PANCREATIC CANCER

Epidemiology

- Pancreatic cancer is the fourth most common malignancy in developed countries.
- The annual incidence rate is almost identical to the mortality rate, with an estimated incidence of 37.170 new cases diagnosed and 33.370 deaths.
- About 10 – 20% of patients have resectable disease at the time of pancreatic cancer diagnosis; of those, the curative rate is only 14% and median survival of 15- 19 months.
- The 5-year survival rate following resection is 25 – 30% for node-negative disease.
- The high risk of local and systemic disease recurrence as well as overall poor prognosis laid down the rationale for adjuvant therapy after resection of pancreatic adenocarcinoma.

Initial Workup:

All recommendations are (category 2A)

If Pancreatic mass present	**If there are no masses in the pancreas (Clinical suspicion or dilated ducts)**
Triphasic cross-sectional thin slices CT scan of the abdomen. PET scan may be considered if CT scan equivocal. Chest imaging. CBC, full biochemistry. CA19-9 (category 3) as it may increase in biliary obstruction, benign, or malignant tumors.	Liver function tests. Chest imaging. ERCP or EUS.

TNM Staging of Pancreatic Cancer
American Joint Committee on Cancer (AJCC) (8th ed., 2017)

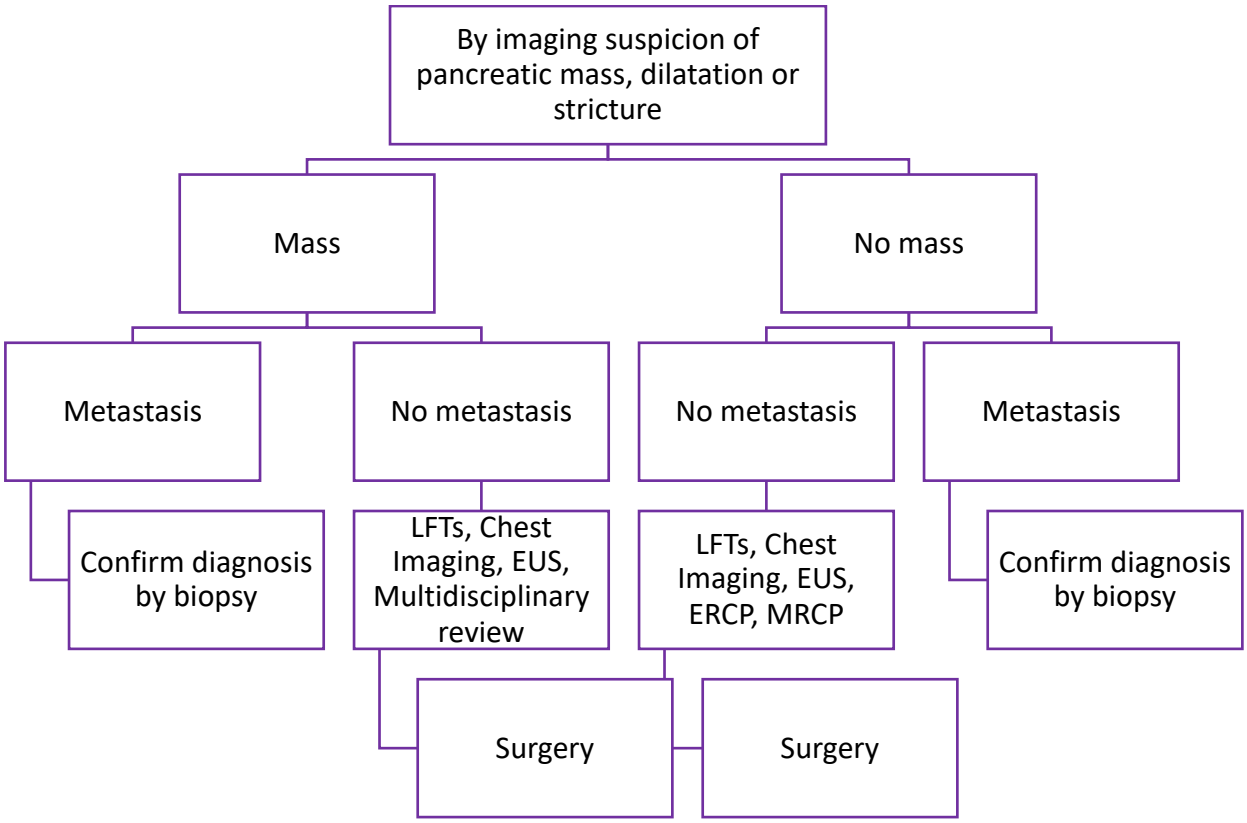
Tumor	
T	Primary Tumor
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ.* This includes: High-grade pancreatic intraepithelial neoplasia (PanIn-3), Intraductal papillary mucinous neoplasm with high-grade dysplasia, Intraductal tubulopapillary neoplasm with high-grade dysplasia, and Mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

