WHO 5th edition 2019 GIT Blue Book

What's new ??

@CaDxPath

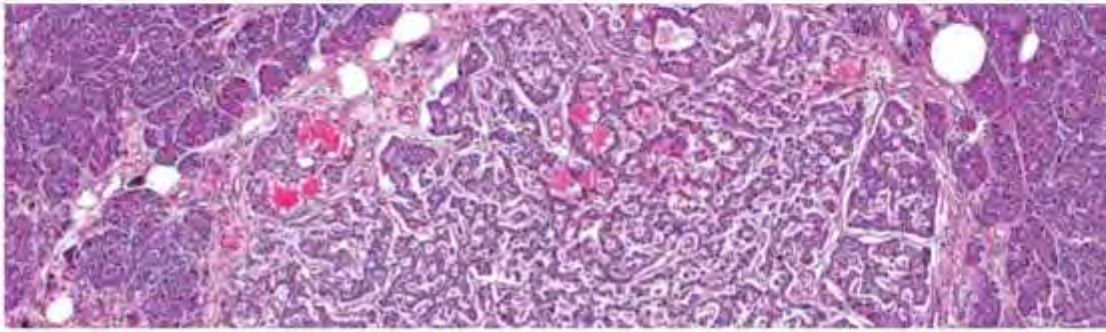
Anthony Gill MD FRCPA

Dr Gill has no conflicts of interest to disclose

International Agency for Research on Cancer

World Health Organization

WHO Classification of Tumours



WHO CLASSIFICATION OF TUMOURS - PUBLICATIONS

Publications - Fifth Edition

The 5th edition commenced in June 2019 with the publication of Digestive System Tumours. T
edition is the first to be led by an editorial board, with standing members and expert members w
closely to evaluate the evidence underpinning the classification of tumours. As in previous editio
books include numerous colour images, which provide the standards needed by pathologists to ur
their diagnoses. In the 5th edition, there is increased emphasis on molecular pathology and ge
Other innovations include standardization of headings within sections, lists of essential diagnostic c
and maps (produced by IARC scientists) illustrating the epidemiology of common tumours.

The 5th editions of Breast Tumours and Soft Tissue and Bone Tumours will be available later in 201

WHO Classification of Tumours of the Digestive System
5th Edition, Volume 1

Edited by the WHO Classification of Tumours Editorial Board
Publication: 2019

More information

https://shop.iarc.fr/collections/all

World Health Organization

IARC E-BOOKSHOP

Search all products... Cart

HOME ORDERING ABOUT US

Home Products

E-BOOKS

Sort by Alphabetically, A-Z

Annual subscription to WHO Classification of Tumours Online

~~€150.00~~ **€100.00**

WHO Classification of Tumours of the Eye (PDF)

€110.00

WHO Classification of Tumours of Female Reproductive Organs (PDF)

€110.00

WHO Classification of Tumours of Soft Tissue and Bone (PDF)

€110.00

WHO Classification of Tumours of the Breast (PDF)

€110.00

WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart (PDF)

€110.00

World Cancer Report 2014 (PDF / EPUB)

FREE

QUICK LINKS

Digital Rights Management (DRM)

Terms of Use

Refund Policy

Privacy Policy

NEWSLETTER

Email Address Sign Up

WHO Classification of Tumours Online

For the first time, WHO Classification of Tumours Online presents the authoritative content of the renowned classification series in a convenient digital format. Now combining the six most recent volumes of the series with whole slide images in a searchable format, WHO Classification of Tumours Online is indispensable for pathologists and cancer specialists worldwide. New volumes will be added regularly, ensuring immediate access to the latest content.

Subscribe now

MEMBER LOGIN

Email address

Password

Log in

Don't have a subscription? Sign up.
Forgot password?

The definitive resource for tumour classification worldwide

The concise and authoritative information that characterizes the print books, enhanced with whole slide images and zoom

Trustworthy content

Compiled and reviewed by an international editorial board

Whole slide images

Digital pathology enhancements

Deep zoom functionality

See images in their full detail

https://tumourclassification.iarc.who.int/home

International Agency for Research on Cancer

World Health Organization

WHO Classification of Tumours

Home | About Us | Contact Us | Search | My Account | Logout

BOOKS CATALOG

Digestive system tumours (5th ed)

Breast tumours (5th ed, beta version)

Endocrine tumours (4th ed)

Eye tumours (4th ed)

Skin tumours (4th ed)

Head and neck tumours (4th ed)

https://tumourclassification.iarc.who.int/chapters/40

Digestive system tumours (5th ed)

Definition:-

Acinar cell carcinoma of the pancreas is a malignant pancreatic epithelial neoplasm showing acinar cell differentiation.

ICD-O coding:

85503 Acinar cell carcinoma

ICD-11 coding:

2C10.0 & XH3P09 Adenocarcinomas of pancreas & Acinar cell carcinoma

Related terminology:

None

Subtype(s):-

Acinar cell cystadenocarcinoma (8551/3); mixed acinar-ductal carcinoma (8552/3); mixed acinar-neuroendocrine carcinoma (8154/3); mixed acinar-ductal-neuroendocrine carcinoma (8154/3)

Localization:-

Acinar cell carcinomas may arise in any portion of the pancreas, but they are most frequent in the head, followed by the tail and the body [23026909 , 27339862]

Clinical features:-

Presenting symptoms are usually related to tumour growth and/or metastatic spread and include weight loss, abdominal pain, vomiting, and nausea. Jaundice can be present but is rare. Patients with extensive metastatic disease may show symptoms due to lipase hypersecretion, which include subcutaneous fat necrosis and polyarthralgia [1304374 , 23026909 , 27339862 , 28137443]. Rare patients, especially when young, can show increased blood levels of AFP [10981264 , 25353355]

Epidemiology:-

Acinar cell carcinomas account for about 1–2% of pancreatic neoplasms in adults and about 15% in children [27339862]. The average age of adult patients is approximately 60 years (range: 26–88 years). Males are more commonly affected, with an M:F ratio of 2.1:1 [23026909 , 27339862 , 12453412]

Etiology:-

Although most acinar cell carcinomas are sporadic, rare cases diagnosed in the context of Lynch syndrome, Carney complex, or familial adenomatous polyposis have been documented [11998286 , 27652078 , 25516281 , 19858001 , 14636255]

Pathogenesis:-

Little is known about the pathogenesis. Although some cytogenetic similarities between acinar cell carcinomas and ductal adenocarcinomas have been observed, the cytogenetic profile is globally different between the two entities. Acinar cell carcinomas show a mutation signature associated with failure to use and defective DNA repair [29155823]. Acinar cell carcinomas show chromosomal instability characterized by high degrees of allelic loss and gains. The regions most frequently involved by losses included 1p, 3p, 5q, 6q, 8p, 9p, 11, 17p, and 18q, whereas the gained regions were mainly 1q, 7, 8q, 12, 17q, and 20q [24291291 , 9382971 , 19862816 , 35398239]. Interestingly, a hierarchical clustering of comparative genomic hybridization findings did not find differences between pure acinar cell carcinomas, cystic acinar cell carcinomas, and mixed acinar-neuroendocrine carcinomas, indicating that these subtypes have the same cytogenetic background [25306229]. MYC alterations, including gene amplification and/or chromosome 8 polysomy, have been described in a subset of acinar cell carcinomas and in all mixed acinar-neuroendocrine carcinomas investigated, but they were not associated with a different prognostic signature [25306229 , 28723493]. Loss of 18q has been correlated with loss or substantial reduction of the protein DCC and has been considered an early step in the development of acinar cell carcinoma [35398239]. Acinar cell carcinomas show low levels of hypermethylation, and no tumours characterized by concerted hypermethylation of multiple loci have been identified. However, some genes, including RASSF1 and APC, are frequently methylated [24568468].

Macroscopic appearance:-

Acinar cell carcinomas are generally well circumscribed, at least partially encapsulated, solid, and large (average diameter: 8–10 cm). They have a homogeneous pink to tan cut surface and are fleshy or even friable in consistency. Haemorrhage and necrosis are not infrequent [1304374 , 23026909 , 27339862]. Acinar cell carcinomas exclusively characterized by variable sized cysts are defined as acinar cell cystadenocarcinomas [10019019].

Histopathology:-

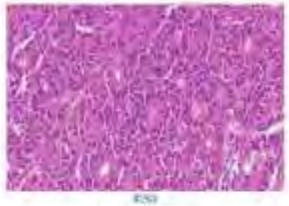
Histologically, acinar cell carcinomas are highly cellular, with scant fibrous stroma showing a lobular pattern of growth and frequent necrosis. The cells have moderate amounts of granular eosinophilic cytoplasm containing zymogen granules, which are PASD-positive. Nuclei are generally uniform and a single prominent nucleolus is characteristic. The mitotic rate is variable but generally high [23026909]. Acinar cell carcinomas may have different architectural features. The acinar pattern is characterized by structures resembling normal acini, sometimes with minute lumina. Cells are distributed in a monolayer, with basally located nuclei. The glandular pattern is characterized by acinar structures with dilated lumina. The trabecular pattern is characterized by ribbons of cells strongly resembling those of pancreatic neuroendocrine tumours (PanNETs). The solid pattern is characterized by large sheets of cells without lumina that can also resemble the appearance of PanNETs. The most frequent patterns are acinar and solid, although a mixture is frequently found within an individual acinar cell carcinoma. In addition, uncommon subtypes including oncocytic, spindle, clear, and pleomorphic cell types have been described [23026909 , 26137845]. Intraductal growth and papillary features are also described [17394477]. The lack of squamoid nests is helpful for the differential diagnosis with pancreatoblastoma (see >>16.3.4>>Pancreatoblastoma), a pancreatic neoplasm showing predominantly acinar differentiation.

Immunohistochemistry plays a key diagnostic role in demonstrating acinar cell differentiation, but antibodies commonly used in routine practice (trypsin, chymotrypsin, lipase, amylase) show different sensitivity [23026909 , 19858001]. The monoclonal antibody directed against the COOH-terminal portion of the BCL10 protein (clone 331.3), which recognizes the COOH-terminal portion of pancreatic carboxyl ester lipase, is highly specific and sensitive in detecting acinar differentiation [19858001]. Amylase is rarely expressed, and lipase antibodies show low sensitivity. Trypsin, chymotrypsin, and BCL10 antibodies are the most sensitive. Simultaneous use of two of them allows the detection of nearly 100% of acinar cell carcinomas [19858001 , 23026909]. Acinar cell carcinomas may also express CK7 and CK19, and are positive for PDX1. Nuclear expression of β-catenin is found in about 10% of cases [23026909]. Markers typically expressed in hepatocellular carcinoma, including AFP, Hep Par-1, glypican-3 (GPC3), and albumin mRNA (by in situ hybridization), can be found in acinar cell carcinomas [21425398]. Scattered neuroendocrine cells positive for chromogranin A and/or synaptophysin can be observed.

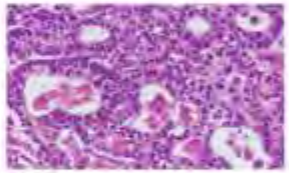
Mixed acinar carcinomas

#200
Acinar cell carcinoma

#201
Acinar cell carcinoma



#203
Acinar cell carcinoma



Definition:-

Acinar cell carcinoma of the pancreas is a malignant pancreatic epithelial neoplasm showing acinar cell differentiation.

ICD-O coding:-

8550/3 Acinar cell carcinoma

ICD-11 coding:-

2C10.0 & XH3PG9 Adenocarcinoma of pancreas & Acinar cell carcinoma

Related terminology:-

None

Subtype(s):-

Acinar cell cystadenocarcinoma (8551/3); mixed acinar-ductal carcinoma (8552/3); mixed acinar neuroendocrine carcinoma (8154/3); mixed acinar-ductal neuroendocrine carcinoma (8154/3)

Localization:-

Acinar cell carcinomas may arise in any portion of the pancreas, but they are most frequent in the head, followed by the tail and the body { 23026929 ; 27320062 }.

Clinical features:-

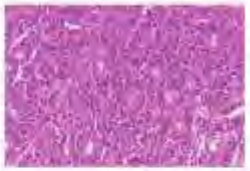
Presenting symptoms are usually related to tumour growth and/or metastatic spread and include weight loss, abdominal pain, vomiting, and nausea. Jaundice can be present but is rare. Patients with extensive metastatic disease may show symptoms due to lipase hypersecretion, which include subcutaneous fat necrosis and polyarthralgia { 1384374 ; 23026929 ; 27320062 ; 26137463 }. Rare patients, especially when young, can show increased blood levels of AFP { 10987254 ; 25353285 }.

Epidemiology:-

Acinar cell carcinomas account for about 1–2% of pancreatic neoplasms in adults and about 15% in children { 27320062 }. The

#260
Acinar cell carcinoma

#261
Acinar cell carcinoma



#263
Acinar cell carcinoma

International Agency for Research on Cancer
World Health Organization
WHO Classification of Tumours

Definition:-

Acinar cell carcinoma of the pancreas is a malignant pancreatic epithelial neoplasm sh

ICD-O coding:-

8550/3 Acinar cell carcinoma

ICD-11 coding:-

2C10.0 & XH3PG9 Adenocarcinoma of pancreas & Acinar cell carcinoma

Related terminology:-

None

Subtype(s):-

Acinar cell cystadenocarcinoma (8551/3); mixed acinar-ductal carcinoma (8552/3); mixed acinar neuroendocrine carcinoma (8154/3); mixed acinar-ductal neuroendocrine carcinoma (8154/3)

Localization:-

Acinar cell carcinomas may arise in any portion of the pancreas, but they are most frequent in the head, followed by the tail and the body { 23026929 ; 27320062 }.

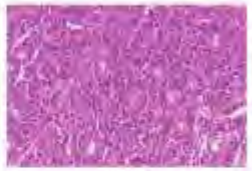
Clinical features:-

Presenting symptoms are usually related to tumour growth and/or metastatic spread and include weight loss, abdominal pain, vomiting, and nausea. Jaundice can be present but is rare. Patients with extensive metastatic disease may show symptoms due to lipase hypersecretion, which include subcutaneous fat necrosis and polyarthralgia { 1384374 ; 23026929 ; 27320062 ; 26137463 }. Rare patients, especially when young, can show increased blood levels of AFP { 10987254 ; 25353285 }.

Epidemiology:-

Acinar cell carcinomas account for about 1–2% of pancreatic neoplasms in adults and about 15% in children { 27320062 }. The

#261
Acinar cell carcinoma



#263
Acinar cell carcinoma

Definition:-

Acinar cell carcinoma of the pancreas is a malignant pancreatic epithelial neoplasm showing acinar cell differentiation.

