

Pancreatic Carcinoma

Ductal adenocarcinoma

Ductal adenocarcinoma: molecular pathogenesis, morphology and clinical implications

Molecular pathogenesis | Morphology | Clinicopathologic correlation

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What this lecture will establish

- Identify the defining pathologic features of pancreatic ductal adenocarcinoma (PDAC).
- Explain major risk factors, precursors and molecular alterations.
- Connect tumor location and invasive behavior with clinical presentation.
- Interpret the limits of detection and the importance of resectability.

Pancreatic ductal adenocarcinoma: The entity

- Infiltrating ductal adenocarcinoma is the most common exocrine malignancy of the pancreas.
- Neoplastic epithelium forms malignant glands and often produces mucin.
- Deep invasion, marked desmoplasia and late diagnosis dominate its behavior.

Exocrine ductal phenotype + infiltrative growth + fibrotic stroma

Exocrine versus endocrine pancreatic tumors

DUCTAL / EXOCRINE

- The subject of this lecture
- Gland-forming, mucin-producing epithelial malignancy
- Typically marked desmoplasia

ENDOCRINE

- Distinct pancreatic neoplasm group
- Discussed elsewhere
- Do not equate with PDAC

Scope: Infiltrating exocrine ductal adenocarcinoma, not pancreatic neuroendocrine neoplasms.

A high-fatality malignancy

12%

Five-year survival reported

- Textbook estimate refers to the population reflected by its data.
- This is not a stage-specific or individual prognostic estimate.
- Late presentation is the dominant explanatory factor.

Most patients present beyond surgery

>80%

Unresectable at initial
presentation

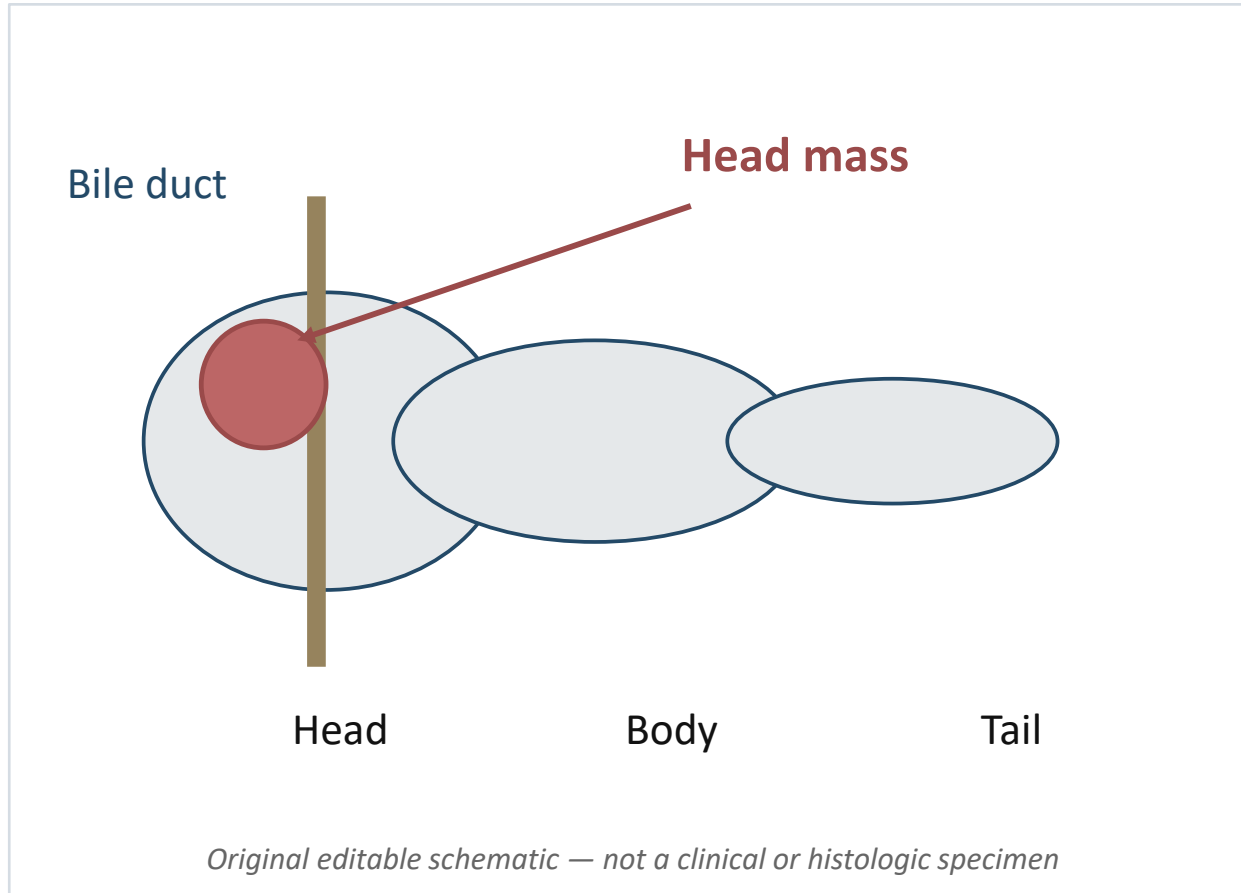
- Vascular/adjacent-structure involvement can prevent resection.
- Some patients already have distant metastatic disease.
- Earlier detection before dissemination is therefore critical.

Pancreatic cancer: Anatomic distribution

Site	Approximate proportion	Pathologic/clinical implication
Head	60%	Often obstructs the distal common bile duct
Body	15%	May enlarge before causing biliary symptoms
Tail	5%	Usually no early biliary obstruction
Diffuse pancreatic involvement	20%	Disease extends through the pancreas

Percentages are approximate and come from the source morphology section.

Anatomic location predicts obstruction



- Carcinoma in the head lies near the intrapancreatic common bile duct.
- Distal common bile duct obstruction causes upstream biliary dilatation.
- Body and tail tumors may remain clinically occult longer.

