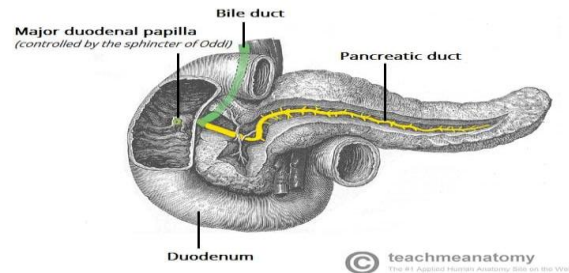


PANCREATIC CANCER

GENERAL OVERVIEW

- **Epidemiology.** Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy and a leading cause of cancer death; most patients present with unresectable or metastatic disease.
- **Histology.** PDAC is by far the most frequent exocrine pancreatic malignancy. Neuroendocrine tumours require a different guideline.
- **Risk factors.** Age, tobacco, obesity, chronic pancreatitis, diabetes/new-onset diabetes, heavy alcohol exposure and selected hereditary syndromes.
- **Hereditary disease.** Approximately 5-10% have an inherited predisposition. BRCA2 is among the most frequent actionable germline alterations.
- **Symptoms.** Weight loss, abdominal/back pain, jaundice, anorexia, steatorrhoea and new/worsening diabetes.



GERMLINE AND SOMATIC TESTING

- **Germline testing.** Offer germline multigene testing to young patients with PDAC, or positive family history. At minimum consider BRCA1/2, PALB2 and other hereditary pancreatic-cancer genes according to the genetics panel.
- **Tumour profiling.** Perform molecular profiling in unresectable/metastatic PDAC when feasible. KRAS is mutated in >90%; in KRAS-wild-type disease actively search for rare actionable alterations/fusions.
- **Clinically relevant rare subsets.** BRCA1/2/PALB2 or other homologous-recombination deficiency; MSI-H/dMMR; NTRK/NGR1/RET/ALK/ROS1 fusions; BRAF V600E; KRAS G12C; and, increasingly, the specific RAS variant because direct RAS inhibitors are entering practice.
- **Tumour marker.** CA19-9 is useful for monitoring disease burden when secreted, but is not suitable as a population screening test and should be interpreted after biliary decompression when relevant.

DIAGNOSTIC WORK-UP

- **Imaging.** Pancreas-protocol multiphasic CT (pancreatic/arterial and portal venous phases) of chest/abdomen/pelvis; MRI can complement CT, particularly for liver lesions or when CT is inconclusive.
- **Tissue diagnosis.** EUS-guided tissue acquisition is preferred before systemic therapy. Histological confirmation is not mandatory before immediate surgery when imaging is unequivocally resectable, but MDT discussion is essential.
- **Fitness/supportive care.** Assess ECOG PS, nutritional status, biliary obstruction, pancreatic exocrine insufficiency, diabetes and thromboembolic risk.

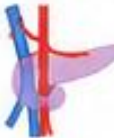
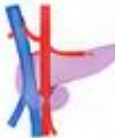
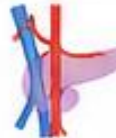
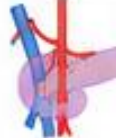
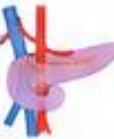
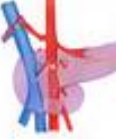
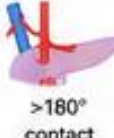
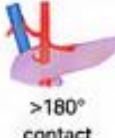
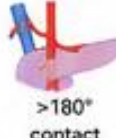
PANCREATIC CANCER

STAGING AND RESECTABILITY

AJCC 8 - TNM DEFINITIONS

- **T1.** Tumour ≤ 2 cm (T1a ≤ 0.5 cm; T1b >0.5 to <1 cm; T1c 1-2 cm).
- **T2.** Tumour >2 cm and ≤ 4 cm.
- **T3.** Tumour >4 cm.
- **T4.** Tumour involves the coeliac axis, superior mesenteric artery and/or common hepatic artery, irrespective of size.
- **N1 / N2.** N1 = 1-3 positive regional lymph nodes; N2 = ≥ 4 positive regional lymph nodes.
- **M1.** Distant metastasis.

