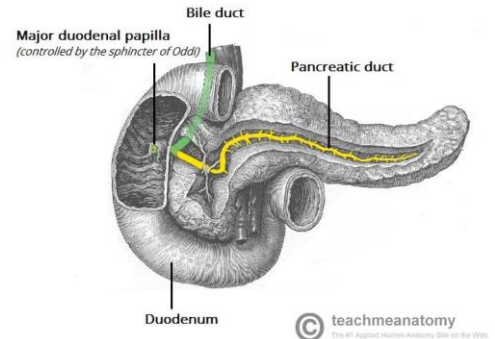


PANCREATIC CANCER

General Overview

- 4th most common cause of cancer death in Europe
- Diagnosed at an advanced stage due to its aggressive biology and non-specific symptoms. Only 5% of PDAC patients survive 10y
- Adenocarcinoma (PDAC) is the most frequent histology type.
- Risk factors: age, tobacco, alcohol, overweight, new onset diabetes, pancreatitis, Helicobacter pylori infection
- Familial pancreatic cancer (4-10%), variants with BRCA2 are the most common pathogenic germline alterations
- Clinical symptoms: weight loss, pain, jaundice



Staging (AJCC Version 8) and Prognosis

- CT three-phase (pancreatic, arterial and portal).

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed	Nx: LN cannot be assessed	M0: no distant M+
T0: No evidence of primary tumor	N0: no regional LN	M1: distant M+
Tis: Ca in situ, high grade dysplasia	N1: M+ in 1-3 regional LN	
T1: tumor ≤ 2 cm in greatest dim	N2: M+ in 4 or more reg LN	
T1a: tumor ≤ 0.5 cm		
T1b: $0.5 <$ tumor < 1 cm		
T1c: tumor 1-2 cm		
T2: $2 <$ tumor ≤ 4 cm in greatest dim		
T3: tumor > 4 cm in greatest dim		
T4: tumor involves celiac axis, sup mesenteric artery, and/or common hepatic artery (regardless of size)		

Prognostic stage group	TNM	5y survival (%)
IA	T1 N0 M0	39
IB	T2 N0 M0	34
IIA	T3 N0 M0	28
IIB	T1 N1 M0	21
	T2 N1 M0	
III	T1 N2 M0	11
	T2 N2 M0	
	T3 N2 M0	
	T4, any N M0	
IV	Any T any N M1	

Treatment

- Upfront surgery if possible.
- Contra-indications for surgery:
 - Encasement or occlusion / thrombus of the superior mesenteric artery
 - Unreconstructable superior mesenteric vein or SMV-portal vein confluence occlusion
 - Direct involvement of the inferior vena cava, aorta, celiac axis or hepatic artery
- **Resectable disease** : Adjuvant mFOLFIRINOX is the standard adjuvant therapy for fit patients (PS 0-1). For Frail patients (PS 2) or older patients adjuvant gemcitabine might be an alternative.
- **Borderline resectable (BR) disease**: Induction chemotherapy with either FOLFIRINOX or Gemcitabine albumin-bound (Nab)paclitaxel. Re-evaluation of resectability after 3 months.
- **Metastatic disease**
 - 1st line: Chemotherapy regimens mFOLFIRINOX and gemcitabine / Nabpaclitaxel have been shown superior to gemcitabine monotherapy. In less fit patients monotherapy with gemcitabine is an alternative.
 - Patients with germline BRCA 1 and BRCA2 mutations (4-7% of patients) may benefit of frontline platinum based chemotherapy followed by maintenance with Olaparib (cfr POLO trial). Minimum of 16 weeks of platinum based chemotherapy
 - 2nd line: For a fit patient who progress to gemcitabine based chemotherapy, a platinum based schedule (ex. FOLFOX) is an option. Alternative nanoliposomal irinotecan (Nal-IRI) and 5-fluorouracil (5-Fu) is an option. After progression to FOLFIRINOX, a gemcitabine based schedule might be proposed.

References

- 1) Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer: The CONKO-001 Randomized Trial. *JAMA*. 2013;310(14):1473–1481. doi:10.1001/jama.2013.279201
- 2) Conroy T, Hammel P, Hebbar M, et al. Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group FOLFIRINOX or Gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018;379(25):2395–406.
- 3) Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817–25. (update *Jama oncol* 2022 Conroy et al)
- 4) Von Hof DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nabpaclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691–703
- 5) Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA mutated metastatic pancreatic cancer. *N Engl J Med*. 2019;381(4):317–27 (update: *JCO* 2022 Kindler et al)
- 6) Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet*. 2016;387:545–57.
- 7) T. Conroy, P. Pfeiffer et al Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up *Annals of oncology* 2023
- 8) Kakar S, Pawlik TM, Allen PJ, Vauthey J-N.. Exocrine pancreas. In: *AJCC Cancer Staging Manual*, 8th, Amin MB (Ed), AJCC, Chicago 2017. p.337

What's new ?

- CD40 agonist mitazalimab with mFOLFIRINOX: Van Laethem et al *Lancet oncol* 2024

- Neoantigen T-cell receptor gene therapy in pancreatic cancer NEJM June 2022
- Personalize RNA neoantigen vaccines in pancreatic cancer Nature June 2023
- Sotorasib in KRAS G12C mutated advanced pancreatic cancer NEJM 2023 (Strickler et al)
- NAPOLI-3: phase 3 randomised between NALIRIFOX and gemcitabine/nabpaclitaxel
 - Wainberg Z et al; Lancet 2023. Superior OS (11.1 vs 9.2m)
- NORPACT-1: neoadj FOLFIRINOX vs upfront surgery for resectable pancreatic head cancer
 - Lancet Gastroenterol Hepatol 2024; Phase 2 ; Negative study !!
- CAR-T CT041 in refractory metastatic pancreatic cancer JCO 2024 Changsong Qi et al