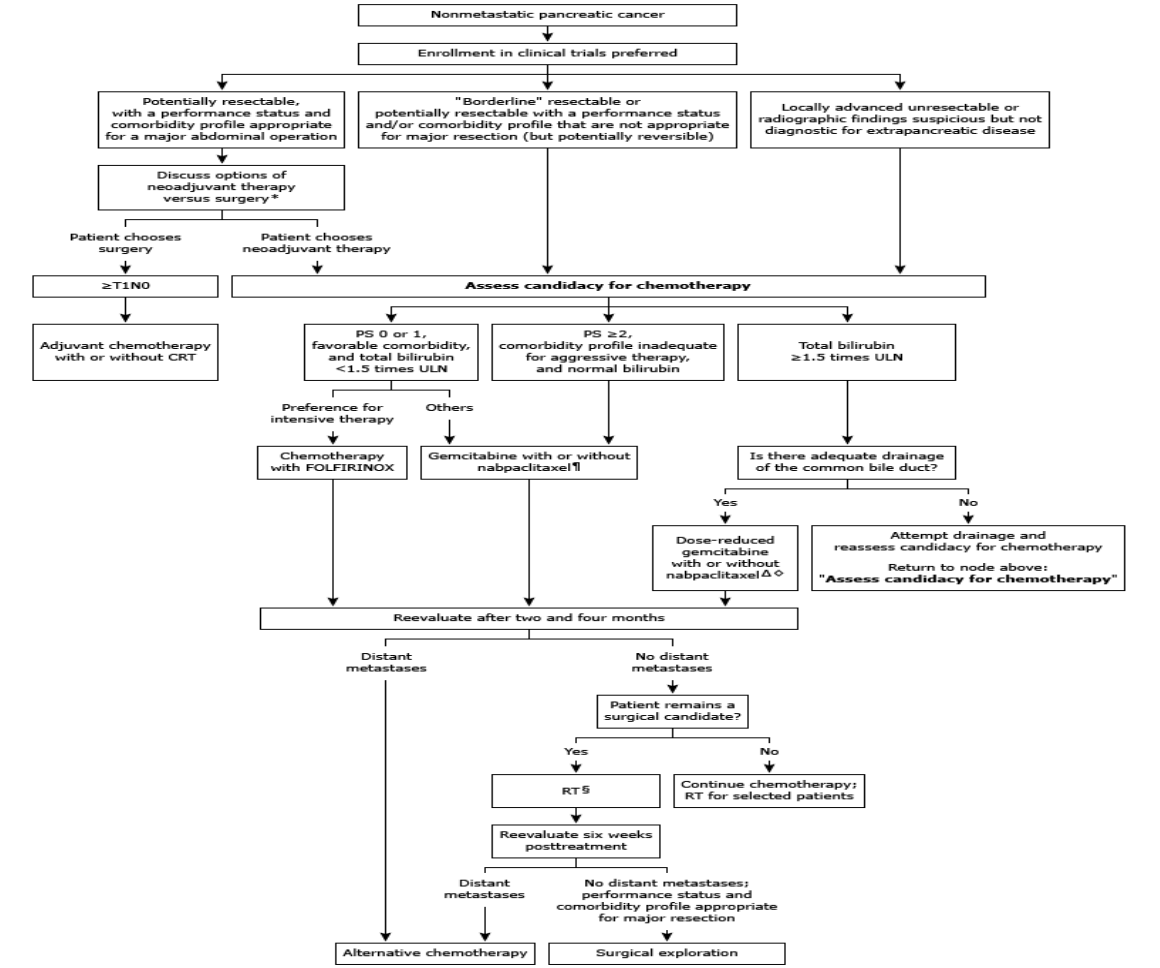
SMV: superior mesenteric vein; SMA: superior mesenteric artery; CT: computed tomography; EUS: endoscopic ultrasound.
Data from:

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology, www.nccn.org.
2. Seufferlein T, Bachet JB, Van Cutsem E, et al. Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 Suppl 7:vii33.
3. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 2009; 16:1727.
4. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014; 371:1039.