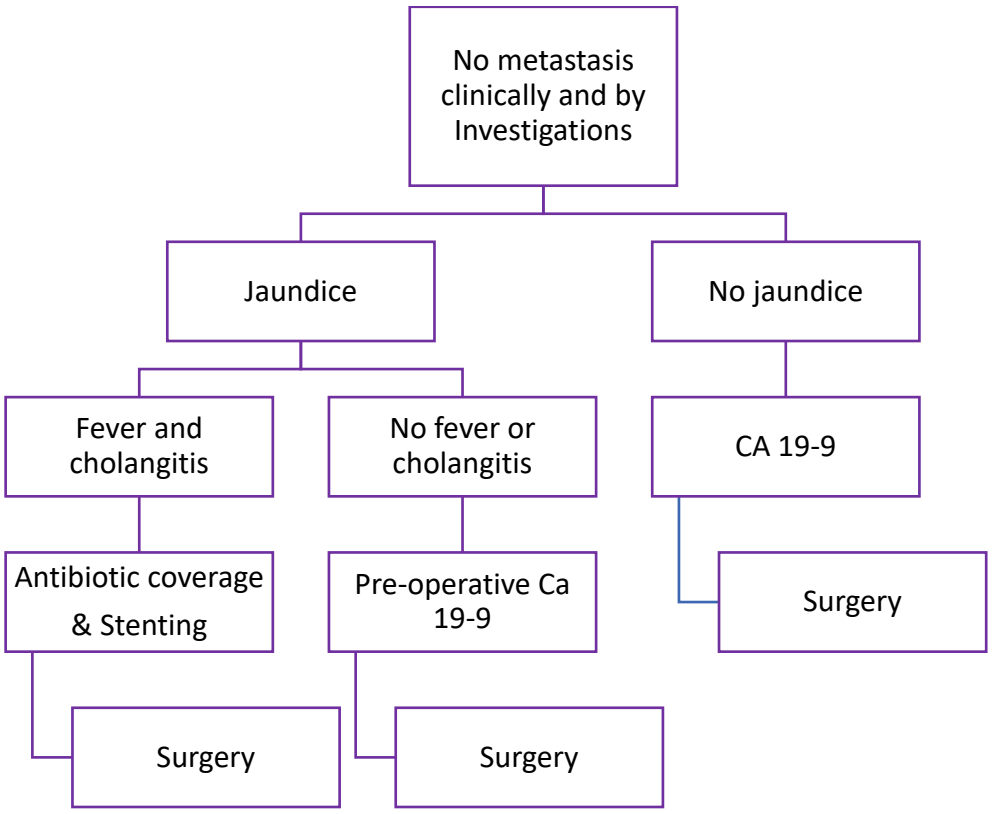
Node Status	
N	Regional Lymph Nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

Metastasis	
M	Distant Metastasis
M0	No distant metastases
M1	Distant metastasis

AJCC Prognostic Groups			
	T	**N**	**M**
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3, T4	N2 Any N	M0 M0
Stage IV	Any T	Any N	M1

Workup Cascade





Assessment of Resectability

Tumors considered "Clearly Resectable" if there are:

- No evidence of metastatic disease.
- No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion.
- Clear fat planes around the celiac axis, hepatic artery, or SMV.
- No evidance of aortic or IVC invasion or encasement.