ICD-O coding:-

8550/3 Acinar cell carcinoma

ICD-11 coding:-

2C10.0 & XH3PG9 Adenocarcinoma of pancreas & Acinar cell carcinoma

Related terminology:-

None

Subtype(s):-

Acinar cell cystadenocarcinoma (8551/3); mixed acinar-ductal carcinoma (8552/3); mixed acinar neuroendocrine carcinoma (8154/3); mixed acinar-ductal neuroendocrine carcinoma (8154/3)

Localization:-

Acinar cell carcinomas may arise in any portion of the pancreas, but they are most frequent in the head, followed by the tail and the body { 23026929 ; 27320062 }.

Clinical features:-

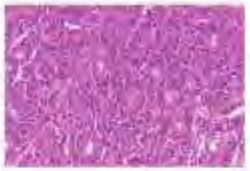
Presenting symptoms are usually related to tumour growth and/or metastatic spread and include weight loss, abdominal pain, vomiting, and nausea. Jaundice can be present but is rare. Patients with extensive metastatic disease may show symptoms due to lipase hypersecretion, which include subcutaneous fat necrosis and polyarthralgia { 1384374 ; 23026929 ; 27320062 ; 26137463 }. Rare patients, especially when young, can show increased blood levels of AFP { 10987254 ; 25353285 }.

Epidemiology:-

Acinar cell carcinomas account for about 1–2% of pancreatic neoplasms in adults and about 15% in children { 27320062 }. The

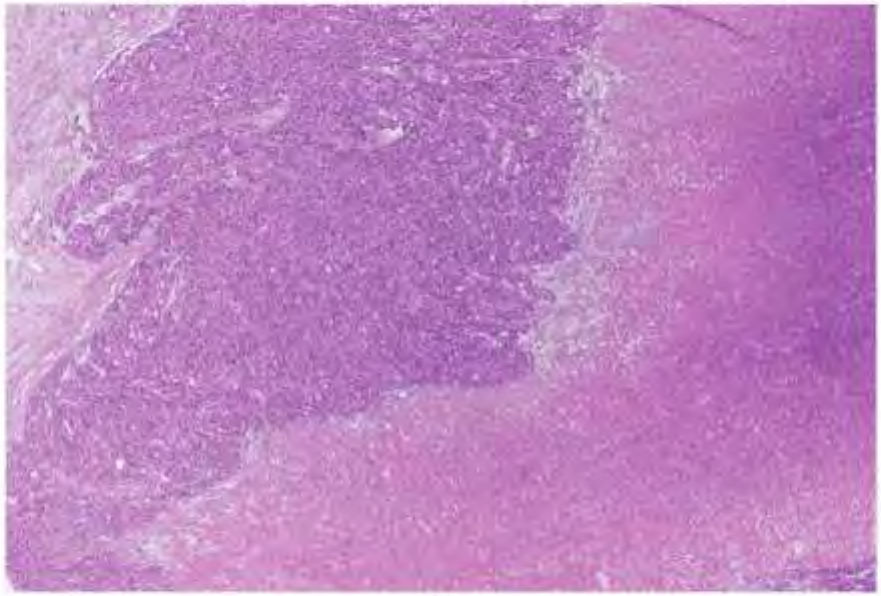
#260
Acinar cell carcinoma

#261
Acinar cell carcinoma



#263
Acinar cell carcinoma

Attachment



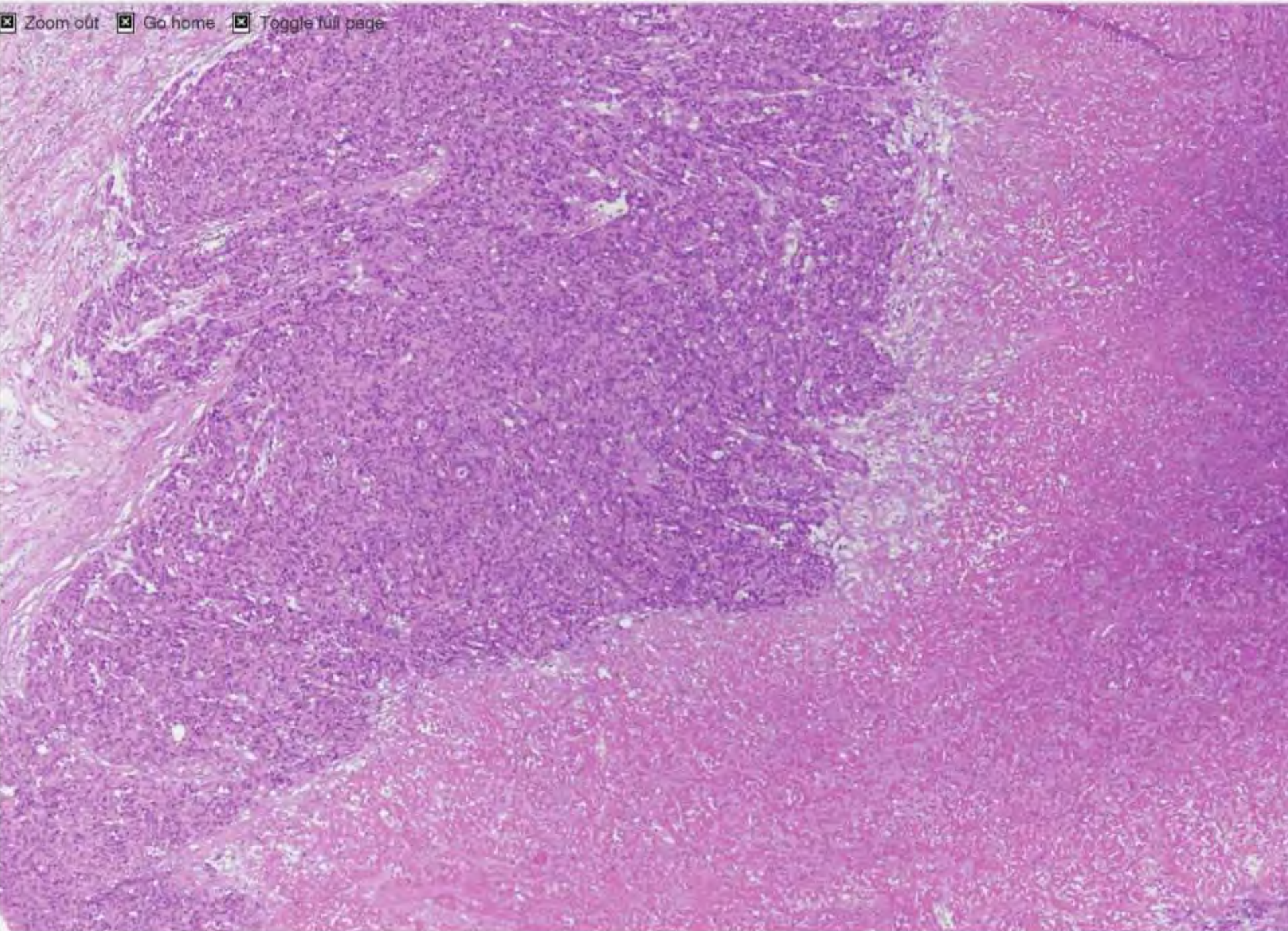
#261

View Original

Diagnosis:
Acinar cell carcinoma

Legend:
At low power, acinar cell carcinoma appears as a highly cellular tumour with scant fibrous stroma showing a lobular pattern of growth and necrosis.

Source:
La Rosa Stefano



Definition:-

Acinar cell carcinoma of the pancreas is a malignant pancreatic epithelial neoplasm showing acinar cell differentiation.

ICD-O coding:-

8550/3 Acinar cell carcinoma

ICD-11 coding:-

2C10.0 & XH3PG9 Adenocarcinoma of pancreas & Acinar cell carcinoma

Related terminology:-

None

Subtype(s):-

Acinar cell cystadenocarcinoma (8551/3); mixed acinar-ductal carcinoma (8552/3); mixed acinar neuroendocrine carcinoma (8154/3); mixed acinar-ductal neuroendocrine carcinoma (8154/3)

Localization:-

Acinar cell carcinomas may arise in any portion of the pancreas, but they are most frequent in the head, followed by the tail and the body { 23026929 ; 27320062 }.

Clinical features:-

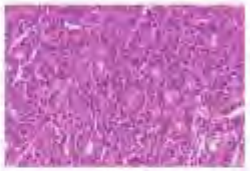
Presenting symptoms are usually related to tumour growth and/or metastatic spread and include weight loss, abdominal pain, vomiting, and nausea. Jaundice can be present but is rare. Patients with extensive metastatic disease may show symptoms due to lipase hypersecretion, which include subcutaneous fat necrosis and polyarthralgia { 1384374 ; 23026929 ; 27320062 ; 26137463 }. Rare patients, especially when young, can show increased blood levels of AFP { 10987254 ; 25353285 }.

Epidemiology:-

Acinar cell carcinomas account for about 1–2% of pancreatic neoplasms in adults and about 15% in children { 27320062 }. The

#260
Acinar cell carcinoma

#261
Acinar cell carcinoma



#263
Acinar cell carcinoma

Definition:-

Serous cystadenoma of the pancreas is a benign epithelial neoplasm composed of uniform cuboidal, glycogen-rich cells that often form cysts containing serous fluid. The diagnosis of malignancy in pancreatic serous neoplasms is restricted to cases with unequivocal distant metastasis beyond the pancreatic/peripancreatic bed.

ICD-O coding:-

8441/0 Serous cystadenoma

8441/3 Serous cystadenocarcinoma

ICD-11 coding:-

2E92.8 & XH8TJ0 Benign neoplasm of pancreas & Serous cystadenoma NOS

2C10.Y & XH7A08 Other specified malignant neoplasms of pancreas & Serous cystadenocarcinoma NOS

Related terminology:-

Serous cystadenoma

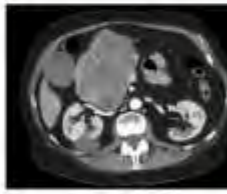
Acceptable: microcystic adenoma; glycogen-rich adenoma; oligocystic ill-demarcated adenoma.

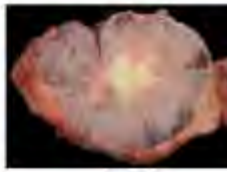
Subtype(s):-

Microcystic serous cystadenoma; macrocystic (oligocystic) serous cystadenoma; solid serous adenoma; von Hippel–Lindau syndrome–associated serous cystic neoplasm; mixed serous-neuroendocrine neoplasm

Localization:-

Serous cystadenomas can occur anywhere in the pancreas, but they arise most frequently (50–75%) in the pancreatic body or tail and are generally solitary { 21468008 ; 22415666 ; 26045140 ; 26559376 }. Unless associated with germline alterations in *VHL*, these neoplasms rarely involve the full length of the pancreas or are multifocal { 22370733 ; 28697137 ; 23543325 }. Serous


#517
Serous cystadenoma


#518
Serous cystadenoma


#520
Serous cystadenoma

Definition:-

Serous cystadenoma of the pancreas is a benign epithelial neoplasm composed of uniform cuboidal, glycogen-rich cells that often form cysts containing serous fluid. The diagnosis of malignancy in pancreatic serous neoplasms is restricted to cases with unequivocal distant metastasis beyond the pancreatic/peripancreatic bed.

ICD-O coding:-

8441/0 Serous cystadenoma

8441/3 Serous cystadenocarcinoma

ICD-11 coding:-

2E92.8 & XH8TJ0 Benign neoplasm of pancreas & Serous cystadenoma NOS

2C10.Y & XH7A08 Other specified malignant neoplasms of pancreas & Serous cystadenocarcinoma NOS

Related terminology:-

Serous cystadenoma

Acceptable: microcystic adenoma; glycogen-rich adenoma; oligocystic ill-demarcated adenoma.

Subtype(s):-

Microcystic serous cystadenoma; macrocystic (oligocystic) serous cystadenoma; solid serous adenoma; von Hippel–Lindau syndrome–associated serous cystic neoplasm; mixed serous-neuroendocrine neoplasm

Localization:-

Serous cystadenomas can occur anywhere in the pancreas, but they arise most frequently (50–75%) in the pancreatic body or tail and are generally solitary { 21468008 ; 22415666 ; 26045140 ; 26559376 }. Unless associated with germline alterations in *VHL*, these neoplasms rarely involve the full length of the pancreas or are multifocal { 22370733 ; 28697137 ; 23543325 }. Serous