TREATMENT OPTIONS FOR PANCREATIC CANCER

- Surgical
- Nonsurgical

Treatment algorithm for nonmetastatic exocrine pancreatic cancer



CRT: chemoradiotherapy; PS: Eastern Cooperative Oncology Group performance status; ULN: upper limit of normal; FOLFIRINOX: oxaliplatin plus irinotecan with leucovorin and short-term infusional fluorouracil; nabpaciltaxel: nanoparticle albumin-bound paclitaxel; RT: radiation therapy.

* Although the available supporting data for neoadjuvant therapy in patients with potentially resectable disease are limited, given the overall poor prognosis even after complete resection and adjuvant therapy, we consider neoadjuvant therapy to be a reasonable alternative to upfront surgery, as long as performance status and comorbidity are sufficient to tolerate treatment. However, for the rare patient with a <2 cm apparently node-negative tumor (as determined by pretreatment imaging), neoadjuvant therapy is probably not warranted.

¶ For patients with a known *BRCA* mutation, a platinum-based chemotherapy regimen is preferred.

Δ Many clinicians would not administer gemcitabine for total bilirubin above 2.5 ng/mL.

◇ If poor performance status is due to recent infection (eg, cholangitis) and the patient is recovering well after intervention, dose-adjusted combination chemotherapy is preferred over single-agent gemcitabine. If performance status is poor due to locally advanced disease causing disabling pain and/or gastric outlet obstruction, aggressive symptom management should be undertaken prior to initiating chemotherapy.

§ At some institutions, patients with a very good response to neoadjuvant chemotherapy would be taken directly to surgical exploration. Fluorouracil-based chemoradiotherapy (or stereotactic body RT, refer to UpToDate text) should be considered if further tumor shrinkage might increase the chance of a microscopically complete (R0) resection. It is unknown whether RT contributes to the R0 resection rate after chemotherapy (especially for combination regimens such as FOLFIRINOX). Another alternative is two to three months of additional chemotherapy alone.

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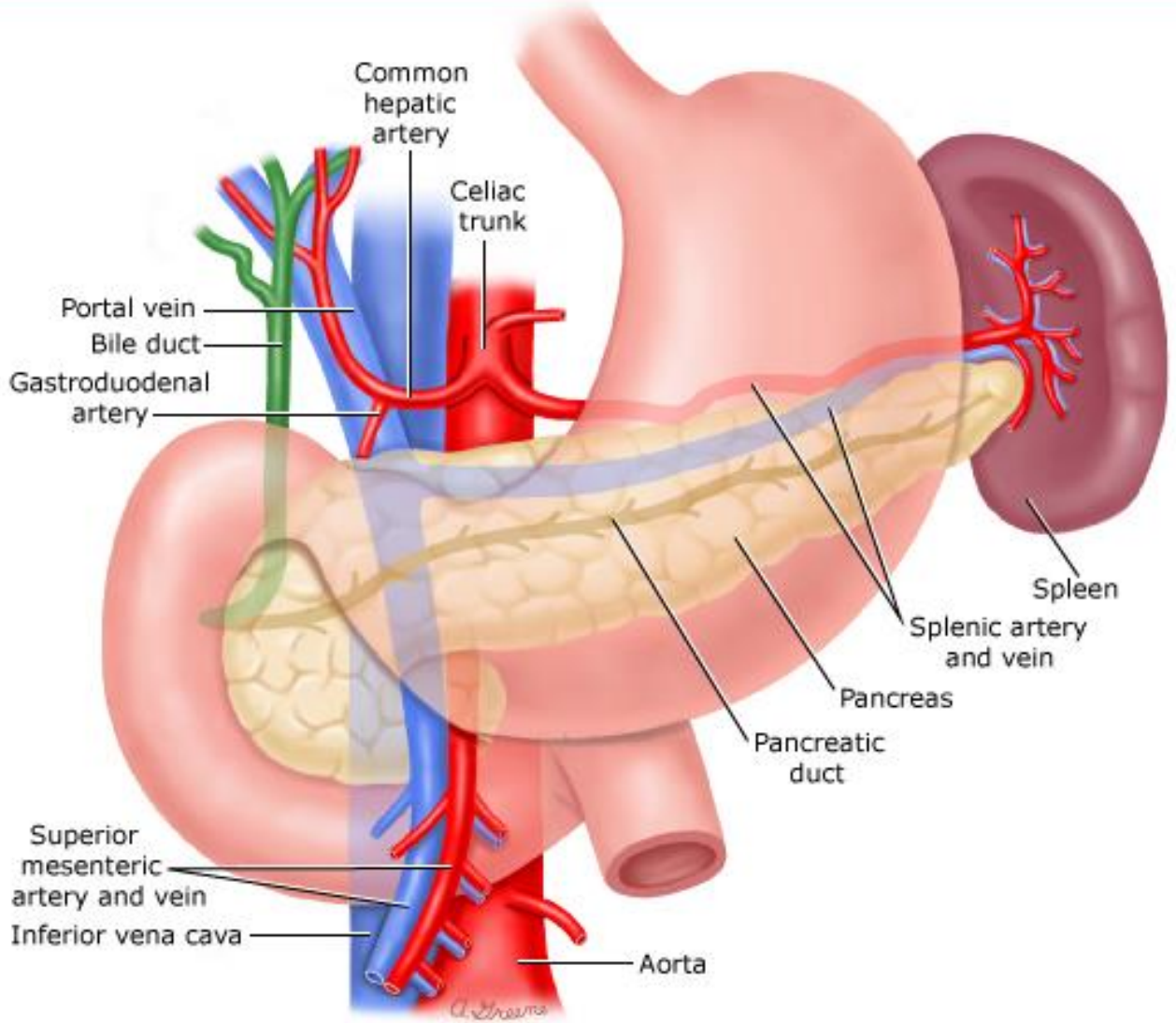
SURGICAL MANAGEMENT:

- Knowledge of basic anatomy is key
- Staging is variable due to new regimens.
- Pre-operative biliary drainage is controversial
- Anastomotic technique
- Vascular resection

Anatomy for pancreatic adenocarcinoma



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MEDICAL MANAGEMENT: LOCALLY ADVANCED PANCREATIC CANCER

- Criteria for unresectability
  - Based on CT findings
  - Accurate staging is essential

Stage 3 LAPC: Systemic chemotherapy.

SYSTEMIC CHEMOTHERAPY:

- FOLFIRINOX and Gemcitabine – higher response rates. > 4-6 cycles
- Fitness is assesses prior to initiation of chemo
- If not fit, < 4 weeks used to improve limitations.

- RADIATION THERPAY
- Ideal for patients that do not progress after induction therapy.

Neoadjuvant FOLFIRINOX in patients with locally advanced unresectable or borderline resectable pancreatic cancer

Authors, year	Number of patients	Regimen	Radiographic response rate	Number of patients with subsequent resection	R0 resections	Median survival for resected patients (months)
Conroy T, 2005	11	FOLFIRINOX	3 of 11 (27%)	0	0	–
Peddi PF, 2012	19	FOLFIRINOX then RT (n = 4)	6 of 18* (33%)	8 of 23 (35%)	Not reported	Not reported
Vasile E, 2012	15	FOLFIRINOX then CRT (n = 3)	6 of 15 (40%)	5 (33%)	–	30.1 (all 15 patients)
Mahaseth H, 2013	24	FOLFIRINOX then CRT (n = 14)	Not stated	6 (25%)	Not reported	Not reported
Hosein PJ, 2013¶	18	FOLFIRINOX then CRT (n = 10)	Not stated	6 after CT, 3 after CRT (50%)	8 of 9 (89%)	Not reported
Boone BA, 2013	13	FOLFIRINOX then SBRT (n = 5)	Not stated	2 (15%)	1 of 2 (50%)	Not reported
Christians KK, 2014¶	18	FOLFIRINOX then CRT	Not stated	12 (67%)	12 of 12 (100%)	7 of 12 alive at median 22 months after diagnosis
Marthey L, 2015	77	FOLFIRINOX then RT (n = 24)	22 of 77 (28%)	28 (36%)	25 of 28 (89%)	24.9
Ferrone CR, 2015	40	FOLFIRINOX then CRT (n = 24)	36 of 40 (90%)	40 (100%)	37 (92%)	Approximately 32
Blazer M, 2015	43	FOLFIRINOX then CRT (n = 23)	9 of 40 (23%)Δ	22 (51%)	19 (86%)	34.0
Mellon EA, 2015◇	159	FOLFIRINOX (n = 23), GTX (n = 94), Gem (n = 28), or Gem/Abrax (n = 8), then SBRT	Not stated	61 (38%)	59 (96%)	34.2
Sadot E, 2015	101	FOLFIRINOX then CRT (n = 63)	(29%)	31 (31%)	16 of 31 (55%)	Not yet reached (median follow-up 12 months)
Stein SM, 2016	31	FOLFIRINOX	5 of 29 (17%)	13 (42%)	13 of 13 (100%)	Not reported
Kim SS, 2016	26	FOLFIRINOX then RT (n = 4)	13 of 26 (50%)	26 of 26 (100%)	24 of 26 (92%)	Not yet reached (median follow-up 27.6 months)
Katz MH, 2016	22	FOLFIRINOX then CRT	6 of 22 (27%)	15 (68%)	14 of 15 (93%)	Median 21.7
Murphy JE, 2018	48	FOLFIRINOX then short-course CRT (n = 27) or long-course CRT (n = 17)	19 of 48 (44%)	32 (65%)	31 of 32 (97%)	Two-year overall survival 72%

FOLFIRINOX: short-term infusional fluorouracil plus leucovorin, irinotecan, and oxaliplatin; R0: microscopically complete; RT: radiation therapy; CRT: chemoradiotherapy; CT: computed tomography; SBRT: stereotactic body radiation therapy; GTX: gemcitabine plus docetaxel plus capecitabine; Gem: gemcitabine; Gem/Abrax: gemcitabine/nanoparticle albumin-bound placitaxel.