Tumors considered "Borderline Resectable" if there are:

- Venous involvement of SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal,allowing for safe resection and replacement.
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
- Tumor abutment of SMV not greater than 180 degrees of its circumference.

Treatment

1. Resectable:

Surgical resection followed by Adjuvant therapy

Regimen	Supporting evidence
Adjuvant chemotherapy: **modified FOLFIRINOX (category 1)** - fluorouracil [5-FU], - Leucovorin, - Irinotecan, - Oxaliplatin	**[Unicancer GI PRODIGE 24/CCTG PA.6 trial]:** Median overall survival was 54.4 months compared to 35.0 months with gemcitabine.
Adjuvant chemotherapy: **Gemcitabine combined with Capecitabine (category-1)**	**[ESPAC-4 study]** Combination regimen was superior compared to gemcitabine alone. (HR, 0.82; 95% CI, 0.68, 0.98; *P* = .032).
Adjuvant single-agent chemotherapy: - Gemcitabine (preferred) - 5-FU - Capecitabine.	**CONKO-001 & ESPAC-3 trials[(3)]**
Adjuvant chemo-irradiation with 5FU	**EORTC trial**

Principles of chemotherapy and radiotherapy:

- Role of chemotherapy should be discussed with the patient prior initiation of the therapy.
- The **CONKO 001 trial** demonstrated significant improvement in DFS & OS with the use of postoperative Gemcitabine as adjuvant chemotherapy in resectable pancreatic cancer. [(3)]
- **MPACT trial** showed improvement in OS & DFS with Nab-Paclitaxel plus Gemcitabine better than Gemcitabine single agent for patients with advanced pancreatic cancer with good PS. [(5)]
- **ESPAC 3 study** results showed no significant difference in OS between 5-FU/Leucovorin versus Gemcitabine following surgery. [(9)]
- No significant difference was observed in **RTOG 97-04 study** comparing pre- and post- chemo-radiation 5-FU with pre- and post-chemoradiation Gemcitabine for postoperative adjuvant treatment. [(10)]
- Second line therapy may consist of Gemcitabine for those patients not previously treated with the drug. Other options include Capecitabine, or FOLFOX, or XELOX. [(11)]

2. Unresectable, Locally Advanced, or Metastatic:

I. Good Performance Status (PS)		
Preferred Regimens	**Other Recommended Regimens**	**Others in Certain Circumstances**
FOLFIRINOX (category 1)[4]	**Gemcitabine + Erlotinib** (category 1)[6]	**Induction chemotherapy:** with any of the preferred/other regimens (≥4–6 cycles) followed by **chemoradiation, or SBRT** [12] [in selected patients, a locally advanced disease without systemic metastases [13]]
Nab- paclitaxel + Gemcitabine (category 1)[5]	**Gemcitabine + Capecitabine**[7]	**Chemoradiation or SBRT** [in select patients who are not candidates for combination therapy].
	(GTX regimen): **Fixed-dose rate Gemcitabine, Docetaxel, Capecitabine** (category 2B) [8]	**Chemoradiation** (if not previously given) only an option for: (1) Locally advanced disease if the primary site is the sole site of progression. (2) Select patients with recurrent disease in combination with systemic therapy.
	Gemcitabine + cisplatin (only for known *BRCA1/2* or *PALB2* mutations)	**Pembrolizumab** (only for MSI-H or dMMR tumors).
	5-FU + Leucovorin + Liposomal Irinotecan (if no prior irinotecan)	

(II) Poor Performance Status (PS):
• Monotherapy, single-agent gemcitabine (category 1) • Fixed dose rate of gemcitabine (10 mg/m2/minute) (catogery 2B). • Capecitabine or continuous infusion of 5-FU (category 2B). • Best Supportive Care.

In Jaundiced Patients:	
With Resectable disease	**With Unresectable disease**
Proceed to **temporary stent** then Resection followed by adjuvant treatment.	Proceed for a **permanent stent** with concomitant chemo-radiotherapy or Palliative chemotherapy only.

Principles of Palliation and Supportive Care:

The aim is to prevent and ameliorate suffering while ensuring optimal Quality of Life.