Stage	TNM
IA	T1 N0 M0
IB	T2 N0 M0
IIA	T3 N0 M0
IIB	T1-3 N1 M0
III	T4 Any N M0 OR T1-3 N2 M0
IV	Any T Any N M1

Assessment of resectability: key vascular relationships (Lancet Oncology, 2021)					
Resectability	Arterial involvement			Venous involvement	
	Celiac axis (CA)	SMA	Common hepatic artery (CHA)	Portal vein (PV)	SMV
Resectable	 No contact	 No contact	 No contact	 No contact or $\leq 180^\circ$	 No contact or $\leq 180^\circ$
Borderline resectable	 $\leq 180^\circ$ contact	 $\leq 180^\circ$ contact	 $\leq 180^\circ$ contact	 $> 180^\circ$ contact (occlusion amenable to resection and reconstruction)	 $> 180^\circ$ contact (occlusion amenable to resection and reconstruction)
Locally advanced (unresectable)	 $> 180^\circ$ contact	 $> 180^\circ$ contact	 $> 180^\circ$ contact	Unreconstructable occlusion	Unreconstructable occlusion

— Artery — Vein Pancreas

schematic of pancreatic resectability based on vascular involvement (adapted from Lancet Oncology 2021).

Radiological resectability - practical UZA approach

- **Resectable.** No distant metastases and no prohibitive arterial or venous involvement; vascular contact is interpreted in an experienced pancreatic MDT.
- **Borderline resectable.** Limited vessel involvement for which an R0 resection may become feasible after induction therapy and/or vascular reconstruction.
- **Locally advanced/unresectable.** Arterial encasement or venous involvement not amenable to safe reconstruction, in the absence of distant metastases.
- **Important.** Do not use a single radiological phrase in isolation: resectability should be decided in a high-volume pancreatic MDT with dedicated radiology and surgery.

SURGICAL PRINCIPLES

- **Upfront surgery.** Appropriate for clearly resectable PDAC in fit patients, preferably in a high-volume centre.
- **Goal.** R0 resection with oncological lymphadenectomy; pancreaticoduodenectomy for most head lesions and distal pancreatectomy for body/tail lesions.
- **Biliary drainage.** Avoid routine preoperative drainage if prompt surgery is feasible; drain when cholangitis, marked hyperbilirubinaemia, delayed surgery or neoadjuvant therapy makes it clinically necessary.

PANCREATIC CANCER

LOCALIZED / POTENTIALLY CURABLE DISEASE

RESECTABLE PDAC

- **Preferred sequence.** Upfront surgery remains a standard for clearly resectable disease. Routine neoadjuvant FOLFIRINOX is not established after the negative NORPACT-1 trial.
- **Adjuvant treatment.** For fit patients (ECOG 0-1), modified FOLFIRINOX for 6 months is the preferred adjuvant regimen (PRODIGE 24). Start as soon as adequately recovered, ideally within 12 weeks.
- **If not fit for mFOLFIRINOX.** Gemcitabine + capecitabine or gemcitabine alone can be considered depending on age, comorbidity and recovery. Treatment choice should prioritise delivery of approximately 6 months of systemic therapy.
- **Radiotherapy.** No routine role after an R0 resection. Discuss exceptional R1/high-risk situations in MDT.