* The 19th patient did not have imaging available after three cycles of chemotherapy.

¶ These series include patients treated with FOLFIRINOX for both unresectable or borderline resectable locally advanced pancreatic carcinoma.

Δ Three patients died before restaging scans were completed.

◇ Data not reported separately for each neoadjuvant chemotherapy regimen. However, of the 49 patients with locally advanced pancreatic cancer, 5 responded sufficiently on imaging to undergo R0 resection after neoadjuvant therapy. All received FOLIRINOX.

Data from:

1. *Conroy T, Paillot B, François E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer – a Groupe Tumeurs Digestives of the Fédération Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol 2005; 23:1228.*
2. *Peddi PF, Lubner S, McWilliams R, et al. Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. JOP 2012; 13:497.*
3. *Vasile E, De Lio N, Cappelli C, et al. Neoadjuvant modified FOLFOXIRI in locally advanced pancreatic cancer. Ann Oncol 2012; 23 Suppl 9:ix241. Abstr 726P.*
4. *Mahaseth H, Brutcher E, Kauh J, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas 2013; 42:1311.*
5. *Hosein PJ, Macintyre J, Kawamura C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline resectable locally advanced pancreatic adenocarcinoma. BMC Cancer 2012; 12:199.*
6. *Boone BA, Steve J, Krasinskas AM, et al. Outcomes with FOLFIRINOX for borderline resectable and locally unresectable pancreatic cancer. J Surg Oncol 2013; 108:236.*
7. *Christians KK, Tsai S, Mahmoud A, et al. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? Oncologist 2014; 19:266.*
8. *Marthey L, Sa-Cunha A, Blanc JF, et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma. Results of an AGEO multicentric prospective observational cohort. Ann Oncol 2015; 22:295.*
9. *Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015; 261:12.*
10. *Blazer M, Wu C, Goldberg RM, et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol 2015; 22:1153.*
11. *Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. Acta Oncol 2015; 54:979.*
12. *Sadot E, Doussot A, O'Reilly EM, et al. FOLFIRINOX induction therapy for stage 3 pancreatic adenocarcinoma. Ann Surg Oncol 2015; 22:3512.*
13. *Stein SM, James ES, Deng Y, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer 2016; 114:737.*
14. *Kim SS, Nakakura EK, Wang ZJ, et al. Preoperative FOLFIRINOX for borderline resectable pancreatic cancer: Is radiation necessary in the modern era of chemotherapy? J Surg Oncol 2016; 114:587*
15. *Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial A021101. JAMA Surg 2016; 151:e161137.*
16. *Murphy JE, Wo JY, Ryan DP, et al. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol 2018; 4:963.*