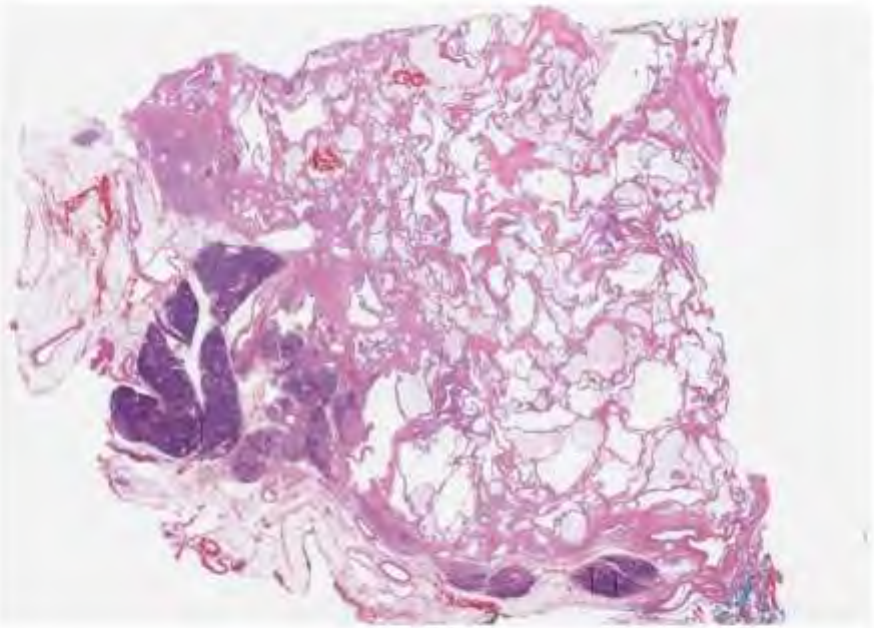
Authors

#526
Serous cystadenoma

#529
Serous cystadenocarcinoma metastatic to the liver

#1205
Serous cystadenoma

Attachment

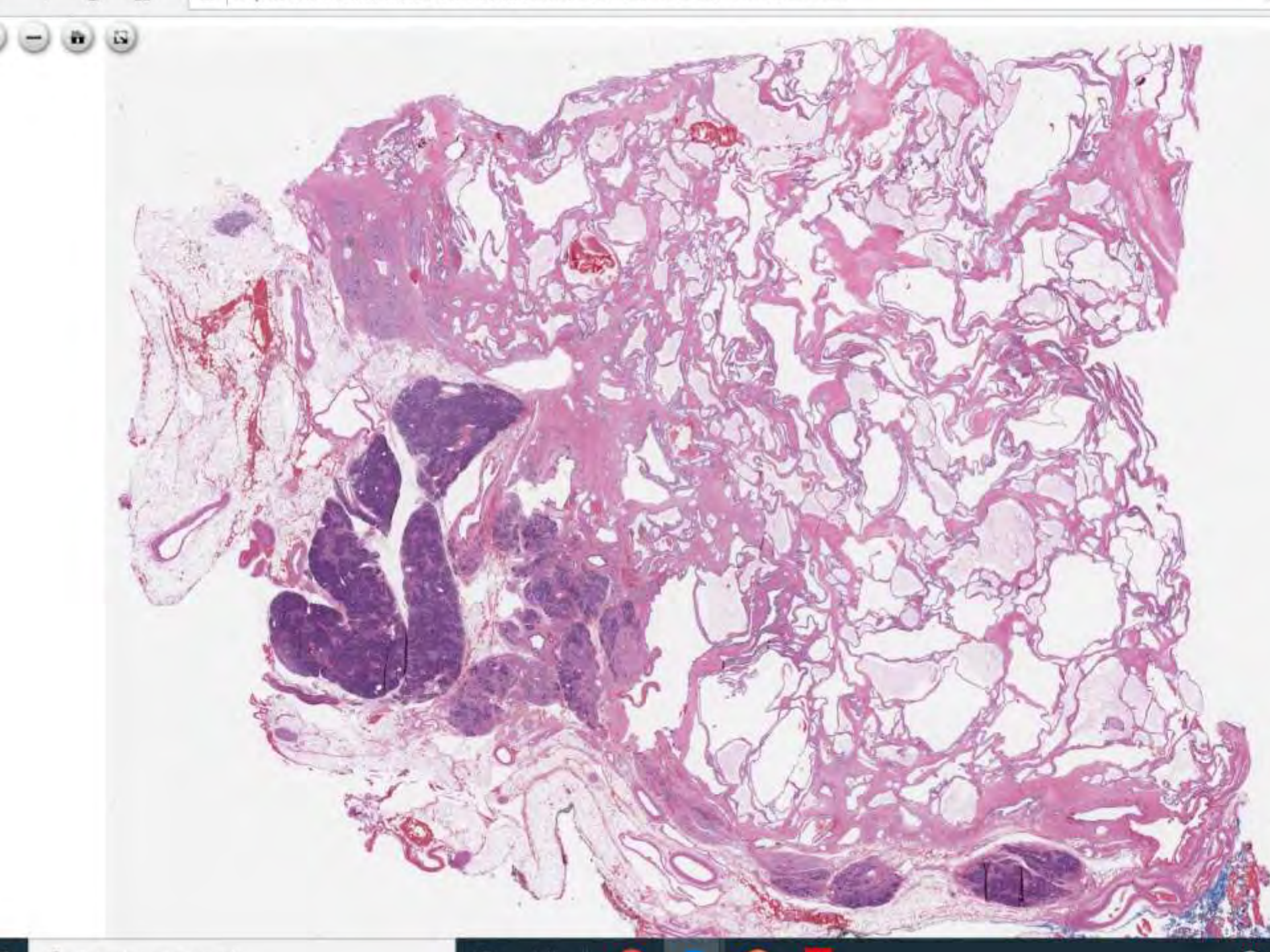


#1205

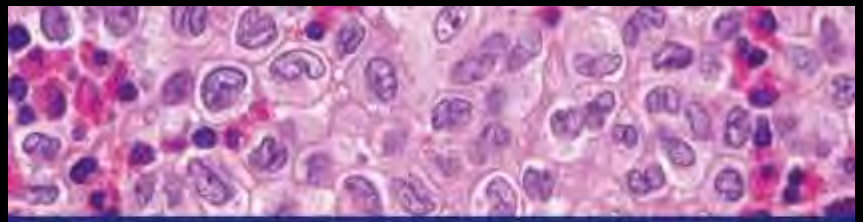
View WSI

Diagnosis:
Serous cystadenoma

Legend:
Microcystic serous cystadenoma consists of numerous tiny cysts lined by a flattened layer of epithelium with rare microscopic papillae that project into the cyst lumen. The cysts contain proteinaceous fluid and are lined by cuboidal epithelium with clear cytoplasm and uniform, round nuclei.



Uniformity Across Blue Books



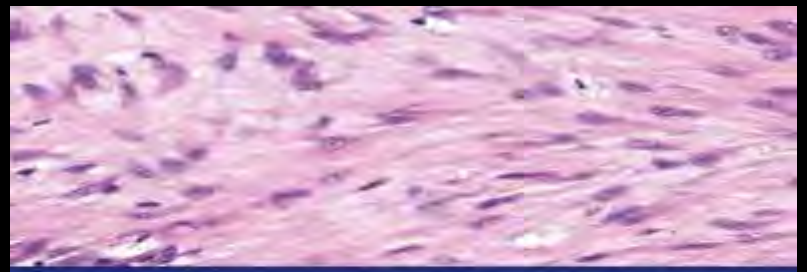
11

Haematolymphoid tumours of the digestive system

Edited by: Chan JKC, Fukayama M

Site-specific haematolymphoid tumours
- MALT lymphoma
- Duodenal-type follicular lymphoma
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Intestinal T-cell lymphoma NOS
- Indolent T-cell lymphoproliferative disorder of the GI tract
- Hepatosplenic T-cell lymphoma
- EBV+ inflammatory follicular dendritic cell sarcoma

Haematolymphoid tumours occurring with some frequency in the digestive system
- Diffuse large B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Burkitt lymphoma
- Plasmablastic lymphoma
- Posttransplant lymphoproliferative disorders
- Extranodal NK/T-cell lymphoma
- Systemic mastocytosis
- Langerhans cell histiocytosis
- Follicular dendritic cell sarcoma
- Histiocytic sarcoma



12

Mesenchymal tumours of the digestive system

Edited by: Fukayama M, Goldblum JR, Lazar AJ, Miettinen M

Gastrointestinal stromal tumour
- Gastrointestinal stromal tumour

Adipose tissue and (myo)fibroblastic tumours
- Inflammatory myofibroblastic tumour
- Desmoid fibromatosis
- Solitary fibrous tumour
- Lipoma
- Inflammatory fibroid polyp
- Plexiform fibromyxoma

Smooth muscle and skeletal muscle tumours
- Leiomyoma
- Leiomyosarcoma
- Rhabdomyosarcoma

Vascular and perivascular tumours
- Haemangioma
- Epithelioid haemangioendothelioma
- Kaposi sarcoma
- Angiosarcoma
- Glomus tumour
- Lymphangioma and lymphangiomatosis

Neural tumours
- Schwannoma
- Granular cell tumour
- Perineurioma
- Ganglioneuroma and ganglioneuromatosis

Tumours of uncertain differentiation
- PEComa, including angiomyolipoma
- Mesenchymal hamartoma of the liver
- Calcifying nested stromal-epithelial tumour of the liver
- Synovial sarcoma
- Gastrointestinal clear cell sarcoma / malignant gastrointestinal neuroectodermal tumour
- Embryonal sarcoma of the liver

Definition:-

Serous cystadenoma of the pancreas is a benign epithelial neoplasm composed of uniform cuboidal, glycogen-rich cells that often form cysts containing serous fluid. The diagnosis of malignancy in pancreatic serous neoplasms is restricted to cases with unequivocal distant metastasis beyond the pancreatic/peripancreatic bed.

ICD-O coding:-

8441/0 Serous cystadenoma

8441/3 Serous cystadenocarcinoma

ICD-11 coding:-

2E92.3 & XH8TJ0 Benign neoplasm of pancreas & Serous cystadenoma NOS

2C10.Y & XH7A08 Other specified malignant neoplasms of pancreas & Serous cystadenocarcinoma NOS

Related terminology:-

Serous cystadenoma

Acceptable: microcystic adenoma; glycogen-rich adenoma; oligocystic ill-demarcated adenoma.

Subtype(s):-

Microcystic serous cystadenoma; macrocystic (oligocystic) serous cystadenoma; solid serous adenoma; von Hippel–Lindau syndrome–associated serous cystic neoplasm; mixed serous-neuroendocrine neoplasm

Localization:-

Serous cystadenomas can occur anywhere in the pancreas, but they arise most frequently (50–75%) in the pancreatic body or tail and are generally solitary { 21468008 ; 22415666 ; 26045140 ; 26559376 }. Unless associated with germline alterations in *VHL*, these neoplasms rarely involve the full length of the pancreas or are multifocal { 22370733 ; 28697137 ; 23543325 }. Serous

#526
Serous cystadenoma

#529
Serous cystadenocarcinoma metastatic to the liver

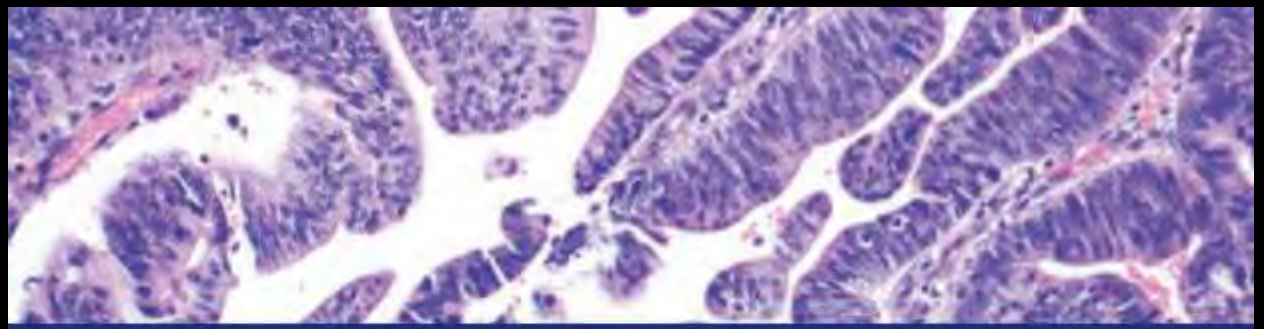
#1205
Serous cystadenoma

What's new ??

@CaDxPath

Anthony Gill MD FRCPA

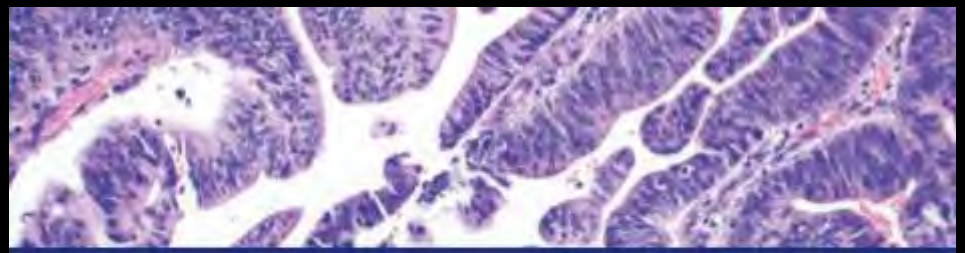
Dr Gill has no conflicts of interest to disclose



4

Tumours of the small intestine and ampulla

Edited by: Klimstra DS, Nagtegaal ID, Rugge M, Salto-Tellez M



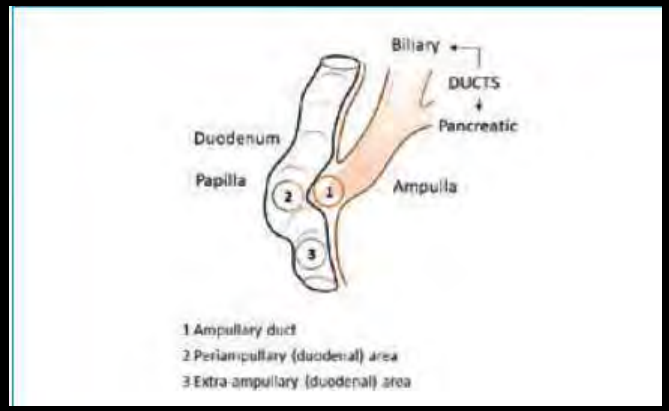
4

Tumours of the small intestine and ampulla

Edited by: Klimstra DS, Nagtegaal ID, Rugge M, Salto-Tellez M

Benign epithelial tumours and precursors
- Non-ampullary adenoma
- Ampullary adenoma

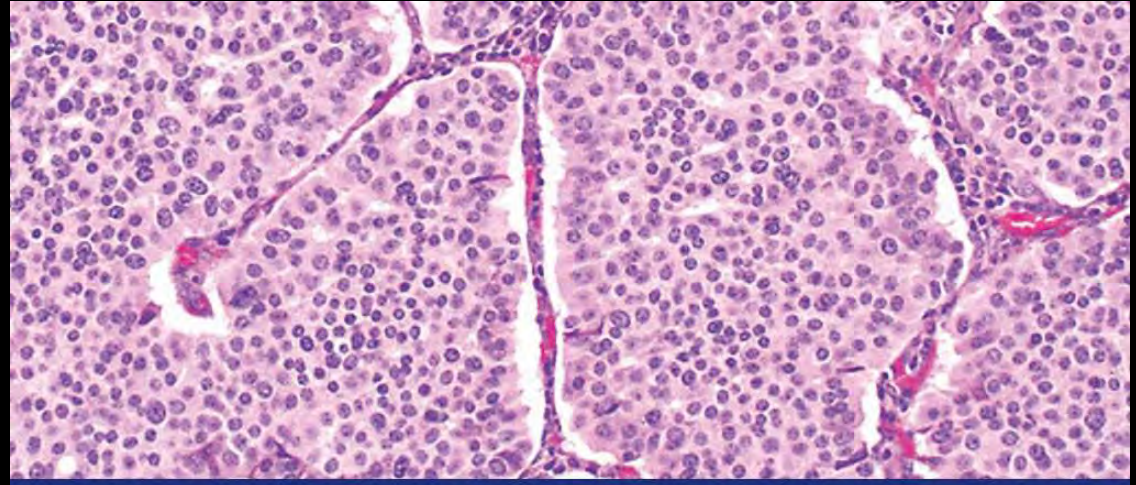
Malignant epithelial tumours
- Non-ampullary adenocarcinoma
- Ampullary adenocarcinoma
- Neuroendocrine neoplasms



The nomenclature in lesions from pancreatic and biliary ducts, the term “intra-ampullary papillary-tubular neoplasm” is now used for preinvasive neoplasms (adenomas and non-invasive papillary neoplasms) occurring almost exclusively within the ampulla. Fundamentally, these are intra-ampullary versions of intraductal papillary neoplasms or intraductal tubulopapillary neoplasms of the pancreas and bile ducts.