Age distribution

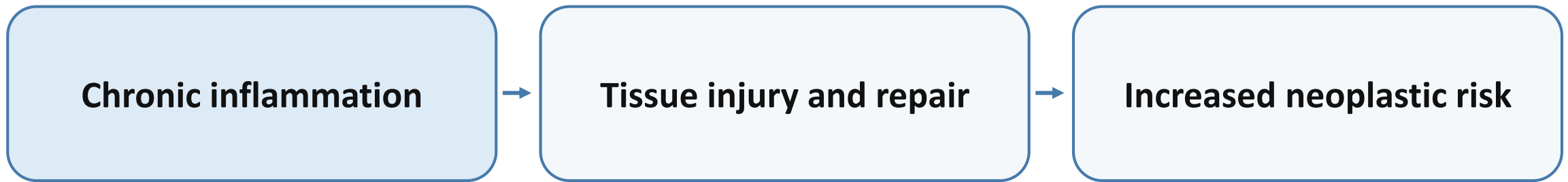
- Pancreatic carcinoma is predominantly a disease of older adults.
- That 80% of cases occur after age 60.
- Age influences pretest probability but is not a stand-alone diagnostic criterion.

Cigarette smoking as an established exposure

- Smoking is described as the strongest environmental influence.
- The source reports approximately twice the risk among smokers.
- Smoking is a risk factor; Most smokers do not develop pancreatic cancer.

Risk ≠ diagnosis; Population associations should not be applied deterministically.

How chronic pancreatitis increases risk



Association grounded in the source; This diagram is not a deterministic progression.

Adiposity and metabolic risk

- Visceral obesity and high body mass index are associated with greater risk.
- Established diabetes mellitus is a modest risk factor.
- These associations complement inherited and smoking-related susceptibility.

Diabetes: Risk factor or early consequence?

PRE-EXISTING DIABETES

- Modest epidemiologic risk factor
- May precede malignant transformation
- Not diagnostic of pancreatic carcinoma

NEW-ONSET DIABETES

- Can precede recognition of occult carcinoma
- Especially relevant in older patients
- Requires clinical context, not indiscriminate screening

The temporal direction of the association is crucial.

A possible preclinical metabolic signal

≤ 2 years

Diabetes or abnormal
glucose tolerance before
clinical signs

- The source states that up to half of patients show this abnormality within this interval.
- It is a possible opportunity for earlier recognition.
- It is not sufficiently specific to diagnose PDAC alone.

Population differences in incidence

- The source reports increased incidence in African Americans, Japanese Americans, Native Hawaiian Islanders and Ashkenazi Jewish people.
- Population patterns do not define causation in an individual.
- Clinical assessment still depends on symptoms, inherited risk and diagnostic findings.

Hereditary contribution

~10%

Patients with a deleterious
germline predisposition or a
first-degree family history

- Family history and germline mutation status are overlapping—but not identical—concepts.
- DNA repair genes are prominent among inherited predisposition genes.
- Identifying a familial mutation has implications for relatives.

DNA repair genes in familial pancreatic cancer

- BRCA2 and ATM are highlighted as common known familial predisposition genes.
- BRCA1 and PALB2 are additional DNA repair-related susceptibility genes.
- These inherited defects are distinct from acquired tumor mutations.

Inherited predisposition: Selected syndromes

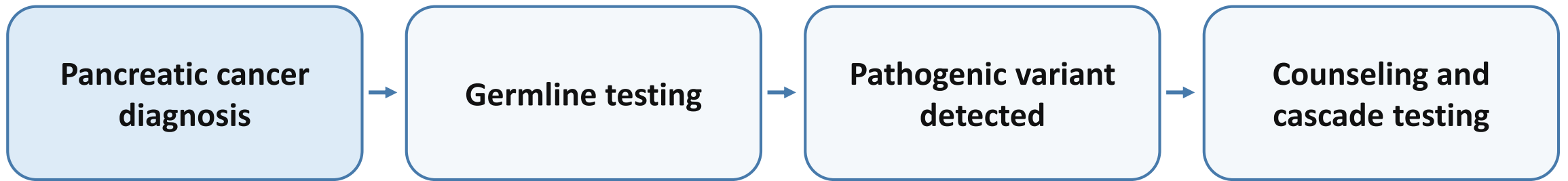
Context	Selected genes	Teaching significance
Peutz–Jeghers syndrome	STK11	Strong predisposition in textbook
Hereditary pancreatitis	PRSS1, SPINK1	Pancreatic injury plus inherited susceptibility
Familial atypical multiple-mole melanoma	CDKN2A	Hereditary tumor-suppressor predisposition
Hereditary breast/ovarian cancer	BRCA1/2, PALB2, ATM	DNA repair pathway involvement

Selected inherited predisposition syndromes; Comparison not exhaustive.

Additional inherited risk settings

Setting	Molecular/family basis	Clinical implication
Lynch syndrome	DNA mismatch-repair genes	Pancreatic risk and possible mismatch-repair deficiency
Strong pancreatic family history	Several affected relatives	Elevated inherited risk even without an identified gene
First-degree relative of a mutation carrier	Shared familial variant possible	Genetic counseling/cascade assessment

From index case to familial risk recognition



Robbins recommends germline testing for all patients with pancreatic cancer.

Genetic results can inform therapy

- Germline and tumor DNA repair defects may define therapeutic vulnerabilities.
- Mismatch-repair deficiency and microsatellite instability are potentially actionable.
- Do not confuse a susceptibility marker with proof of a particular treatment response.

Precursor lesions establish a progression model

- Most pancreatic cancers are believed to arise from microscopic PanIN lesions.
- A smaller fraction arise from recognizable mucinous cystic precursors.
- The distinction is important for interpreting precursor morphology and early detection.

PanIN is the dominant precursor

>85%

Estimated pancreatic cancers
arising from PanIN

- PanIN develops in small pancreatic ducts and is often microscopic.
- Low-grade PanIN can be encountered in older individuals.
- High-grade PanIN is uncommon without associated invasive carcinoma.