(all recommendations are category 2A)

Biliary Obstruction:

- Endoscopic stent
- Percutaneous biliary stent with subsequent internalization
- Surgical biliary-enteric bypass

Gastric outlet obstruction:

Good PS	Poor PS
• Gastrojejunostomy • Enteral tube	• Enteral stent • PEG tube

Severe tumor-associated abdominal pain:

- Celiac plexus block
- Consider palliative Radiation therapy if not used before.

Pancreatic Insufficiency (inadequate production of digestive enzymes):

- Pancreatic enzyme replacement

Thromboembolic manifestation:

- Low molecular weight heparin better than warfarin.

Follow up

After adjuvant treatment :

- Every 3 months for the first 2 years then annually with
- History and physical examination.
- CA 19-9 (catogery 2B).
- CT scan every 6 months(category 2B).

Locally advanced or metastatic disease:

- History and physical examination.
- Other investigations, as indicated clinically.

Chemotherapy Regimens

Gemcitabine	
Single-agent Gemcitabine	1000 mg/m^2 IV infusion over 30 minutes on days 1, 8 and 15
Till DP or toxicity.	

5-FU + Folinic acid	
5-FU	425mg/m^2/d IV bolus days 1 – 5
Folinic acid	20mg/m^2/d IV bolus days 1 – 5
Repeat for 6 cycles	

Gemcitabine + Nab-Paclitaxel	
Gemcitabine	1000 mg/m^2 days 1, 8, and 15; IV infusion in 250 mL NS over 30 minutes
Nab-Paclitaxel	125 mg/m^2 days 1, 8, and 15; IV infusion over 30 minutes
Repeat every 28 days to a maximum of 12 cycles.	

Gemcitabine + Cisplatin	
Gemcitabine	1000 mg/m^2 IV infusion over 30 minutes on days 1 and 15
Cisplatin	50 mg/m^2 IV infusion over 1 hour on days 1 and 15
Repeat every 4 weeks	

Gemcitabine + Capecitabine	
Gemcitabine	1000 mg/m^2 IV infusion over 30 minutes on days 1 and 8
Capecitabine	650 mg/m^2 bid PO days 1 – 14
Repeat every 3 weeks	

Gemcitabine + Oxaliplatin	
Gemcitabine	1000 mg/m^2 IV infusion over 100 minutes on day 1
Oxaliplatin	100 mg/m^2 IV infusion over 2 hours on day 2
Repeat every 2 weeks	

Gemcitabine + Erlotinib		
Gemcitabine	1000 mg/m^2 IV infusion over 30 minutes weekly	For 6 cycles

	or 2000 mg/m^2 IV infusion over 90 minutes biweekly	
Erlotinib	100 mg/d PO daily till DP or toxicity	

5-FU + Oxaliplatin + Irinotecan + Folinic acid	
5-FU	2400 mg/m^2 IV infusion 46 hours
Oxaliplatin	85 mg mg/m^2 IV infusion day 1
Irinotecan	150 mg/m^2 IV infusion
Folinic acid	400 mg/m^2 IV infusion day 1

Note: This is modified FOLFIRINOX regimen recommended for adjuvant setting for cancer of pancreas. It's different from standard FOLFIRINOX used in colon cancer.

Gemcitabine + Radiotherapy	
Gemcitabine	600 mg/m^2 IV infusion over 30 minutes on day 1 weekly
Radiotherapy	50.4 Gray (Gy) over 28 fractions

Gemcitabine + 5-FU + Radiotherapy followed by Gemcitabine	
Gemcitabine	200 mg/m^2 IV infusion on day 1
5-FU	200 mg/m^2 continuous IV infusion days 1 – 5
Radiotherapy	50.4 Gy over 28 fractions
Followed by	
Gemcitabine	1000 mg/m^2 IV infusion over 30 minutes weekly 3/4
Repeated for 4 cycles	

Liposomal Irinotecan + Leucovorin + 5-FU	
Liposomal Irinotecan	70 mg/m^2 IV infusion over 90 minutes
Leucovorin	400 mg/m^2 IV infusion over 30 minutes
5-FU	2400 mg IV infusion over 46 hours
Repeated every 2 weeks	

Pembrolizumab	
Pembrolizumab	200 mg IV infusion over 30 minutes
It is repeated every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.	

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