For intestinal adenomas that arise (and grow) predominantly on the duodenal surface of the ampulla (“periampullary duodenum”), the term “adenoma” (of intestinal phenotypes) is retained, in parallel with the terminology used in the intestinal tract .

In the section on ampullary adenocarcinoma, we adopt the classification of ampullary carcinomas into four anatomically based subtypes, which also have some degree of histological correlation: intra-ampullary papillary-tubular neoplasm–associated carcinoma (carcinomas arising from intraluminal-growing preinvasive neoplasms), ampullary-ductal carcinoma (arising and growing along the walls of intra-ampullary ducts), (peri)ampullary-duodenal carcinoma (growing on the duodenal surface of the ampulla), and ampullary carcinoma NOS.
This subdivision is driven by the anatomical complexity at that site and also affects the difficulty in tumour staging



10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

- Benign epithelial tumours and precursors
  - Acinar cystic transformation
  - Serous neoplasms
  - Intraepithelial neoplasia
  - Intraductal papillary mucinous neoplasm
  - Intraductal oncocytic papillary neoplasm
  - Intraductal tubulopapillary neoplasm
  - Mucinous cystic neoplasm
- Malignant epithelial tumours
  - Ductal adenocarcinoma
  - Acinar cell carcinoma
  - Pancreatoblastoma
  - Solid pseudopapillary neoplasm
- Neuroendocrine neoplasms
  - Non-functioning neuroendocrine tumours
  - Functioning neuroendocrine tumours
    - Insulinoma
    - Gastrinoma
    - VIPoma
    - Glucagonoma
    - Somatostatinoma
    - ACTH-producing neuroendocrine tumour
    - Serotonin-producing neuroendocrine tumour
  - Neuroendocrine carcinoma
  - MiNENs

WHO 2010 Grading System

World Health Organization Classification 2010 for Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	≤ 2 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3*	>20 %	>20/10 HPF
Mixed adenoneuroendocrine carcinoma (MANEC)		

*"NET G3" has been used for this category but is not advised since NETs are by definition well differentiated

WHO 2017 Grading System

World Health Organization Classification 2010 for Neuroendocrine Neoplasms

Well differentiated NENs	<3%	**Mitotic index**
Neuroendocrine tumour (NET) G1		<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20%	>20/10 HPF
POORLY DIFFERENTIATED NENs		
Neuroendocrine Carcinoma (NEC) G3	>20%	>20/10 HPF

MENEN (mixed endocrine neuroendocrine carcinoma)

*"NET G3" has been used for this category but is not advised since NETs are by definition well differentiated

WHO 2017 Grading System

TABLE 1

World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index*|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	<3 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20 %	>20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3	>20 %	>20/10 HPF
Small cell type		
Large cell type		

Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)

* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm^2) in areas of higher density and expressed per 10 HPF (2.0 mm^2); the final grade based on which ever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation ("eyeballing") is not recommended; manual counting of printed images is suggested {25412850}.

WHO 2019 Grading System for NETs

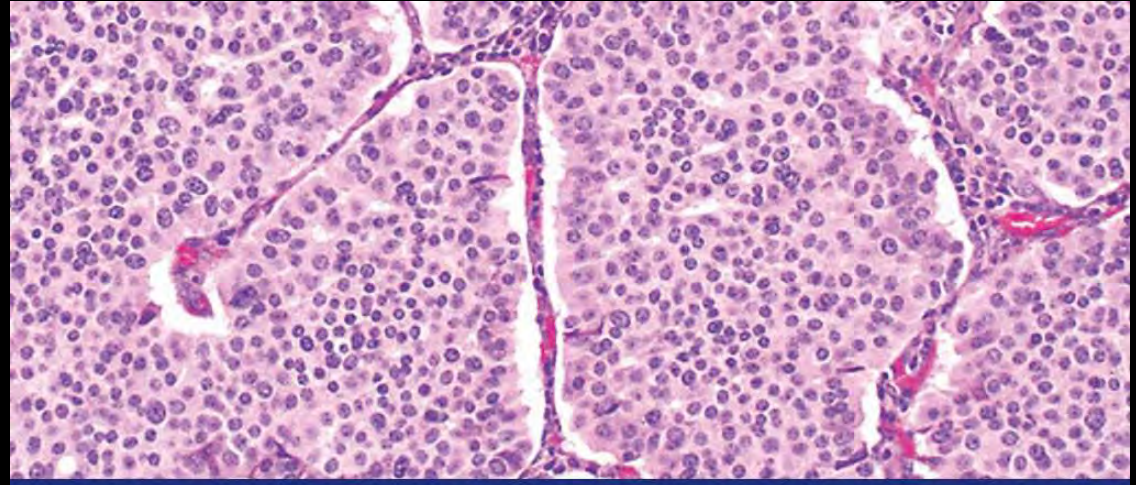
TABLE 1

World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index*|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	<3 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20 %	>20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC)	>20 %	>20/10 HPF
Small cell type		
Large cell type		

Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)

* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm^2) in areas of higher density and expressed per 10 HPF (2.0 mm^2); the final grade based on which ever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation ("eyeballing") is not recommended; manual counting of printed images is suggested {25412850}.



10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

- Benign epithelial tumours and precursors
  - Acinar cystic transformation
  - Serous neoplasms
  - Intraepithelial neoplasia
  - Intraductal papillary mucinous neoplasm
  - Intraductal oncocytic papillary neoplasm
  - Intraductal tubulopapillary neoplasm
  - Mucinous cystic neoplasm
- Malignant epithelial tumours
  - Ductal adenocarcinoma
  - Acinar cell carcinoma
  - Pancreatoblastoma
  - Solid pseudopapillary neoplasm
- Neuroendocrine neoplasms
  - Non-functioning neuroendocrine tumours
  - Functioning neuroendocrine tumours
    - Insulinoma
    - Gastrinoma
    - VIPoma
    - Glucagonoma
    - Somatostatinoma
    - ACTH-producing neuroendocrine tumour
    - Serotonin-producing neuroendocrine tumour
  - Neuroendocrine carcinoma
  - MiNENs

Acinar Cystic Transformation

10.1.1

Acinar cystic transformation of the pancreas

Singhi AD
Adsay NV
Hruban N
Terris B

Definition
Acinar cystic transformation of the pancreas is a non-neoplastic cystic lesion lined by benign-appearing acinar and ductal epithelium

ICD-O coding
None

ICD-11 coding
2E92.6 Benign neoplasm of pancreas

Related terminology
Acceptable: acinar cell cystadenoma

Subtype(s)
None

Localization
These lesions can occur throughout the pancreas, but they are more common in the pancreatic head; some diffusely involve the entire gland [3734,1566,3061,3559].

Clinical features
Fewer than 50 cases have been described, with a mean age at presentation of 43 years (range 9–83 years) and a female predominance of 3:1 [3734,97,569,685,1651,2102,3588,1566,3061,3509,3759]. Cases are divided into two categories: clinically recognized macroscopic lesions and incidental microscopic findings. Patients with macroscopic lesions may present with abdominal pain, dyspepsia, and/or a palpable mass, but a substantial proportion are asymptomatic [1566,3061,3509,3759]. Incidental cases are only detected upon pathological review of pancreata removed for other indications.

Epidemiology
Unknown

Etiology
The etiology is unknown, but some cases may occur because of obstruction [3759].

Pathogenesis
Recent evidence suggests that this lesion represents a non-neoplastic dilatation of the acinar and ductal epithelium [3061,307]. Chromosomal gains, but not losses, were reported for one case by array comparative genomic hybridization and suggest a possible neoplastic process [1566]. However, a subsequent study found a random X-chromosome inactivation pattern for 5 cases, which would support these lesions as non-neoplastic [3061]. Unlike in pancreatic ductal adenocarcinoma and its cystic precursor neoplasms, alterations in *KRAS*, *GNAS*, *RNF43*, *TP53*, *CDKN2A*, and *SMAD4* have not been reported in these lesions [3059].

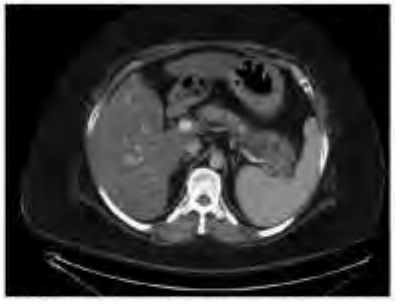
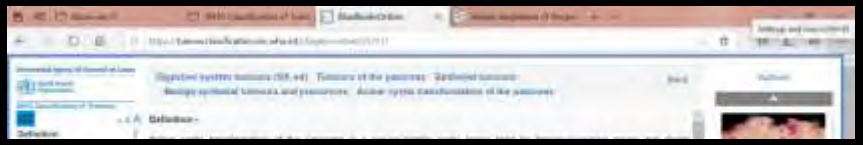


Fig. 10.XX Acinar cystic transformation. CT of an acinar cystic transformation involving the pancreatic tail.

Fig. 10.XX Acinar cystic transformation. With multilocular lesions involving the entire length of the pancreas.

Macroscopic appearance
Clinically recognized lesions measure 1.5–19.7 cm (mean 5.8 cm) in diameter and form multilocular or unilocular cystic masses [3588,1566,3061,3559]. Multicentricity is common and may diffusely involve the entire gland. The cyst wall is typically thin, smooth and translucent, and filled with clear watery fluid. Incidentally detected cases are usually < 1.0 cm and unilocular, and they may not be apparent grossly. Communication with the main pancreatic duct is rare.

Acinar Cystic Transformation



10.11

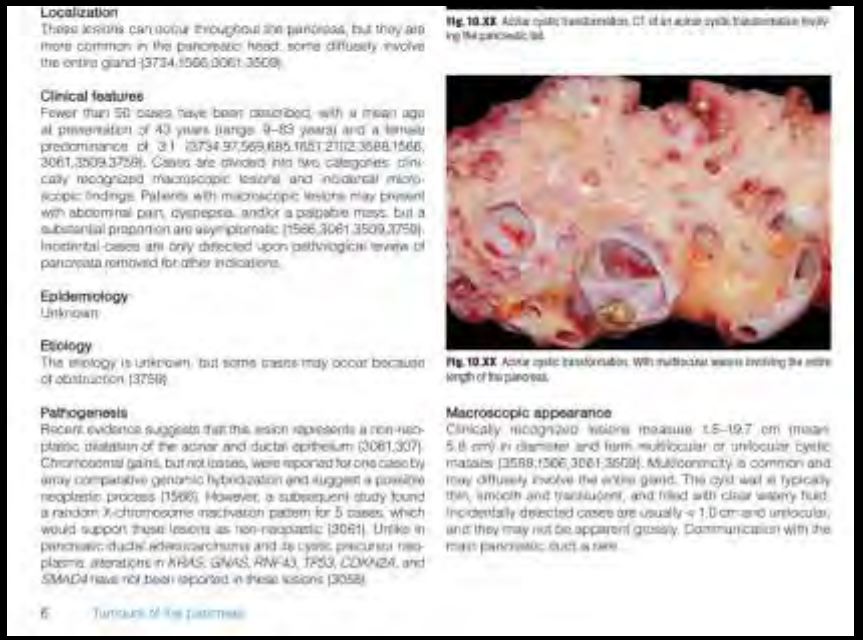
Acinar cystic transformation of the pancreas

Singh AD
Adsay NV
Hruban N
Terris B

Definition
Acinar cystic transformation of the pancreas is a non-neoplastic cystic lesion lined by benign-appearing acinar and ductal epithelium

ICD-O coding
None

Acinar cystic transformation of the pancreas is a non-neoplastic cystic lesion lined by benign-appearing acinar and ductal epithelium



Localization
These lesions can occur throughout the pancreas, but they are more common in the pancreatic head, some diffusely involve the entire gland [3734,1566,3061,3509].

Clinical features
Fewer than 50 cases have been described, with a mean age at presentation of 43 years (range 9–83 years) and a female predominance of 3:1 [3734,97,569,685,1651,2112,3588,1566, 3061,3509,3759]. Cases are divided into two categories: clinically recognized macroscopic lesions and incidental microscopic findings. Patients with macroscopic lesions may present with abdominal pain, dyspepsia, and/or a palpable mass, but a substantial proportion are asymptomatic [1566,3061,3509,3759]. Incidental cases are only detected upon pathological review of pancreata removed for other indications.

Epidemiology
Unknown

Etiology
The etiology is unknown, but some cases may occur because of obstruction [3759].

Pathogenesis
Recent evidence suggests that this lesion represents a non-neoplastic dilatation of the acinar and ductal epithelium [3061,307]. Chromosomal gains, but not losses, were reported for one case by array comparative genomic hybridization and suggest a possible neoplastic process [1566]. However, a subsequent study found a random X-chromosome inactivation pattern for 5 cases, which would support these lesions as non-neoplastic [3061]. Unlike in pancreatic ductal adenocarcinoma and its cystic precursor neoplasms, alterations in *KRAS*, *GNAS*, *RNF43*, *TP53*, *CDKN2A*, and *SMAD4* have not been reported in these lesions [3059].

Fig. 10.XX Acinar cystic transformation. CT of an acinar cystic transformation involving the pancreatic tail.

Fig. 10.XX Acinar cystic transformation. With multilocular lesions involving the entire length of the pancreas.

Macroscopic appearance
Clinically recognized lesions measure 1.5–19.7 cm (mean 5.8 cm) in diameter and form multilocular or unilocular cystic masses [3588,1566,3061,3509]. Multilocularity is common and may diffusely involve the entire gland. The cyst wall is typically thin, smooth and translucent, and filled with clear watery fluid. Incidentally detected cases are usually < 1.0 cm and unilocular, and they may not be apparent grossly. Communication with the main pancreatic duct is rare.

Definition:-

Acinar cystic transformation of the pancreas is a non-neoplastic cystic lesion lined by benign-appearing acinar and ductal epithelium.

ICD-O coding:-

None

ICD-11 coding:-

DC30.0 Cyst of pancreas

Related terminology:-

Acceptable: acinar cell cystadenoma.

Subtype(s):-

None

Localization:-

These lesions can occur throughout the pancreas, but they are more common in the pancreatic head; some diffusely involve the entire gland { 12023573 ; 23060352 ; 24076773 ; 27086062 }.