Low-grade versus high-grade PanIN

LOW-GRADE PanIN

- Microscopic intraductal epithelial atypia
- Formerly classified as PanIN-1A/1B/2
- May be isolated, particularly in older patients

HIGH-GRADE PanIN

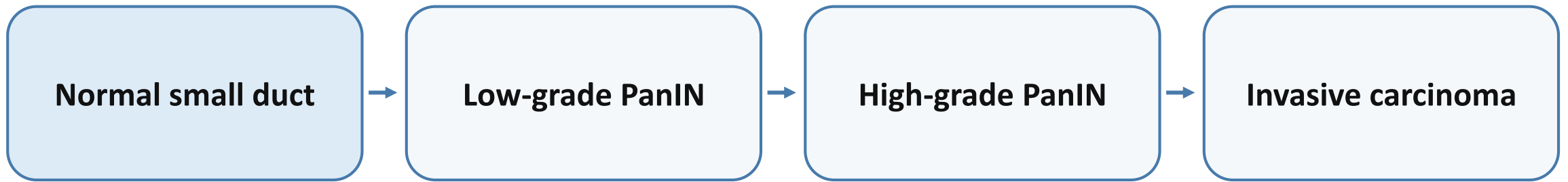
- Markedly dysplastic precursor epithelium
- Formerly termed PanIN-3 / carcinoma in situ
- Often found with invasive carcinoma

Both are noninvasive; Invasion is a separate decisive event.

Evidence connecting PanIN with carcinoma

- PanIN and PDAC share multiple genetic and epigenetic alterations.
- PanIN often occurs in non-neoplastic pancreas adjacent to PDAC.
- Engineered mouse models and rare longitudinal human reports support progression.

PanIN progression: Conceptual stages



Model of cumulative alterations; Not every lesion necessarily progresses.

Telomere erosion occurs early

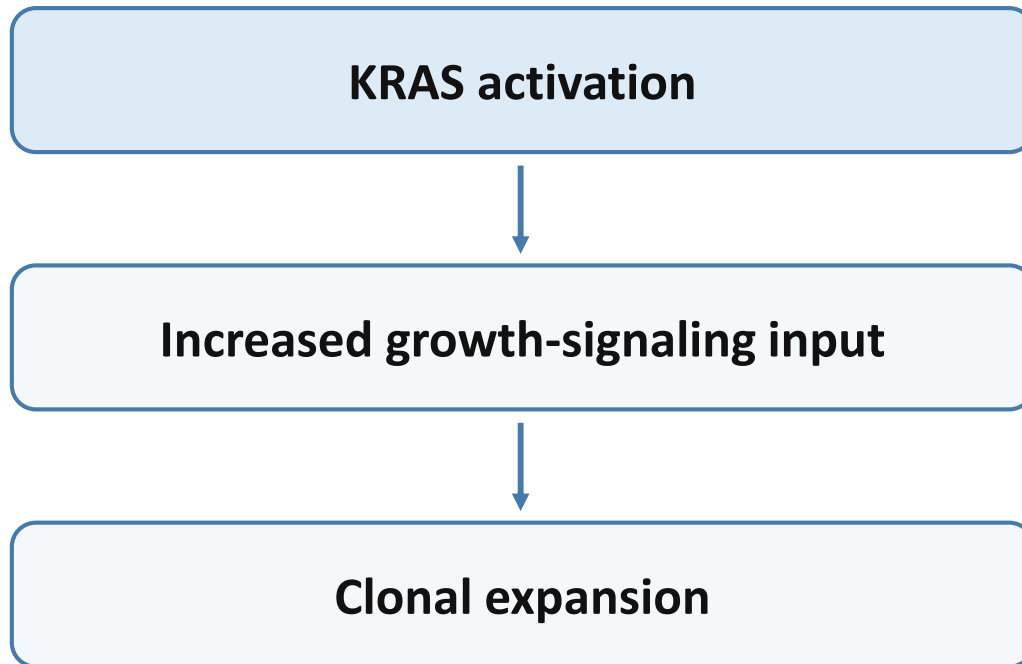
- The source describes striking telomere shortening in PanIN epithelial cells.
- Short telomeres may favor chromosomal instability and accumulation of alterations.
- Telomere shortening is a pathobiologic feature—not a routine diagnostic assay.

Cumulative mutation burden matters more than order

- A general sequence of molecular events.
- Individual lesions need not acquire alterations in a rigid chronological order.
- Progressive loss of regulatory safeguards facilitates invasion.

Progression model: A framework, not an obligatory genetic itinerary.

KRAS: Early oncogenic activation



Original editable schematic — not a clinical or histologic specimen

- Activating KRAS mutations are the most frequent oncogenic event.
- KRAS functions as a growth-signal transducer.
- Early KRAS activation alone does not establish invasive cancer.

KRAS alteration is exceptionally common

>90%

PDACs with activating KRAS
mutation

- KRAS is located at chromosome 12p.
- Mutation frequency refers to pancreatic carcinomas, not all pancreatic tumors.
- Ongoing trials targeting mutant RAS proteins.

CDKN2A: Impaired cell-cycle restraint

CDKN2A / p16 loss



Reduced cell-cycle restraint

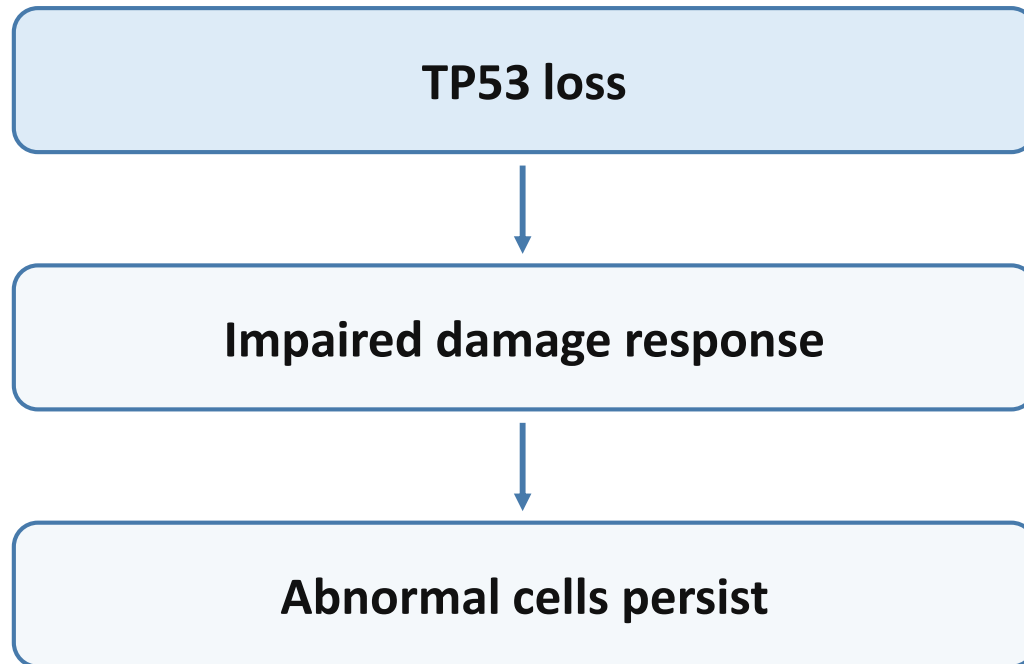


Proliferation permitted

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- CDKN2A at 9p encodes p16/INK4a and ARF tumor suppressors.
- Its loss weakens normal safeguards against inappropriate proliferation.
- Inactivation in approximately 30% of PDAC.