BORDERLINE RESECTABLE PDAC

- **UZA principle.** Use neoadjuvant/induction systemic therapy in fit patients, typically mFOLFIRINOX; gemcitabine + nab-paclitaxel is an alternative when an irinotecan/oxaliplatin-containing regimen is unsuitable.
- **Reassessment.** Restage after approximately 2-3 months and again after planned induction therapy. CA19-9 kinetics and absence of metastatic progression are important alongside CT appearance.
- **Surgery.** Proceed to exploration/resection when an R0 resection is considered technically realistic and there is no systemic progression.
- **Chemoradiotherapy.** May be considered selectively for local control or margin optimisation; PREOPANC-2 did not show an OS advantage of neoadjuvant FOLFIRINOX over gemcitabine-based chemoradiotherapy.

LOCALLY ADVANCED / UNRESECTABLE, NON-METASTATIC

- **Induction.** Systemic chemotherapy is the backbone: mFOLFIRINOX or gemcitabine + nab-paclitaxel in fit patients; treat initially as systemic disease and reassess for conversion.
- **Conversion surgery.** Can be considered in highly selected patients with sustained disease control and technically resectable anatomy at expert MDT review.
- **Chemoradiotherapy.** CONKO-007 did not establish routine CRT after induction as a superior strategy for conversion; reserve for selected local-control scenarios.
- **Tumor Treating Fields.** PANOVA-3 showed an OS benefit when TTFields were added to gemcitabine/nab-paclitaxel in locally advanced PDAC (16.2 vs 14.2 months; HR 0.82), but practical access, regulatory status and Belgian reimbursement must be considered before use.

PANCREATIC CANCER

METASTATIC DISEASE - FIRST LINE

FIT PATIENT (ECOG 0-1)

- **mFOLFIRINOX.** Preferred standard in fit patients with adequate organ function; phase III survival benefit versus gemcitabine.
- **NALIRIFOX.** EMA-authorised first-line option (NAPOLI-3) with OS benefit versus gemcitabine/nab-paclitaxel. Belgian reimbursement for Onivyde currently covers the post-gemcitabine setting, not first-line NALIRIFOX.
- **Gemcitabine + nab-paclitaxel.** Established first-line standard and useful when FOLFIRINOX is less suitable or when a gemcitabine backbone is preferred.
- **BRCA1/2/PALB2 or HRD phenotype.** Prefer a platinum-containing regimen when clinically appropriate, particularly for germline BRCA1/2/PALB2-mutated disease.

LESS FIT PATIENT

- **ECOG 2 / relevant comorbidity.** Gemcitabine-based therapy, dose-attenuated combination therapy or gemcitabine monotherapy depending on goals and tolerance.
- **ECOG 3-4.** Best supportive care is usually appropriate unless poor PS is clearly reversible (e.g. biliary sepsis/obstruction).

MAINTENANCE OLAPARIB - BELGIUM

- **Who.** Metastatic pancreatic adenocarcinoma with a pathogenic germline BRCA1/2 mutation and no progression after at least 16 weeks of first-line platinum-containing chemotherapy.
- **Evidence.** POLO improved PFS (7.4 vs 3.8 months) but did not demonstrate a clear OS benefit.
- **Belgian reimbursement.** Olaparib is reimbursed for this exact maintenance indication under Chapter IV conditions, with germline BRCA1/2 confirmation by a recognised genetics centre and MOC approval.
- **Practical point.** Discuss maintenance versus continued platinum/fluoropyrimidine according to response, cumulative toxicity and patient preference.

PANCREATIC CANCER

SECOND LINE, LATER LINES AND PRECISION MEDICINE

SECOND-LINE SYSTEMIC THERAPY

- **After gemcitabine-based first line.** 5-FU/LV + nanoliposomal irinotecan (nal-IRI; NAPOLI-1) is an evidence-based option. In Belgium, Onivyde is reimbursed after progression on gemcitabine-based therapy for ECOG ≤ 2 provided the patient has not previously received irinotecan.
- **After FOLFIRINOX / irinotecan-containing first line.** Gemcitabine + nab-paclitaxel or another gemcitabine-based regimen is a common option in fit patients.
- **Oxaliplatin-based 5-FU.** Can be considered after gemcitabine in selected fit patients, but evidence is less consistent than for nal-IRI + 5-FU/LV.
- **Third line.** Clinical trial is preferred when feasible. Treatment should be individualised according to PS, prior exposure, residual toxicity and molecular profile.