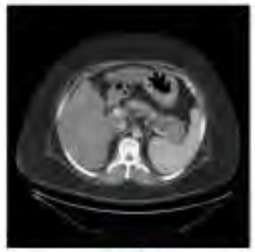
Clinical features:-

Fewer than 50 cases have been described, with a mean age at presentation of 43 years (range: 9–83 years) and a female predominance of 3:1 { 12023573 ; 12004359 ; 12162680 ; 12483157 ; 10721803 ; 20438912 ; 23605178 ; 23060352 ; 24076773 ; 27086062 ; 28599853 }. Cases are divided into two categories: clinically recognized macroscopic lesions and incidental microscopic findings. Patients with macroscopic lesions may present with abdominal pain, dyspepsia, and/or a palpable mass, but a substantial proportion are asymptomatic { 23060352 ; 24076773 ; 27086062 ; 28599853 }. Incidental cases are only detected upon pathological review of pancreata removed for other indications.

Epidemiology:-

Authors

#504
Acinar cystic transformation



#1019
Acinar cystic transformation

#1204
Acinar cystic transformation of the pancreas

Digestive syster
Benign epithe

Definition:-

Acinar cystic tran
epithelium

ICD-O coding:-

None

ICD-11 coding:-

DC30.0 Cyst of pa

Related terminolo

Acceptable: acinar

Subtype(s):-

None

Localization:-

These lesions can
entire gland (1202

Clinical features:-

Fewer than 50 ca
predominance of 3
27086062 ; 285998
findings. Patients v
proportion are as
pathological review

Epidemiology:-

Brick

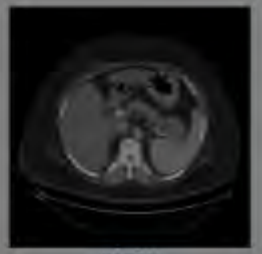
inar and ductal

sely involve the

) and a female
52 ; 24076773 ;
ntal microscopic
ut a substantial
detected upon

Authors

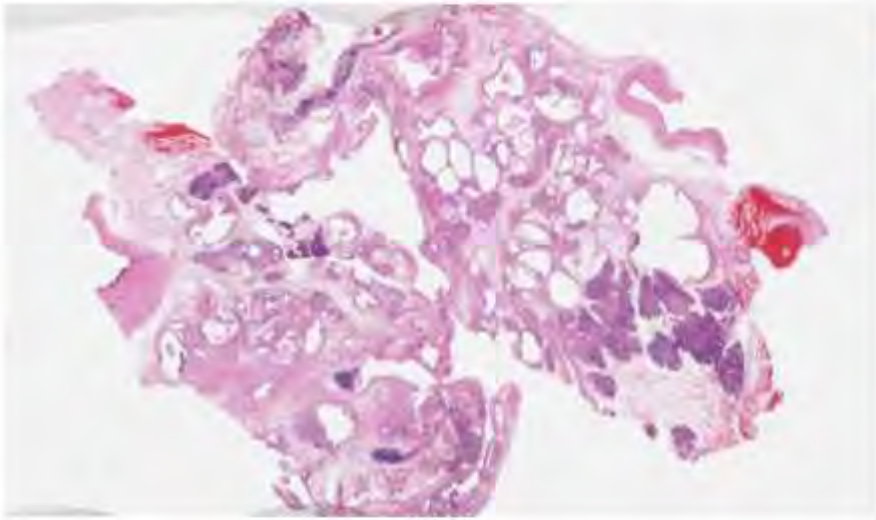
#504
Acinar cystic transformation



#1019
Acinar cystic transformation

#1204
Acinar cystic transformation of the pancreas

Attachment



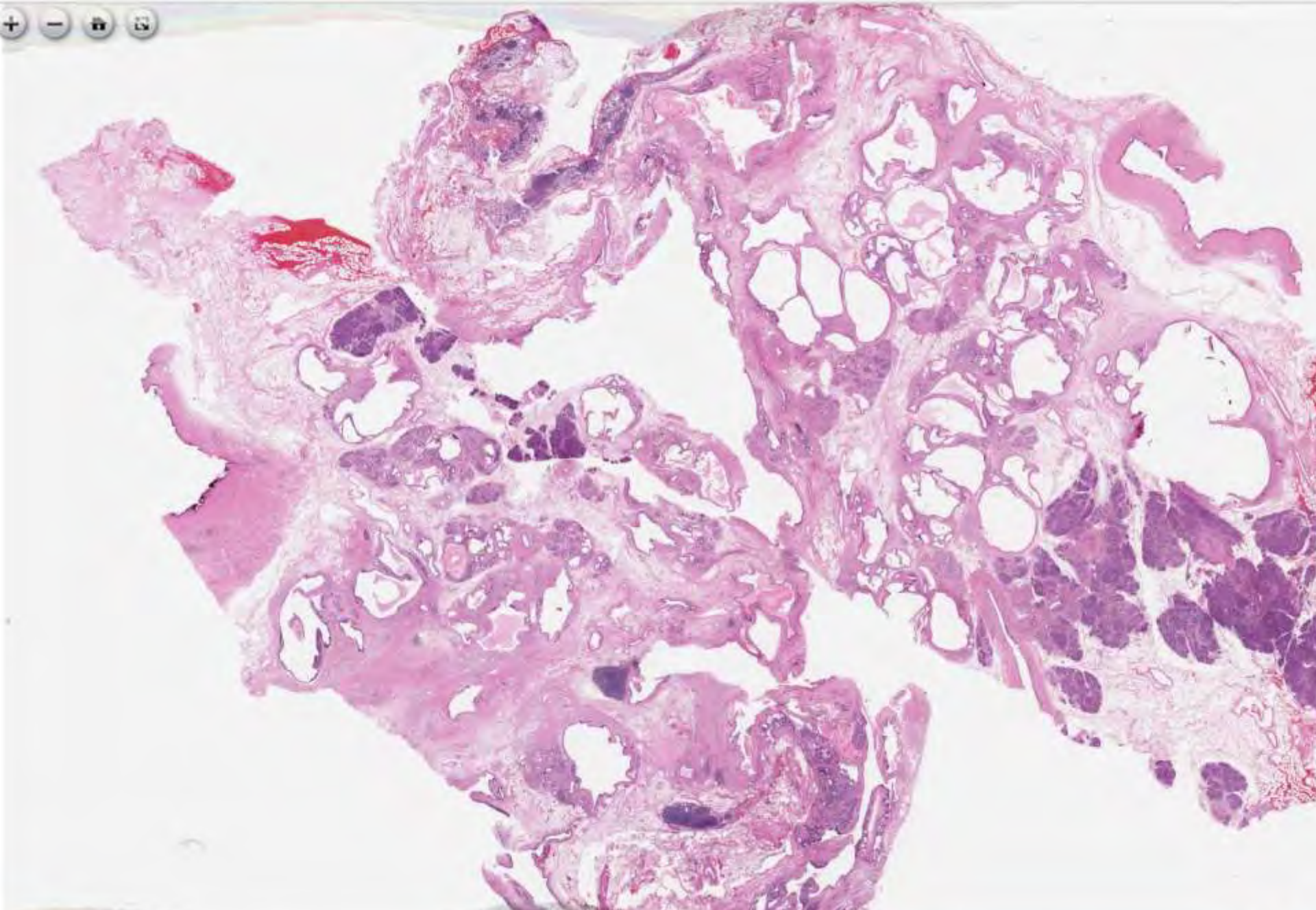
#1204

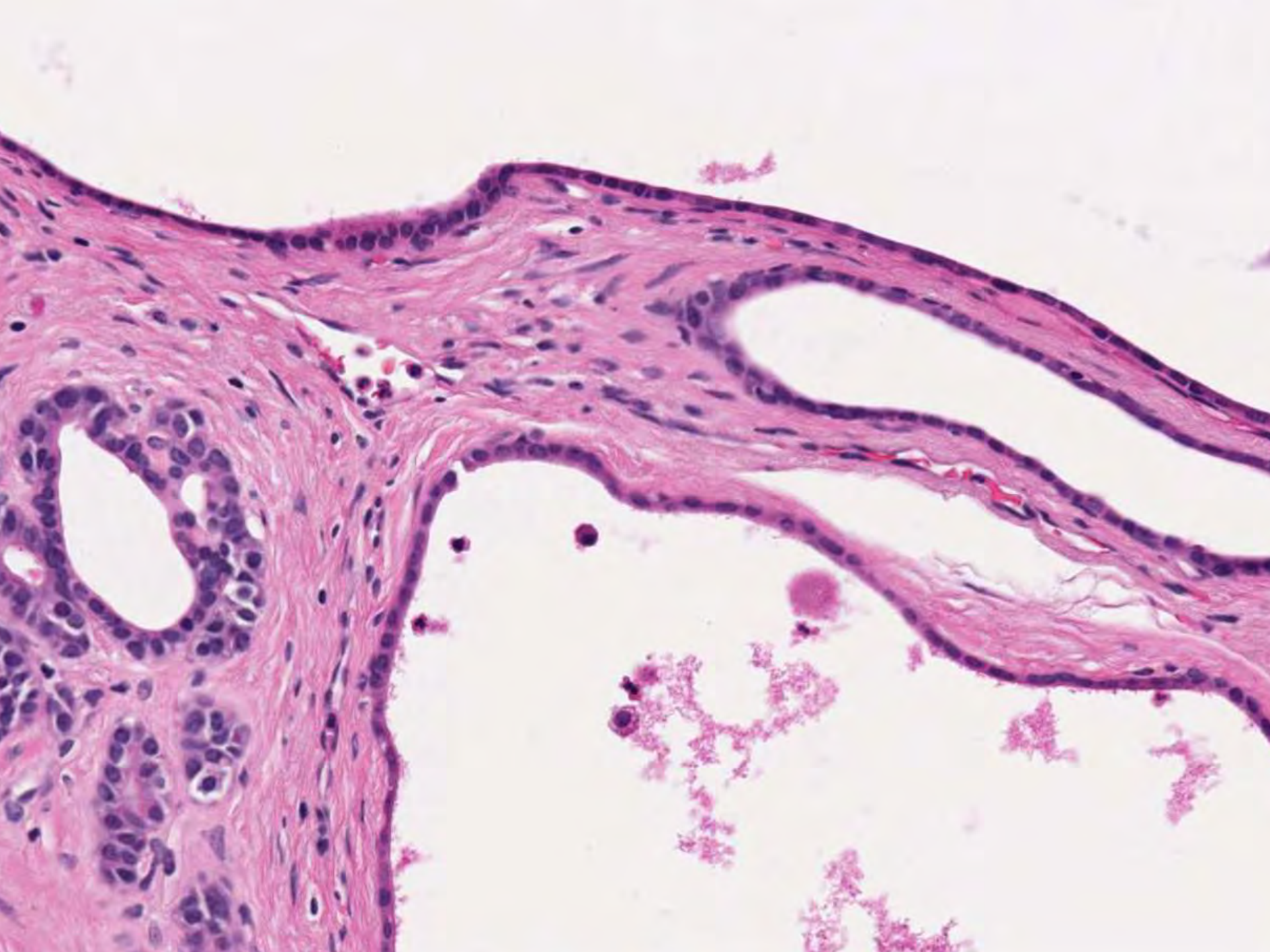
View WSI

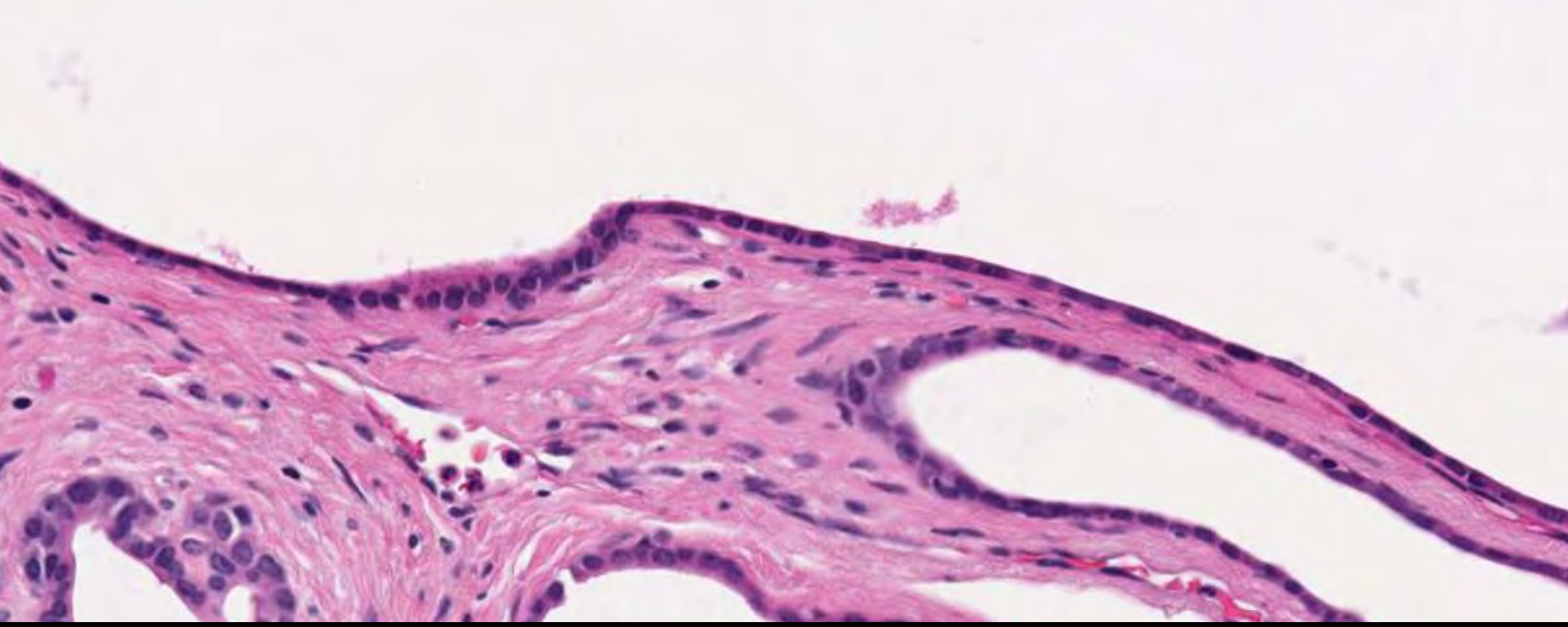
Diagnosis:
Acinar cystic transformation of the pancreas

Legend:
Multilocular acinar cystic transformation consists of variably sized cysts with incomplete septa that appear as broad papillary projections and are surrounded by fibrotic and atrophic pancreatic parenchyma.