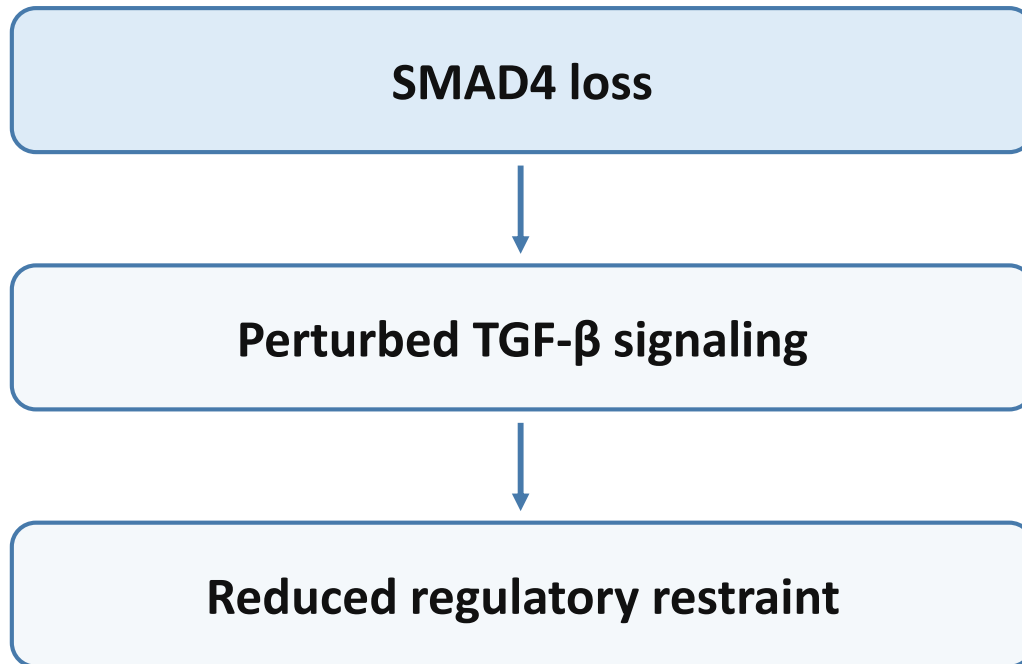
TP53: Compromised response to DNA damage



Original editable schematic — not a clinical or histologic specimen

- TP53 at 17p encodes p53, a tumor suppressor.
- Its inactivation undermines cellular responses to DNA damage.
- The source reports alteration in 70–75% of carcinomas.

SMAD4: Defective TGF- β growth regulation



Original editable schematic — not a clinical or histologic specimen

- SMAD4 at 18q participates in TGF- β pathway signaling.
- It is inactivated in approximately 55% of PDAC.
- Loss is relatively uncommon across other cancer types, but not exclusive to PDAC.

Core molecular alterations in PDAC

Gene	Role	Approximate alteration frequency
KRAS	Oncogenic signal transducer	>90%
TP53	DNA damage response	70–75%
SMAD4	TGF- β pathway tumor suppressor	55%
CDKN2A	Cell-cycle restraint (p16/ARF)	30%

Frequencies are textbook estimates; A tumor may harbor several alterations simultaneously.

Less-common molecular events

Group	Selected genes	Interpretation
DNA damage response	ATM, BRCA2	Subset with DNA repair defects
Chromatin regulation	ARID1A, KMT2C, KDM6A	Altered transcriptional control
Growth signaling	AKT2, BRAF, MYC	Additional oncogenic mechanisms
Wnt-associated restraint	RNF43	Disrupted pathway regulation

Selected molecular alterations; Not an exhaustive diagnostic panel.

Epigenetic dysregulation

Promoter hypermethylation



Tumor-suppressor silencing



Reduced growth control

Example: CDKN2A silencing. Hypomethylation can have the opposite transcriptional effect.

Two transcriptomic phenotypes

BASAL-LIKE

- Transcriptomic subtype
- More aggressive behavior reported
- Can coexist with classic subtype elements

CLASSICAL

- Transcriptomic subtype
- Relatively more favorable prognosis
- May shift under treatment pressure

Basal-like/classic phenotypic heterogeneity and plasticity; Clinical selection is still under investigation.

Tumor heterogeneity changes interpretation

- Different molecular phenotypes may coexist within one tumor.
- Expression programs can show plasticity during chemotherapy.
- A subtype assignment need not represent every tumor cell at every time point.

Microscopic versus cystic precursor routes

PanIN ROUTE

- Small ducts; Usually microscopic
- Histologic low-grade/high-grade progression
- Major presumed source of PDAC

CYSTIC MUCINOUS ROUTE

- Macroscopic lesions may be detectable
- IPMN and mucinous cystic neoplasm
- Subset progresses to invasive carcinoma

Related topics are used only to explain the origin of invasive ductal cancer.