MOLECULARLY SELECTED OPTIONS

- **RAS-mutated PDAC - daraxonrasib.** RASolute 302 is a major phase III breakthrough in previously treated metastatic PDAC: median OS 13.2 vs 6.6 months in the RAS G12 population and PFS 7.3 vs 3.5 months. As of August 2026 daraxonrasib is under EMA phased review and is not yet an authorised/reimbursed Belgian standard.
- **KRAS G12D - setidegrasib.** Phase I protein-degrader data show activity (ORR 24% in the 600-mg PDAC cohort), but this remains investigational.
- **KRAS G12C.** Sotorasib/adagrasib have demonstrated activity in rare KRAS G12C PDAC, but pancreatic use is not a reimbursed Belgian standard.
- **MSI-H/dMMR.** Checkpoint inhibition can produce durable responses, but pancreatic cancer is rare in this subset and Belgian reimbursement is not a general tumour-agnostic pancreatic indication.
- **KRAS wild type / rare fusions.** For NTRK and other actionable fusions, discuss tumour-agnostic targeted therapy and reimbursement according to the exact alteration and current Belgian criteria.

PANCREATIC CANCER

WHAT'S NEW? - 2024-2026

RAS-TARGETED THERAPY - THE BIGGEST CHANGE

- **Daraxonrasib phase I/II (NEJM 2026)**. Proof-of-concept activity in previously treated RAS-mutated PDAC established that broad RAS(ON) inhibition can produce meaningful responses.
- **RASolute 302 phase III (NEJM 2026)**. Daraxonrasib versus investigator-choice chemotherapy in 500 previously treated metastatic PDAC patients: OS 13.2 vs 6.6 months in RAS G12 disease; PFS 7.3 vs 3.5 months. This is practice-changing evidence, but EU authorisation/reimbursement is pending.
- **Setidegrasib (NEJM 2026)**. First-in-class KRAS G12D targeted protein degrader: ORR 24% and median OS 10.3 months in the 600-mg metastatic PDAC cohort; early-phase only.
- **HRS-4642 + gemcitabine/nab-paclitaxel (Nat Med 2026)**. Phase 1b/2 data in KRAS G12D-mutant advanced PDAC show encouraging activity; not yet a standard.
- **Resistance biology**. Acquired resistance to direct RAS inhibition is already emerging as a key translational question; combination strategies are likely to be needed.

OTHER RECENT SIGNALS

- **Elraglusib + gemcitabine/nab-paclitaxel (Nat Med 2026)**. Randomised phase II first-line study reported improved OS versus chemotherapy alone; requires phase III confirmation.
- **NP137 + mFOLFIRINOX (Nature 2026)**. Phase Ib netrin-1 blockade in locally advanced PDAC: median PFS 10.85 months, median OS 16.43 months and conversion surgery in 23%; promising translational signal, not standard.
- **PANOVA-3 (JCO 2025)**. TTFIELDS + gemcitabine/nab-paclitaxel improved OS in locally advanced disease, although no significant PFS benefit; access and device burden matter.
- **CONKO-007 (JCO 2025)**. After induction chemotherapy in initially unresectable PDAC, adding chemoradiotherapy did not establish a routine superior conversion strategy.
- **PREOPANC-2 (Lancet Oncol 2025)**. Neoadjuvant FOLFIRINOX did not improve OS versus gemcitabine-based chemoradiotherapy in resectable/borderline resectable PDAC.
- **Mutant KRAS vaccine (Nat Commun 2026)**. Phase I adjuvant vaccine + nivolumab/ipilimumab demonstrated strong KRAS-specific immune responses in 12 patients; investigational.

PANCREATIC CANCER

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