Source:
Singhi Aatur D

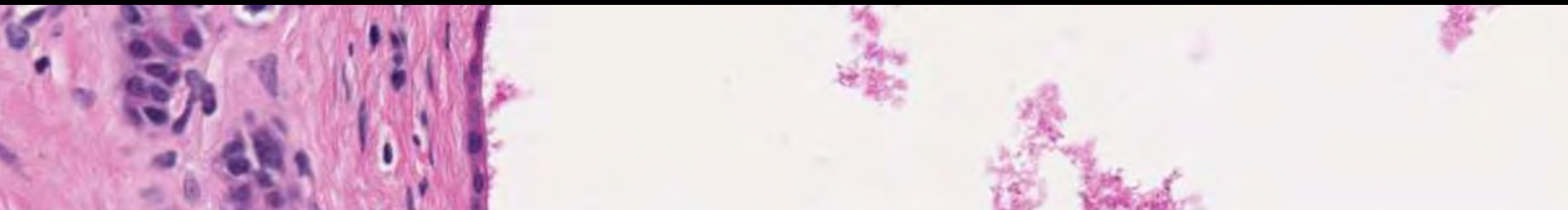






includes serous cystadenomas (pariculatly diffuse type associated with VHL), squamoid
of the pancreatic ducts, intraductal papillary mucinous neoplasms, and mucinous cystic
asms.

recognition of both acinar and ductal differentiation by morphology and IHC
in, chymotrypsin, BCL10, CK19)



10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

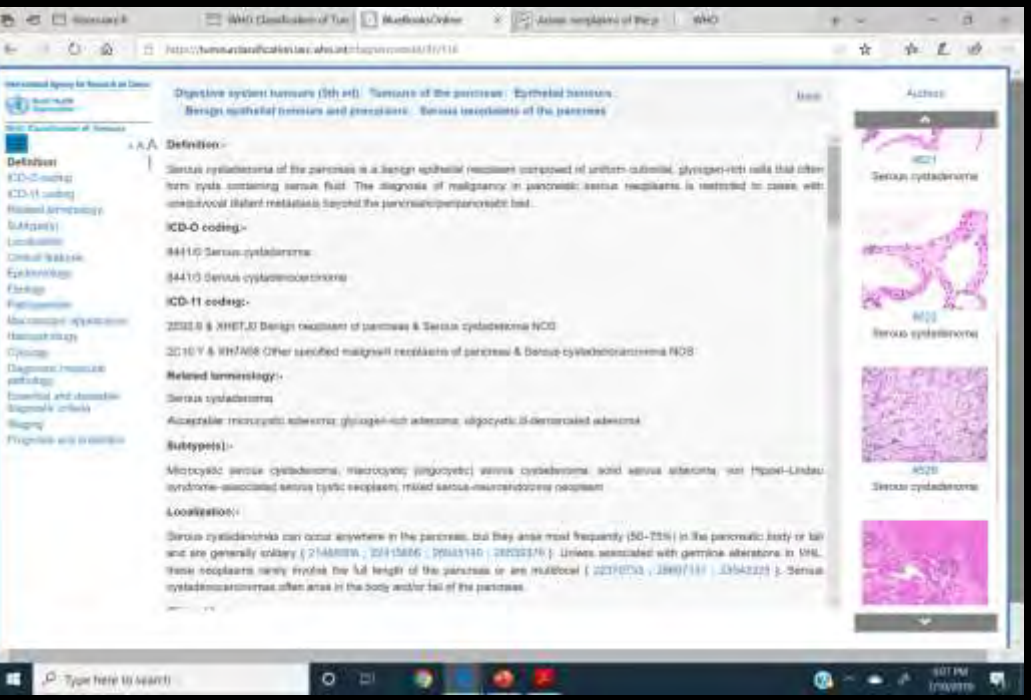
Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

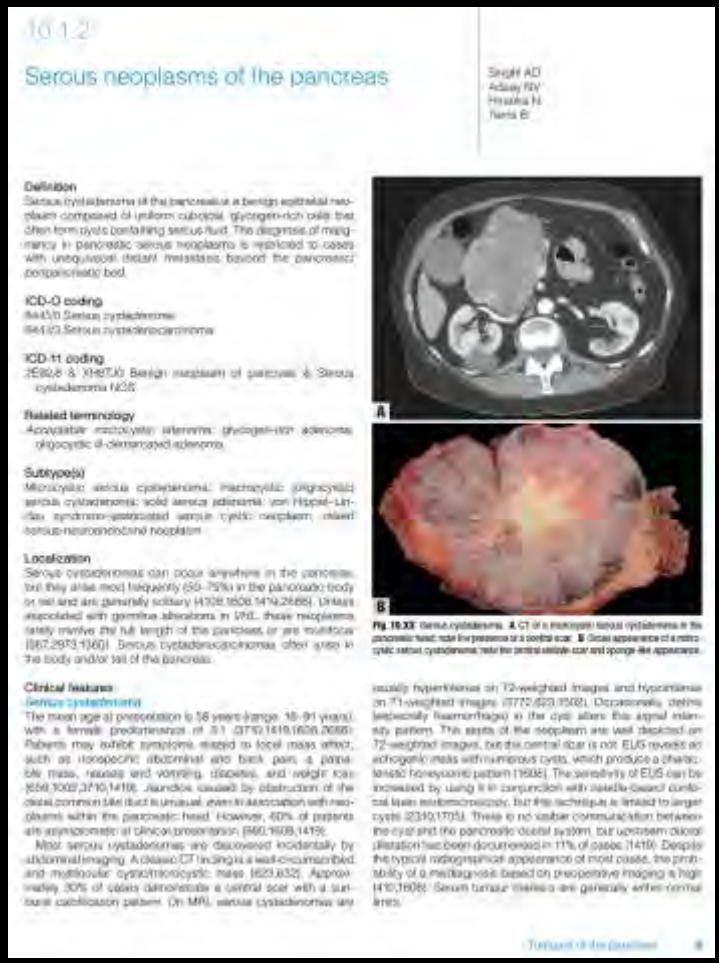
Benign epithelial tumours and precursors
- Acinar cystic transformation
- Serous neoplasms
- Intraepithelial neoplasia
- Intraductal papillary mucinous neoplasm
- Intraductal oncocytic papillary neoplasm
- Intraductal tubulopapillary neoplasm
- Mucinous cystic neoplasm

Malignant epithelial tumours
- Ductal adenocarcinoma
- Acinar cell carcinoma
- Pancreatoblastoma
- Solid pseudopapillary neoplasm

Neuroendocrine neoplasms
- Non-functioning neuroendocrine tumours
- Functioning neuroendocrine tumours
  - Insulinoma
  - Gastrinoma
  - VIPoma
  - Glucagonoma
  - Somatostatinoma
  - ACTH-producing neuroendocrine tumour
  - Serotonin-producing neuroendocrine tumour
- Neuroendocrine carcinoma
- MiNENs

Serous Cystadenoma (serous neoplasms)





Definition:-

Serous cystadenoma of the pancreas is a benign epithelial neoplasm composed of uniform cuboidal, glycogen-rich cells that often form cysts containing serous fluid. The diagnosis of malignancy in pancreatic serous neoplasms is restricted to cases with unequivocal distant metastasis beyond the pancreatic/peripancreatic bed.

ICD-O coding:-

8441/0 Serous cystadenoma

8441/3 Serous cystadenocarcinoma

ICD-11 coding:-

2E92.8 & XH8TJ0 Benign neoplasm of pancreas & Serous cystadenoma NOS

2C10.Y & XH7A08 Other specified malignant neoplasms of pancreas & Serous cystadenocarcinoma NOS

Related terminology:-

Serous cystadenoma

Acceptable: microcystic adenoma; glycogen-rich adenoma; oligocystic ill-demarcated adenoma.

Subtype(s):-

Microcystic serous cystadenoma; macrocystic (oligocystic) serous cystadenoma; solid serous adenoma; von Hippel–Lindau syndrome–associated serous cystic neoplasm; mixed serous-neuroendocrine neoplasm

Localization:-

Serous cystadenomas can occur anywhere in the pancreas, but they arise most frequently (50–75%) in the pancreatic body or tail and are generally solitary { 21468008 ; 22415666 ; 26045140 ; 26559376 }. Unless associated with germline alterations in *VHL*, these neoplasms rarely involve the full length of the pancreas or are multifocal { 22370733 ; 28697137 ; 23543325 }. Serous cystadenocarcinomas often arise in the body and/or tail of the pancreas.

#518
Serous cystadenoma

#520
Serous cystadenoma

#521
Serous cystadenoma

Definition:-

Serous cystadenoma of the pancreas is a benign epithelial neoplasm composed of uniform cuboidal, glycogen-rich cells that often form cysts containing serous fluid. The diagnosis of malignancy in pancreatic serous neoplasms is restricted to cases with unequivocal distant metastasis beyond the pancreatic/p

/0 means benign

ICD-O coding:-

8441/0 Serous cystadenoma

8441/3 Serous cystadenocarcinoma

/3 means malignant

ICD-11 coding:-

2E92.8 & XH8TJ0 Benign neoplasm of pancreas &

2C10.Y & XH7A08 Other specified malignant neoplasms of pancreas & Serous cystadenocarcinoma NOS

Related terminology:-

Serous cystadenoma

Acceptable: microcystic adenoma; glycogen-rich adenoma; oligocystic ill-demarcated adenoma.

Subtype(s):-

Microcystic serous cystadenoma; macrocystic (oligocystic) serous cystadenoma; solid serous adenoma; von Hippel–Lindau syndrome–associated serous cystic neoplasm; mixed serous-neuroendocrine neoplasm

Localization:-

Serous cystadenomas can occur anywhere in the pancreas, but they arise most frequently (50–75%) in the pancreatic body or tail and are generally solitary { 21468008 ; 22415666 ; 26045140 ; 26559376 }. Unless associated with germline alterations in *VHL*, these neoplasms rarely involve the full length of the pancreas or are multifocal { 22370733 ; 28697137 ; 23543325 }. Serous cystadenocarcinomas often arise in the body and/or tail of the pancreas.

#518
Serous cystadenoma

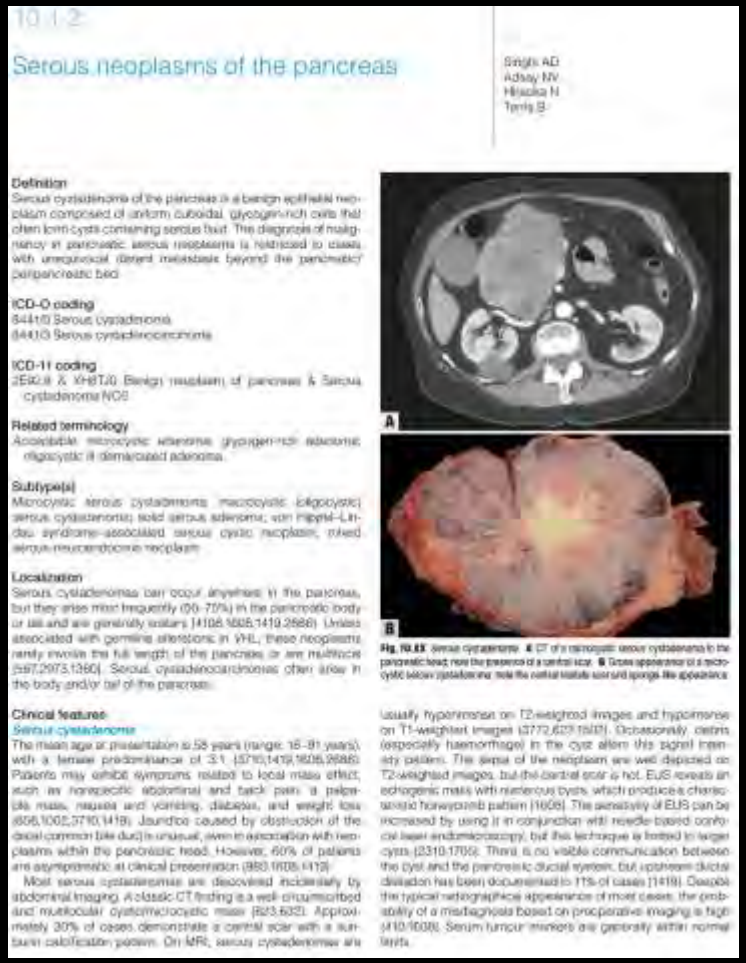
#520
Serous cystadenoma

#521
Serous cystadenoma

Code	Neoplasm
/0	Benign
/1	Uncertain whether benign or malignant
	Borderline malignancy
	Low malignant potential
	Uncertain malignant potential
/2	Carcinoma in situ
	Intraepithelial
	Noninfiltrating
	Noninvasive
/3	Malignant, primary site
/6*	Malignant, metastatic site
	Malignant, secondary site
/9*	Malignant, uncertain whether primary or metastatic site

** Not used by cancer registries (used by some pathologists in some parts of the world)*

Malignancy in Serous Neoplasms



10 | 2

Serous neoplasms of the pancreas

Singhi AD
Adsay NV
Hiraoka N
Terris B

Definition
Serous cystadenoma of the pancreas is a benign epithelial neoplasm composed of uniform cuboidal, glycogen-rich cells that often form cysts containing serous fluid. The diagnosis of malignancy in pancreatic serous neoplasms is restricted to cases with unequivocal (distant metastasis beyond the pancreatic/peripancreatic bed).

ICD-O coding
8441/0 Serous cystadenoma
8441/3 Serous cystadenocarcinoma

ICD-11 coding
2E92.8 & XH8TJ0 Benign neoplasm of pancreas & Serous cystadenoma NOS

Related terminology
Acceptable: microcystic adenoma; glycogen-rich adenoma; oligocystic or dismembered adenoma.

Subtype(s)
Microcystic serous cystadenoma; macrocystic (oligocystic) serous cystadenoma; solid serous adenoma; von Hippel–Lindau syndrome–associated serous cystic neoplasm; mixed serous-neuroendocrine neoplasm

Localization
Serous cystadenomas can occur anywhere in the pancreas, but they arise most frequently (50–75%) in the pancreatic body or tail and are generally solitary [4108,1605,1419,2668]. Unless associated with germline alterations in *VHL*, these neoplasms rarely involve the full length of the pancreas or are multifocal [597,2973,1360]. Serous cystadenocarcinomas often arise in the body and/or tail of the pancreas.

Clinical features
Serous cystadenoma
The mean age at presentation is 58 years (range: 16–91 years), with a female predominance of 3:1 [5710,1419,1605,2668]. Patients may exhibit symptoms related to local mass effect, such as nonspecific abdominal and back pain, a palpable mass, nausea and vomiting, diabetes, and weight loss [605,1002,3710,1419]. Jaundice caused by obstruction of the distal common bile duct is unusual, even in association with neoplasms within the pancreatic head. However, 60% of patients are asymptomatic at clinical presentation [980,1605,1419].