Five-year overall survival for pancreatic adenocarcinoma from the National Cancer Data Base: nonresected[1]

Nonsurgical patients			Observed survival					Median survival, months
Stage	Number of patients	Percent	1-year, percent	2-year, percent	3-year, percent	4-year, percent	5-year, percent	
IA	3412	4.4	29.2	10.5	6.2	4.6	3.8	6.8
IB	4298	5.4	26.0	9.4	5.7	4.0	3.4	6.1
IIA	8486	10.1	25.0	7.7	4.1	2.8	2.4	6.2
IIB	6570	11.8	26.9	7.7	3.8	2.6	2.0	6.7
III	12,981	13.0	27.0	7.3	3.4	2.4	1.8	7.2
IV	64,454	55.2	8.3	2.3	1.2	0.8	0.6	2.5
Total	**100,201**							**3.5**

Reference:

1. *Bilimoria KY, Bentrem DJ, Ko Cy, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. Cancer. 2007; 110(4):738-44, with permission of Wiley.*

IMMUNOTHERAPY FOR PANCREATIC CANCER

- Overall therapies have **encouraging outcomes**
- PD1/PDL-1 (programmed cell death receptor ligand)
  - Enhances anti-tumor immune response: ? In pancreatic cancer
- CTLA-4 (CDi52). Checkpoint receptor target for immunotherapy
  - Controls earl stage T-cell activation
  - Prolongs disease stabilization

SUMMARY AND CONCLUSIONS:

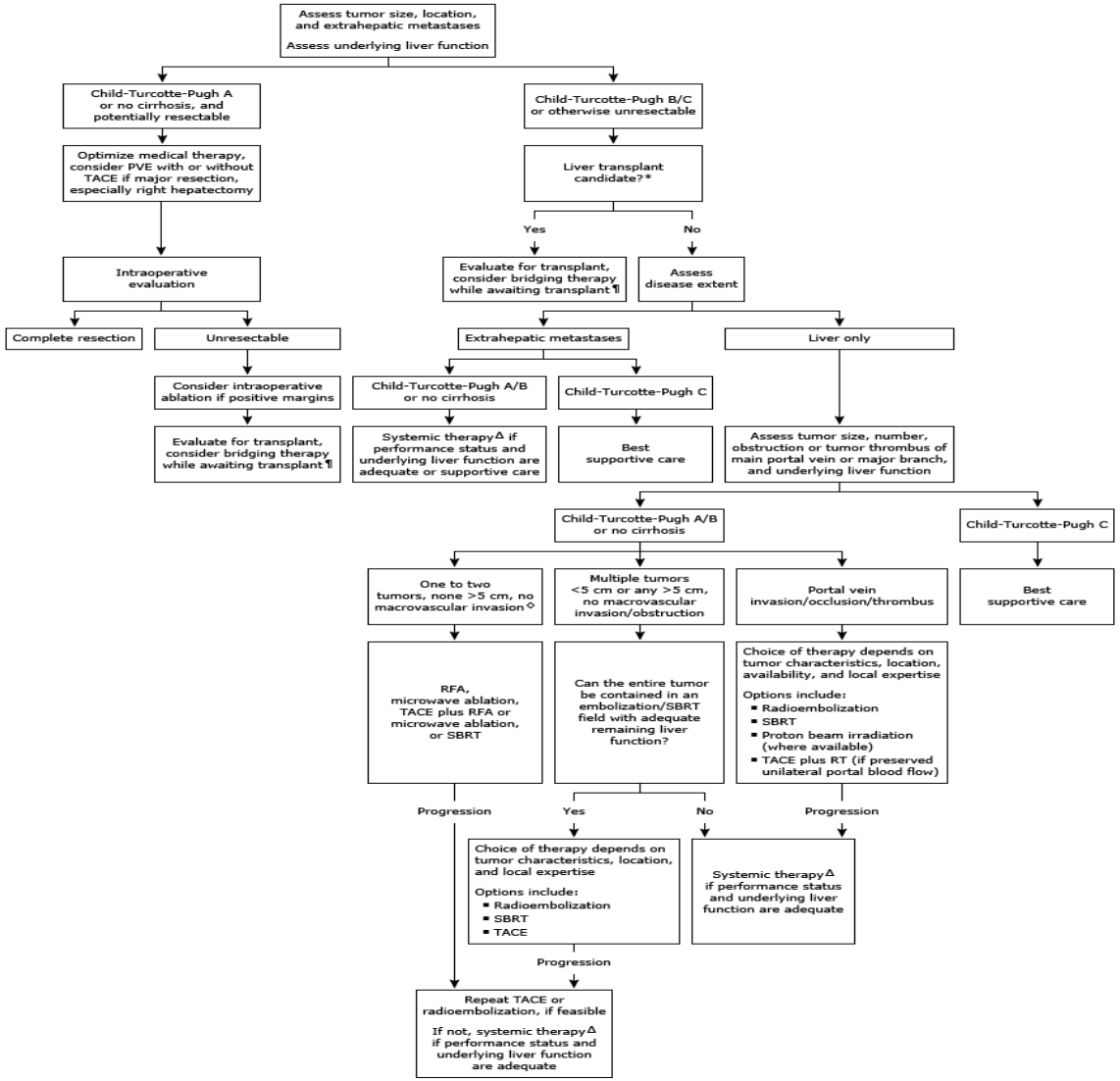
- Survival rates for LAPC are disappointing.
- Early diagnosis presents a challenge due to low incidence of disease
- EUS/FNA and/or MRCP remain best tests, with FNA to allow histologic diagnosis
- Vascular resection of LAPC is increasing mainly due to addition of neoadjuvant therapy
- This leads to significantly higher negative resection margins and disease-free survival

SUMMARY AND CONCLUSIONS:

- Neoadjuvant therapy increases negative resection margins and decreases progression
- At least 33% of initially staged non-resectable tumors are resectable in patients who receive combination chemotherapy.
- Increase in survival times are noted.

THANK YOU!!

Overview of treatment algorithm for hepatocellular carcinoma



PVE: portal vein embolization; TACE: transarterial chemoembolization; RFA: radiofrequency ablation; SBRT: stereotactic body radiation therapy; RT: radiation therapy.

* In the United States, patients with underlying chronic liver disease (cirrhosis, hepatitis C virus infection) are potentially eligible for orthotopic liver transplant if they fulfill the Milan criteria (solitary hepatocellular carcinoma ≤5 cm in diameter or up to three separate lesions, none of which is larger than 3 cm; no evidence of gross vascular invasion; and no regional nodal or distant metastases). If not a liver transplantation candidate because disease is outside transplant (Milan) criteria, downstaging therapy (eg, RFA, TACE) could be considered, followed by reassessment for liver transplantation.

¶ Bridging therapy refers to local treatment (typically RFA or TACE) while awaiting orthotopic liver transplantation in order to reduce the risk of progressing beyond Milan criteria.

Δ Options for initial systemic therapy include participation in a clinical trial (preferred), sorafenib, lenvatinib, or cytotoxic chemotherapy (refer to UpToDate text).

◇ The best results with RFA are in patients with a smaller tumor size, and many institutions restrict RFA to lesions <4 cm.

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