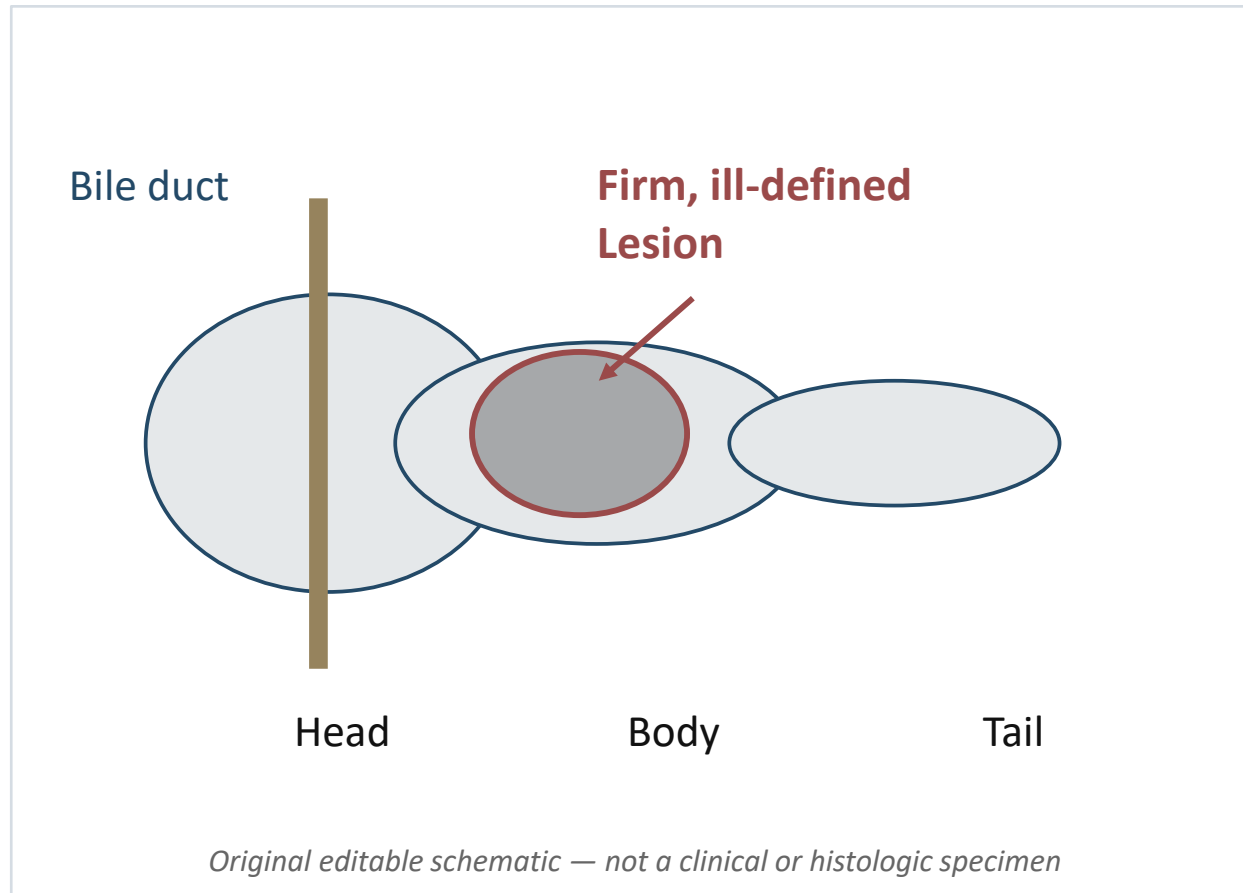
IPMN: A duct-centered precursor

- Intraductal papillary mucinous neoplasm involves main or branch pancreatic ducts.
- Neoplastic epithelium secretes mucin and can progress to invasion.
- GNAS mutations are characteristic of IPMN relative to other cyst types.

Mucinous cystic neoplasm as a precursor

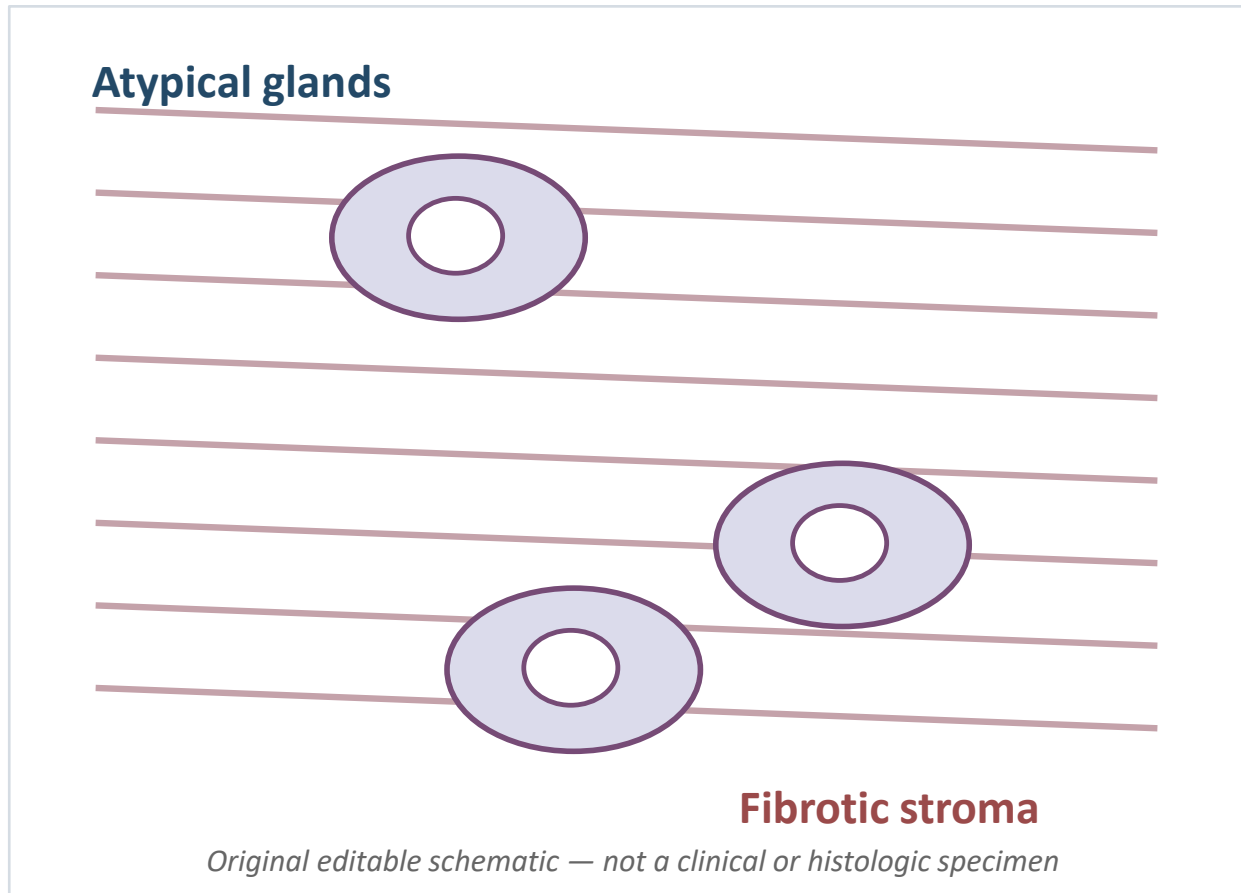
- Mucin-producing cystic epithelium sits above ovarian-type stroma.
- These neoplasms tend to occur in the pancreatic tail and in women.
- An invasive adenocarcinoma can arise within a mucinous cystic neoplasm.