Most serous cystadenomas are discovered incidentally by abdominal imaging. A classic CT finding is a well-circumscribed and multilocular cystic/microcystic mass [823,632]. Approximately 30% of cases demonstrate a central scar with a sunburst calcification pattern. On MRI, serous cystadenomas are usually hyperintense on T2-weighted images and hypointense on T1-weighted images [3772,623,1605]. Occasionally, debris (especially haemorrhage) in the cyst alters this signal intensity pattern. The septa of the neoplasm are well depicted on T2-weighted images, but the central scar is not. EUS reveals an echogenic mass with numerous cysts, which produces a characteristic honeycomb pattern [1605]. The sensitivity of EUS can be increased by using it in conjunction with needle-based confocal laser endomicroscopy, but this technique is limited to larger cysts [2310,1705]. There is no visible communication between the cyst and the pancreatic ductal system, but upstream ductal dilation has been documented in 11% of cases [1419]. Despite the typical radiographical appearance of most cases, the probability of a misdiagnosis based on preoperative imaging is high [410,1605]. Serum tumour markers are generally within normal limits.

Fig. 10.03 Serous cystadenoma. **A** CT of a microcystic serous cystadenoma in the pancreatic head; note the presence of a central scar. **B** Gross appearance of a macrocystic serous cystadenoma; note the central stellate scar and sponge-like appearance.

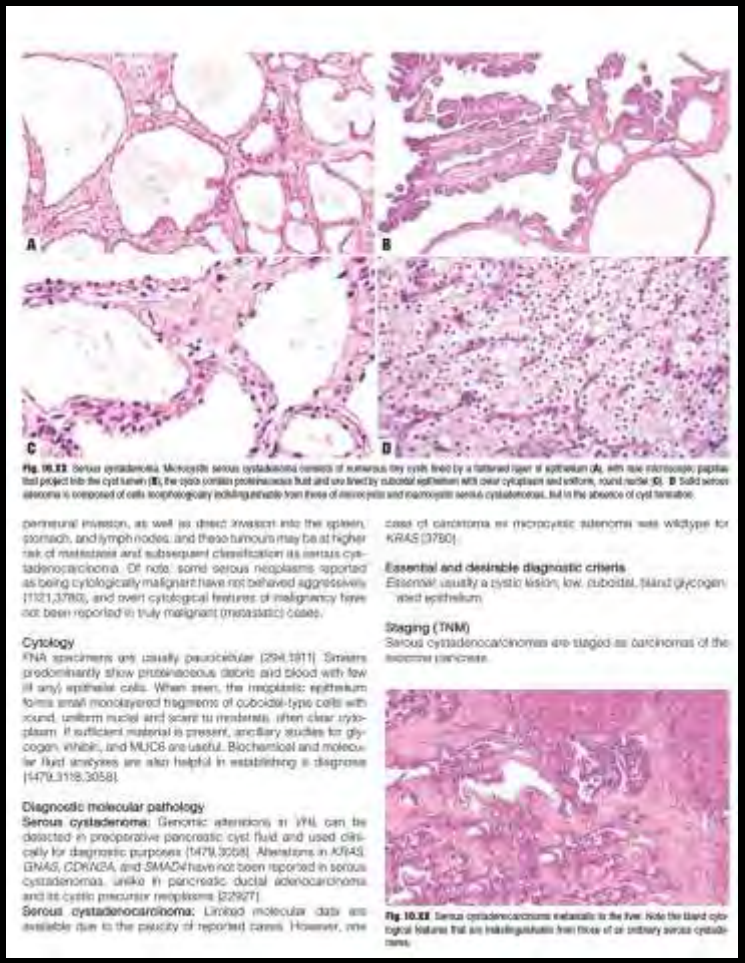


Fig. 10.02 Serous cystadenoma. Microcystic serous cystadenoma consists of numerous tiny cysts lined by a flattened layer of epithelium (**A**), with rare microscopic papillae that project into the cyst lumen (**B**); the cysts contain proteinaceous fluid and are lined by cuboidal epithelium with clear cytoplasm and uniform, round nuclei (**C**). **D** Solid serous adenoma is composed of cells morphologically indistinguishable from those of microcystic and macrocystic serous cystadenomas, but in the absence of cyst formation.

perineural invasion, as well as direct invasion into the spleen, stomach, and lymph nodes, and these tumours may be at higher risk of metastasis and subsequent classification as serous cystadenocarcinoma. Of note, some serous neoplasms reported as being cytologically malignant have not behaved aggressively [1121,3780], and even cytological features of malignancy have not been reported in truly malignant (metastatic) cases.

Cytology
FNA specimens are usually paucicellular [294,1911]. Smears predominantly show proteinaceous debris and blood with few (if any) epithelial cells. When seen, the neoplastic epithelium forms small monolayered fragments of cuboidal-type cells with round, uniform nuclei and scant to moderate, often clear cytoplasm. If sufficient material is present, ancillary studies for glycogen, inhibin, and MUC6 are useful. Biochemical and molecular fluid analyses are also helpful in establishing a diagnosis [1479,3118,3058].

Diagnostic molecular pathology
Serous cystadenoma: Genomic alterations in *VHL* can be detected in preoperative pancreatic cyst fluid and used clinically for diagnostic purposes [1479,3058]. Alterations in *KRAS*, *GNAS*, *CDKN2A*, and *SMAD4* have not been reported in serous cystadenomas, unlike in pancreatic ductal adenocarcinoma and its cystic precursor neoplasms [2292].
Serous cystadenocarcinoma: Limited molecular data are available due to the paucity of reported cases. However, one case of carcinoma ex microcystic adenoma was wild-type for *KRAS* [3780].

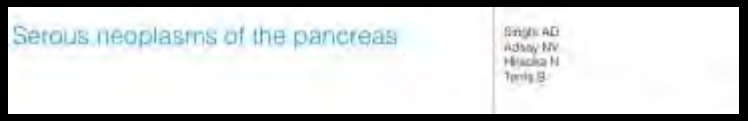
Essential and desirable diagnostic criteria
Essential: usually a cystic lesion; low, cuboidal, bland glycogen-rich epithelium

Staging (TNM)
Serous cystadenocarcinomas are staged as carcinomas of the exocrine pancreas.

Fig. 10.03 Serous cystadenocarcinoma metastatic to the liver. Note the bland cytological features that are indistinguishable from those of an ordinary serous cystadenoma.

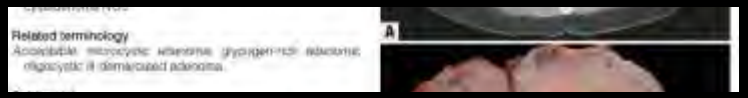
Malignancy in Serous Neoplasms

The diagnosis of malignancy in pancreatic serous neoplasms is restricted to cases with unequivocal distant metastasis beyond the pancreatic/peripancreatic bed


Serous neoplasms of the pancreas

Singhi AD
Adsay NV
Hiraoka N
Terris B

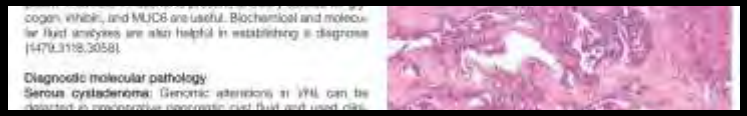
Malignant behaviour of serous neoplasms has been reported (serous cystadenocarcinoma), but it is extraordinarily rare, and the diagnosis of malignancy in pancreatic serous neoplasms is restricted to cases with unequivocal distant metastasis beyond the pancreatic/peripancreatic bed


Related terminology

Although atypical and potentially a sign of aggressive behaviour, vascular, perineural, and adjacent organ and lymph node involvement by direct spread is insufficient for the diagnosis of serous cystadenocarcinoma, which requires metastasis (almost always to the liver)


The mean age at presentation is 58 years (range: 16–91 years), with a female predominance of 3:1 (5710,1479,1606,2686). Patients may exhibit symptoms related to local mass effect, such as nonspecific abdominal and back pain, a palpable mass, nausea and vomiting, diabetes, and weight loss (606,1002,5710,1418). Jaundice caused by obstruction of the

(especially haemorrhage) in the cyst alters this signal intensity pattern. The septa of the neoplasm are well depicted on T2-weighted images, but the central scar is not. EUS reveals an echogenic mass with numerous cysts, which produces a characteristic honeycomb pattern (1606). The sensitivity of EUS can be increased by using it in conjunction with needle-based confo-


cogen, inhibin, and MUC6 are useful. Biochemical and molecular fluid analyses are also helpful in establishing a diagnosis (1479,3118,3058).

Diagnostic molecular pathology

Serous cystadenoma: Genomic alterations in *VHL* can be

Of note, some serous neoplasms reported as being cytologically malignant have not behaved aggressively and overt cytological features of malignancy have not been reported in truly malignant (metastatic) cases.

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

Pancreatic Intra-Epithelial Neoplasia (PanIN)

Pancreatic intraepithelial neoplasia

Definition
Pancreatic intraepithelial neoplasia (PanIN) is a microscopic non-invasive, flat or micropapillary, epithelial neoplasm confined to the pancreatic ducts.

ICD-O coding
8148/0 Glandular intraepithelial neoplasia, low grade
8148/2 Glandular intraepithelial neoplasia, high grade

ICD-11 coding
2E92.8 & XH6AF9 Benign neoplasm of pancreas & Glandular intraepithelial neoplasia, low grade
2B01.Y & XH6BN7 Carcinoma in situ of other specified digestive organs & Glandular intraepithelial neoplasia, high grade

Related terminology
PanIN
Not recommended: mucinous metaplasia, papillary hyperplasia, atypical hyperplasia, ductal dysplasia

High-grade PanIN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world)

Note: The current two-tiered grading system for PanIN recently replaced the former three-tiered grading scheme (PanIN-1, PanIN-2, PanIN-3) [11942788]; neoplasms belonging to the former PanIN-1 and PanIN-2 categories are now categorized as low-grade PanIN, and those belonging to the former PanIN-3 category are now categorized as high-grade PanIN [2659307].

Subtype(s)
Oncocytic and intestinal subtypes of PanIN have been described, but genetic analysis to confirm their neoplastic nature has yet to be published [36].

Localization
PanIN is more common in the head of the pancreas [1882,1933].

Clinical features
Given their microscopic nature, PanIN lesions are asymptomatic, generally cannot be detected on preoperative imaging studies, and are typically found incidentally in pancreatic specimens resected for other reasons. However, in patients with a familial predisposition to pancreatic ductal adenocarcinoma (PDAC), PanIN lesions, especially high-grade lesions, associated with lobulocentric atrophy, are more frequently observed and tend to be multifocal [2967,4281]. It may be possible to detect lobulocentric atrophy on imaging studies such as EUS, suggesting a potential screening tool for identification of individuals at high risk of invasive neoplasia [480].

Epidemiology
Low-grade PanIN is a common incidental finding in the general population [130,1678] and can be found in more than half of all individuals aged > 50 years with thorough examination of the pancreas [1305]. In contrast, high-grade PanIN is seldom seen in pancreata without PDACs [130,2082].

Etiology
Like PDAC, PanIN has been suggested to be associated with advanced age, obesity, pancreatic fatty infiltration, and diabetes mellitus [1895,1903,2013,2669,2682]. Also, PanIN lesions are more numerous and of a higher grade in the pancreata from patients with a familial predisposition to PDAC [2967].

Pathogenesis
Multiple clinicopathological studies suggest that high-grade PanIN is the main precursor of PDAC [130,1695,699,397,2038]. Molecular studies have supported this hypothesis by showing that PanIN lesions share critical genetic abnormalities with associated PDAC, and histological progression of PanIN parallels the accumulation of molecular abnormalities [3561,914,1285,1284]. The evolution of invasive carcinoma from the first genetic change appears to occur over decades, and the relatively common occurrence of low-grade PanIN lesions, most of which never progress to PDAC, suggests that the power of carcinogenesis lies many years.

The histological progression of PanIN to invasive carcinoma is mirrored by genetic progression, manifesting as either an increasing frequency of molecular aberrations overall, or a trend towards a higher degree of clonality for any individual molecular aberration in high-grade PanIN than in low-grade PanIN [3909]. For example, > 90% of PanIN lesions of all grades harbour *KRAS* mutations. However, the mutant allele frequency (a measure of clonality) is substantially higher in high-grade PanIN [1510]. Although the precise sequence of alterations is not well defined, certain genetic abnormalities, such as telomere shortening and activating mutations of the *KRAS* oncogene, are early changes, observed even in low-grade PanIN, and probably contribute to disease initiation. In contrast, widespread clonal copy-number alterations, as well as biallelic inactivation of *CDKN2A* (*P16*), are observed in high-grade PanIN, suggesting an association between these late changes and disease progression [1157,1284]. In contrast to what had been previously reported, recent studies have shown that mutations of *TP53* are rare if not absent, and there are no mutations or homozygous deletions of *SMAD4* in isolated high-grade PanIN lesions, indicating that inactivation of these two genes predominantly occurs in bona fide invasive carcinomas [1284,1167]. Also, some evidence suggests a pathway to invasive carcinoma via chromothripsis-like events (chromosome shattering with chaotic reassembly), which causes sudden, catastrophic

Pancreatic Intra-Epithelial Neoplasia (PanIN)