Gross carcinoma: A firm ill-defined mass



- Tumor invasion and stromal collagen produce a hard mass.
- Gray-white, stellate, poorly demarcated lesions.
- A duct-centered infiltrative mass can blend into adjacent pancreatic parenchyma.

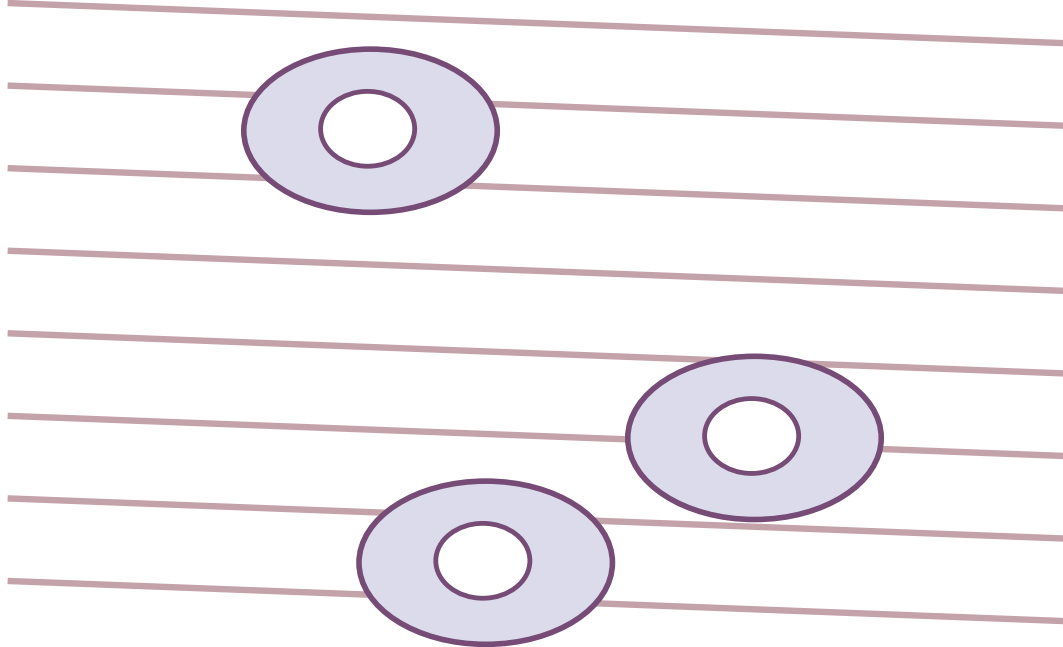
Why the pancreatic mass becomes desmoplastic



- Cancer-associated fibroblastic response deposits dense collagen.
- Malignant duct-like glands are embedded in abundant non-neoplastic stroma.
- The fibrotic component may dominate a small needle biopsy.

Microscopy: Infiltrative malignant gland formation

Atypical glands



Fibrotic stroma

Original editable schematic — not a clinical or histologic specimen

- Abortive, irregular tubular structures and small cell clusters infiltrate tissue.
- Cells range from cuboidal to columnar with nuclear pleomorphism.
- Glands are surrounded by dense fibrotic stroma.

Architectural clues to invasion

- Malignant glands are irregularly distributed rather than neatly organized around preserved ducts.
- Deep infiltration into peripancreatic tissue supports invasive behavior.
- Perineural, lymphatic or vascular invasion supplies additional evidence.

Carcinoma versus chronic pancreatitis

DUCTAL CARCINOMA

- Haphazard atypical invasive glands
- Perineural / vascular invasion may be present
- Desmoplastic tumor-associated stroma

CHRONIC PANCREATITIS

- Benign ducts can show reactive atypia
- Fibrosis can resemble desmoplasia
- Requires careful architectural correlation

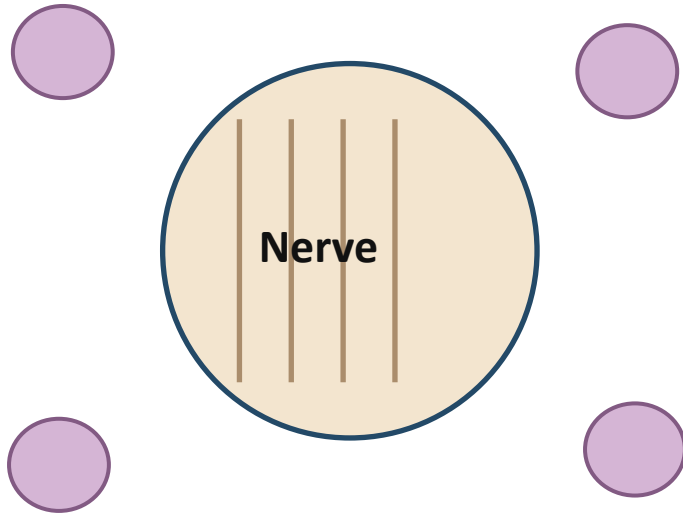
Source explicitly cautions that well-differentiated PDAC can be difficult to distinguish from benign glands in chronic pancreatitis.

Needle biopsy sampling is vulnerable to error

- Dense stroma means the sampled tissue may contain relatively few malignant cells.
- Well-differentiated malignant glands can resemble reactive epithelium.
- Interpret biopsies in clinical and imaging context; Do not assume a sparse sample excludes cancer.

Perineural invasion: Biologic and clinical relevance

Infiltrative tumor glands

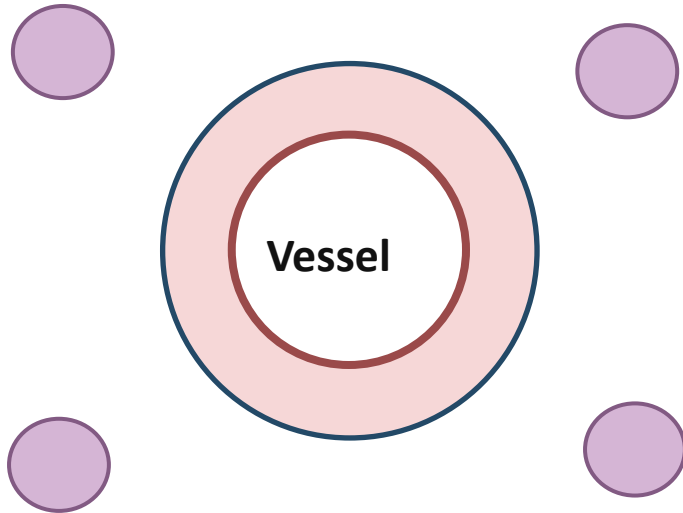


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- Pancreatic carcinoma commonly tracks along and invades nerves.
- Perineural infiltration is an indicator of invasive growth.
- Perineural involvement demonstrates spread beyond ductal epithelium.

Vascular invasion governs spread and resectability

Infiltrative tumor glands



Original editable schematic — not a clinical or histologic specimen

- The tumor may encase or infiltrate major abdominal vessels.
- Vascular invasion contributes to surgical unresectability.
- Hematogenous dissemination can lead to distant metastasis.

Routes of tumor dissemination

Direct local invasion



Lymphatic spread



Blood-borne metastasis

These are parallel potential routes, not necessarily sequential stages.

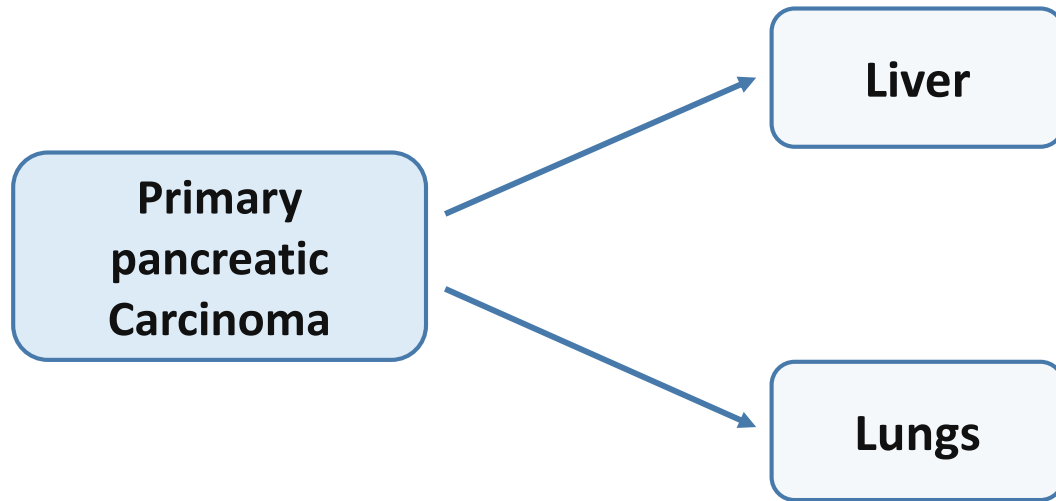
Direct extension into neighboring structures

- Retroperitoneal extension is common.
- The spleen, adrenal glands, stomach and transverse colon may be directly involved.
- Local extension can make a small anatomically strategic tumor unresectable.

Regional lymphatic spread

- Peripancreatic nodes are commonly involved.
- The source also lists gastric, mesenteric, omental and portohepatic nodal groups.
- Lymphatic spread is part of the characteristic invasive phenotype.

Metastatic targets



Original editable schematic — not a clinical or histologic specimen

- Distant spread occurs chiefly to liver and lungs.
- Metastases document spread outside the primary pancreatic site.
- Documented distant metastasis makes curative surgery unrealistic.

Less common histologic variants

- Adenosquamous and colloid carcinomas are recognized variants.
- Medullary, hepatoid and signet-ring cell patterns are described.
- Undifferentiated carcinoma may occur with or without osteoclast-like giant cells.

Head versus body/tail presentation

HEAD OF PANCREAS

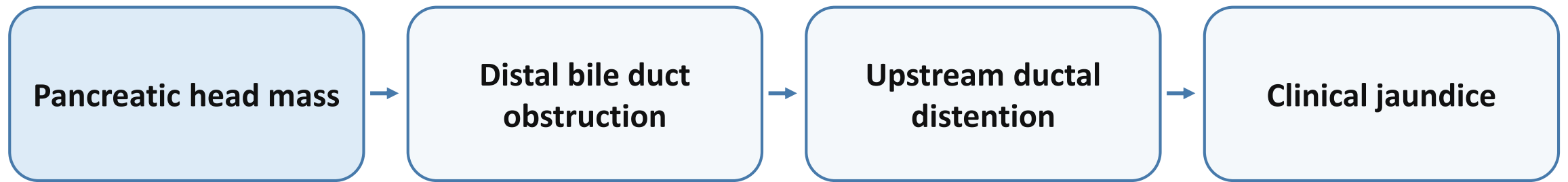
- Common bile duct obstruction
- Obstructive jaundice may reveal the tumor
- Palpable nontender gallbladder can occur

BODY OR TAIL

- Often no early biliary obstruction
- Can grow substantially before symptoms
- May be disseminated at recognition

Anatomic effects help explain presentation; These patterns are not absolute.

Mechanism of obstructive jaundice



The pathway is causal; Jaundice does not prove malignant obstruction.

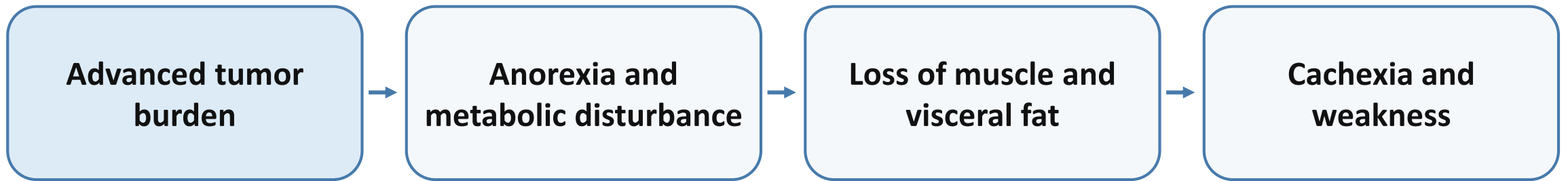
Courvoisier sign in pancreatic carcinoma

- Describes a palpably enlarged, nontender gallbladder associated with painless jaundice.
- It follows distal bile duct obstruction in a compatible clinical setting.
- It is a classic clue rather than a definitive test for carcinoma.

Pain and the silent interval

- Pancreatic carcinomas often remain asymptomatic until obstruction or invasion.
- Pain is frequently the first symptom.
- By the time pain occurs, disease is often beyond curative treatment.

Why systemic decline accompanies advanced cancer



Schematic clinical relationship described in the source.

Trousseau sign: Migratory thrombophlebitis

- Migratory, episodic thrombosis can accompany pancreatic carcinoma.
- This phenomenon in about 10% of patients.
- Cancer-associated procoagulants and platelet-activating factors contribute.

A symptom cluster requiring investigation

- Upper abdominal or back pain, unexplained weight loss and jaundice can coexist.
- New-onset diabetes in an older adult may be a separate early clue.
- These features are nonspecific and require diagnostic evaluation, not assumed PDAC.

What different investigations can and cannot do

Modality	Useful role	Key limitation
CT imaging	Assess suspicious mass and disease extent	Not recommended for general-population screening
Endoscopic ultrasound	Investigate suspected pancreatic lesion	Not general-population screening
CA19-9 / CEA	May aid longitudinal response assessment	Inadequate sensitivity/specificity for early screening
Circulating tumor DNA	Potential tumor-derived signal	Insufficient performance for general screening

CA19-9 is not an early diagnostic solution

- Serum CA19-9 may be elevated in pancreatic carcinoma.
- Limited sensitivity for early disease and limited specificity for population screening.
- It can be useful to follow treatment response in an individual patient.

Circulating tumor DNA: Promise with limitations

- Tumor cells can release DNA fragments into blood.
- Detectable ctDNA can reflect tumor biology or burden.
- Robbins does not support ctDNA as a stand-alone early-detection screening test.

Population screening versus high-risk surveillance

AVERAGE-RISK ASYMPTOMATIC

- Routine screening is not recommended
- False positives and downstream harm are major concerns
- No validated general screening strategy in source

INHERITED HIGH RISK

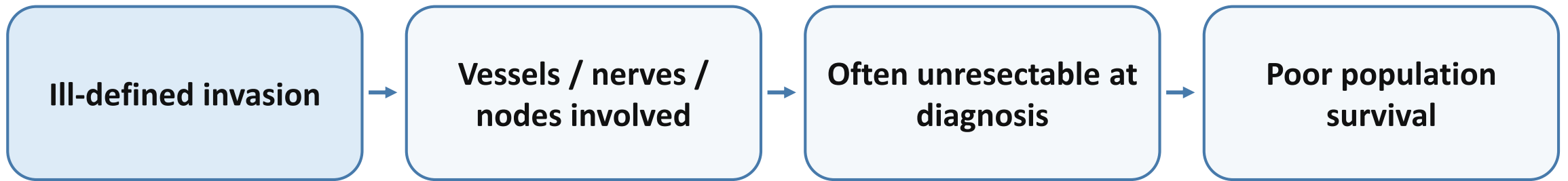
- Longitudinal surveillance may be appropriate
- Consider germline status and family history
- Specialized risk assessment is necessary

Reproduces the textbook framework; Detailed surveillance protocols are not asserted.

Why resection matters

- Advanced disease is usually short-lived after recognition.
- A subset who undergo successful resection may survive substantially longer.
- Anatomic stage and ability to achieve resection are clinically decisive.

Link morphology to clinical outcome



Causal overview—not a formal staging or treatment algorithm.

Case application: Obstructive presentation

Clinical vignette

A 67-year-old develops painless jaundice, a nontender enlarged gallbladder and recent weight loss. Imaging reveals a pancreatic head mass.

Which anatomic mechanism best explains the jaundice?

Discuss the mechanism before revealing the answer in presenter notes.

Case application: A difficult core biopsy

Clinical vignette

A firm pancreatic mass is sampled. The core contains extensive fibrosis and a few atypical glands; Chronic pancreatitis is in the differential.

Which source-described problem makes histologic interpretation difficult?

Discuss the mechanism before revealing the answer in presenter notes.

Case application: Inherited susceptibility

Clinical vignette

A newly diagnosed PDAC patient has several close relatives with cancer. Germline testing detects a pathogenic DNA repair gene variant.

What is the added clinical implication beyond the patient's tumor?

Discuss the mechanism before revealing the answer in presenter notes.

Case application: Screening biomarkers

Clinical vignette

An asymptomatic, average-risk adult requests a screening blood CA19-9 test because a family acquaintance developed PDAC.

What limitation should be explained?

Discuss the mechanism before revealing the answer in presenter notes.

Synthesis: Recognize the pathologic phenotype

- Infiltrative atypical glands plus intense desmoplasia are defining morphologic features.
- Nerve, vessel and peripancreatic tissue invasion reveal the aggressive phenotype.
- Head lesions are more likely to obstruct the distal bile duct.

Synthesis: Connect precursors and mutations

- Microscopic PanIN explains most of the proposed precursor sequence.
- KRAS activation is early and common; Tumor-suppressor loss is cumulative.
- Genetic susceptibility and rare mismatch-repair defects can have family and therapeutic implications.

Synthesis: Clinical decision points

- The prediagnostic interval is often silent.
- Markers and imaging are useful in symptomatic workup or monitoring, not mass screening.
- Inherited high-risk surveillance and assessment of resectability are distinct priorities.

Primary reference and visual provenance

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026). Section: The Pancreas.

Illustrations in this lecture are original editable conceptual PowerPoint schematics. No synthetic microscopy, patient images or textbook figures are presented as clinical evidence.