WHO 2010

PanIN1

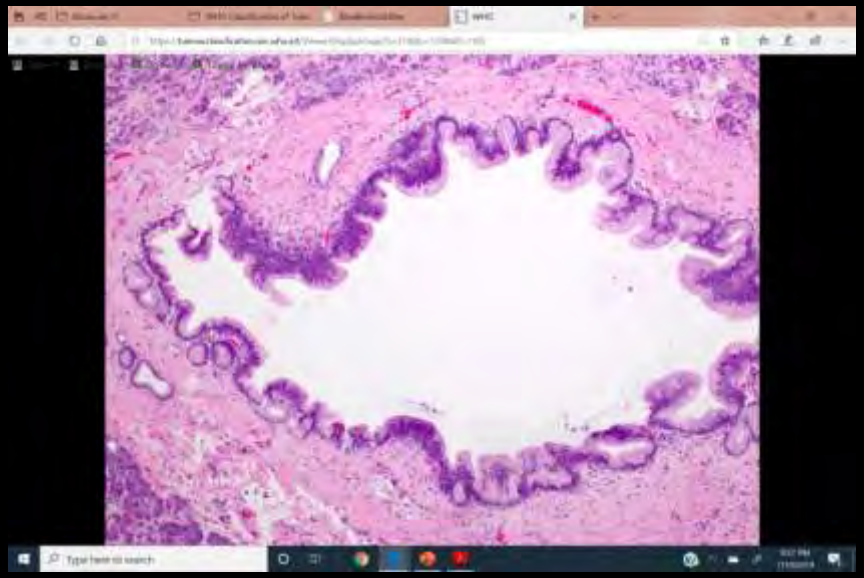
PanIN2

PanIN3

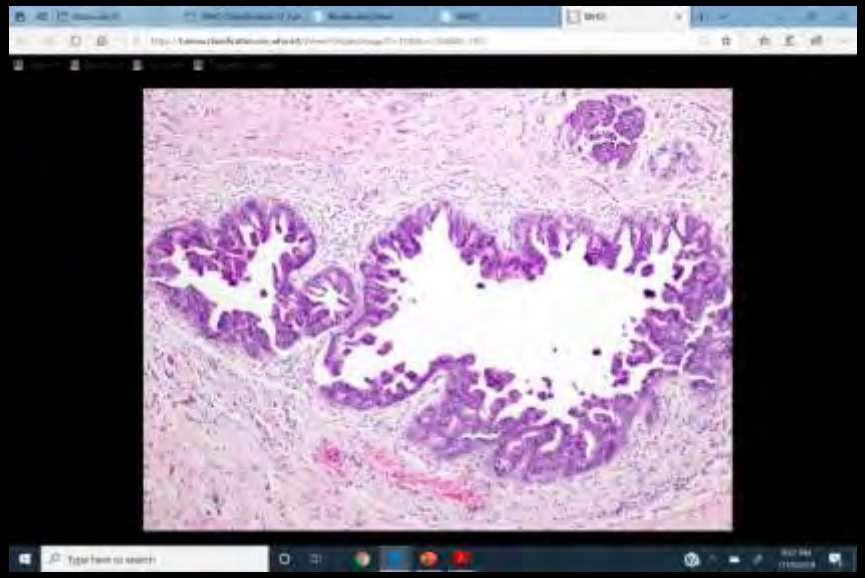
Pancreatic Intra-Epithelial Neoplasia (PanIN)

WHO 2010	WHO 2019
PanIN1	Low Grade *Previously* PanIN1
PanIN2	PanIN2
PanIN3	High Grade *Previously* PanIN3

Pancreatic Intra-Epithelial Neoplasia (PanIN)



Low Grade



High Grade

Pancreatic Intra-Epithelial Neoplasia (PanIN)

Binary grading is in keeping with broad approach across entire WHO GIT 5th Edition blue book

Applying:

- Mucinous Cystic Neoplasms (MCN)

- Intraductal Papillary Mucinous Neoplasms (IPMN)

Low Grade High Grade

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

IPMN, IOPN and ITPN are separated

Pancreatic intraductal papillary mucinous neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Matos A
Zamboni G

Definition
Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a grossly visible (typically ≥ 1.0 cm) intraductal epithelial neoplasm of mucin-producing cells arising in the main pancreatic duct and/or its branches.

ICD-O coding
8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia
8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia

ICD-11 coding
2E82.6 & XHMM02 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia
2E61.Y & XH3MB3 Carcinoma in situ of other specified digestive organs & Intraductal papillary mucinous neoplasm with high-grade dysplasia

Related terminology
High-grade IPMN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world)

Note: The current two-tiered grading system for IPMN recently replaced the former three-tiered grading scheme; neoplasms belonging to the former categories of "IPMN with low-grade dysplasia (LGD)" and "IPMN with intermediate-grade dysplasia" (1301,1306) are now categorized as low-grade IPMN. Those belonging to the former category of "IPMN with high-grade dysplasia (HGD)" are now categorized as high-grade IPMN (267).

Subtype(s)
Gastric-type intraductal papillary mucinous neoplasm; intestinal-type intraductal papillary mucinous neoplasm; pancreatobiliary-type intraductal papillary mucinous neoplasm.

Oncocytic-type intraductal papillary mucinous neoplasm is now recognized as a distinct entity (28,270,2048,285). The designations "main duct-type intraductal papillary mucinous neoplasm", "branch duct-type intraductal papillary mucinous neoplasm", and "mixed duct-type intraductal papillary mucinous neoplasm" are imaging terms used by clinicians (see *Clinical features*, below) rather than pathological subtypes.

Localization
IPMNs can occur anywhere in the main pancreatic duct and/or its branches; however, most are located in the head of the pancreas (212,1663,266). Multicentricity is observed in as many as 40% of cases (35,3241,1939,3091,2560,1423).

Pancreatic intraductal tubulopapillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Matos A
Zamboni G

Definition
Intraductal tubulopapillary neoplasm (ITPN) of the pancreas is an intraductal, predominantly tubule-forming, epithelial neoplasm with high-grade dysplasia and ductal differentiation without (wet) production of mucin. Invasive carcinoma may occur, and these cases are designated ITPN with an associated invasive carcinoma.

ICD-O coding
8503/2 Intraductal tubulopapillary neoplasm
8503/3 Intraductal tubulopapillary neoplasm with associated invasive carcinoma

ICD-11 coding
2E61.Y & XH6457 Carcinoma in situ of other specified digestive organs & Intraductal tubular papillary neoplasm, high grade
2C10.0 & XH9BW1 Adenocarcinoma of pancreas & Intraductal papillary neoplasm with associated invasive carcinoma

Related terminology
Not recommended: intraductal tubular carcinoma

Subtype(s)
None

Localization
About half of all ITPNs occur in the head of the pancreas and a third involve the gland diffusely (263).

Clinical features
ITPNs account for < 1% of all pancreatic exocrine neoplasms and 3% of intraductal neoplasms of the pancreas (3643). ITPNs are slightly more common in females. Patient age ranges from 25 to 84 years (mean 55 years) (263). Patients present with non-specific symptoms including abdominal pain, vomiting, weight loss, steatorrhea, and diabetes mellitus. Obstructive jaundice is uncommon. Some ITPNs are detected incidentally (263).

Epidemiology
Unknown

Etiology
Unknown

Pathogenesis
There are few data on pathogenesis. The genetic features of ITPNs differ from those of ductal adenocarcinomas and other intraductal neoplasms of the pancreas. Most of the reported alterations related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm (IPMN), including *KRAS* mutations, are absent in ITPNs (3643,3641,3642,120). However, certain chromatin remodeling genes (*KMT2A* [*MLL1*], *KMT2B* [*MLL2*], *KMT2C* [*MLL3*], *BAP1*) and PI3K pathway genes (*PIK3CA*, *PTEN*) can be mutated. A subset of cases harbour *FGFR2* fusions (286), which might be targetable.

Macroscopic appearance
ITPNs form solid, fleshy to rubbery, nodular masses within dilated pancreatic ducts (579,1244,2160,3643), but the intraductal growth may be difficult to recognize. Cyst formation is often less evident than in IPMNs. Mucinous secretions are not present. The average ITPN is 4.5 cm in diameter (range: 0.5–15.0 cm).

Histopathology
Microscopically, ITPNs form nodules of back-to-back tubular glands, resulting in large cribriformed structures (263,3208,3643). The intraductal location of at least some of the nodules is evidenced by continuity of the neoplastic epithelium with non-neoplastic ductal epithelium. However, most intraductal tumour nodules obliterate the ductal lumen, appearing as sharply circumscribed nests surrounded by fibrotic stroma. Although most ITPNs are predominantly tubular, papillae may be seen (3643). ITPNs are architecturally complex and typically have high-grade dysplasia. The tumour cells are predominantly cuboidal, with modest amounts of eosinophilic to amphophilic and rarely clear cytoplasm (57,263). In some cases, intraluminal necrosis may be seen. However, intracellular mucin is typically not detectable or is minimal (1760,3643). The nuclei are round to oval and atypical but uniform. Mitotic figures are often readily identifiable (3643). Most cases show foci of necrosis within the nodules, often with a comedo-like pattern.

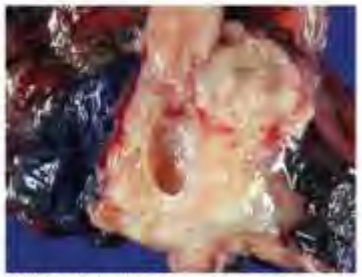


Fig. 10.33 Intraductal tubulopapillary neoplasm. Gross appearance, slice the polypoid component within the dilated main pancreatic duct.

Pancreatic intraductal oncocytic papillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Matos A
Zamboni G

symptoms attributed to chronic pancreatitis and/or to the mass effect of the neoplasm, such as jaundice (28,2048). Endoscopic biopsy or cytology may provide histological confirmation (3712,706,2690).

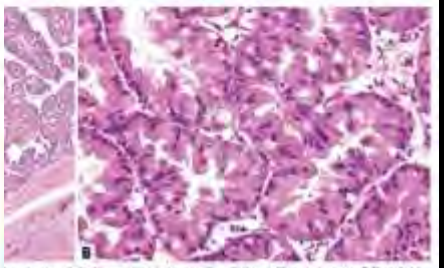
Epidemiology
Unknown

Etiology
Unknown

Pathogenesis
There are few data on pathogenesis. IOPNs typically lack the alterations reported to be related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm, such as mutations in *KRAS*, *GNAS*, and *RNF43* (3922,265,2196,22827,3118). In contrast, genes including *ARHGAP26*, *ASXL1*, *EPHA2*, and *ERBB4* are recurrently mutated in some IOPNs, but there are no entity-defining genomic alterations present in most cases (270).

Macroscopic appearance
Grossly, IOPNs typically form large (average size: 5.5 cm), tan-brown, friable papillary projections of solid nodules within cystically dilated pancreatic ducts, with little intraductal mucin accumulation (29,3487). Occasionally, the connection of the cysts to the ductal system may not be apparent grossly.

Histopathology
Microscopically, the tumours form complex and arborizing papillae with delicate fibrovascular cores. Sometimes the intraductal growth may be difficult to recognize, but at least focal involvement of the ductal system can be demonstrated (28,35,3520).



cores are characterized by complex arborizing papillae with delicate fibrovascular cores. ■ The cells have oat, intracellular lumina are also seen.

Intraductal Papillary Mucinous Neoplasm (IPMN)

Pancreatic intraductal papillary mucinous neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Maitra A
Zamboni G

Definition
Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a grossly visible (typically ≥ 1.0 cm) intraductal epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct and/or its branches.

ICD-O coding
8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia
8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia

ICD-11 coding
2E92.8 & XH8MD2 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia
2E61.Y & XH3MB3 Carcinoma in situ of other specified digestive organs & Intraductal papillary mucinous neoplasm with high-grade dysplasia

Related terminology
High-grade IPMN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world).

Note: The current two-tiered grading system for IPMN recently replaced the former three-tiered grading scheme; neoplasms belonging to the former categories of "IPMN with low-grade dysplasia (LGD)" and "IPMN with intermediate-grade dysplasia" [1301,1306] are now categorized as low-grade IPMN. Those belonging to the former category of "IPMN with high-grade dysplasia (HGD)" are now categorized as high-grade IPMN [267].

Subtype(s)
Gastric-type intraductal papillary mucinous neoplasm; intestinal-type intraductal papillary mucinous neoplasm; pancreatobiliary-type intraductal papillary mucinous neoplasm.

Oncocytic-type intraductal papillary mucinous neoplasm is now recognized as a distinct entity [28,270,2048,265]. The designations "main duct-type intraductal papillary mucinous neoplasm", "branch duct-type intraductal papillary mucinous neoplasm", and "mixed duct-type intraductal papillary mucinous neoplasm" are imaging terms used by clinicians (see *Clinical features*, below) rather than pathological subtypes.

Localization
IPMNs can occur anywhere in the main pancreatic duct and/or its branches; however, most are located in the head of the pancreas [212,1663,266]. Multicentricity is observed in as many as 40% of cases [35,3241,1939,3091,2560,1423].

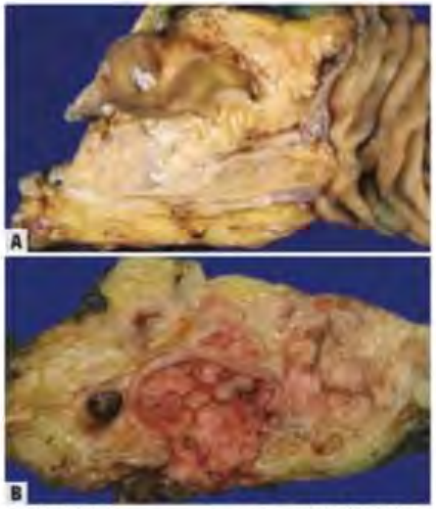


Fig. 10.XX Intraductal papillary mucinous neoplasm (IPMN). **A** Main duct-type IPMN; the duct is diffusely dilated and often filled with sticky mucin. **B** IPMN involving both the main and secondary pancreatic ducts; markedly dilated pancreatic ducts are filled with friable papillary formations.

Clinical features
IPMNs are fairly common, particularly in elderly people. In consecutive CT scans, the prevalence was reported as 1.7%, rising to 6.7% in people in their eighth decade of life [563]. Patients with IPMNs with an associated invasive carcinoma are 3–5 years older than those without an associated invasive carcinoma, suggesting that progression occurs over a period of years [1689,3091]. Clinical symptoms include epigastric pain, chronic pancreatitis, weight loss, diabetes mellitus, and jaundice [3338,1649,3687,2837,3091]. Branch duct-type IPMNs are often detected incidentally [3240].

By imaging, three distinct types of IPMN can be discerned [1663,3239,3240,42]. Main duct-type IPMNs are characterized by primary involvement of the main pancreatic duct with segmental or diffuse dilatation. Branch duct-type IPMNs typically involve the smaller, secondary ducts without affecting the main pancreatic duct [2837,3170,3238,3239]. Mixed duct-type IPMN is a combination of the other two types [3239,3240,42,1640]. Mural nodules and/or irregularities in the duct contours may correspond to HGD or invasive carcinoma [995,1667].

Intraductal Papillary Mucinous Neoplasm (IPMN)

Pancreatic intraductal papillary mucinous neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Maitra A
Zamboni G

Definition
Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a grossly visible (typically ≥ 1.0 cm) intraductal epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct and/or its branches.

ICD-O coding
8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia
8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia

ICD-11 coding
2E92.8 & XH8MD2 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia
2E61.Y & XH3MB3 Carcinoma in situ of other specified digestive organs & Intraductal papillary mucinous neoplasm with high-grade dysplasia

Related terminology
High-grade IPMN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world).

Note: The current two-tiered grading system for IPMN recently replaced the former three-tiered grading scheme; neoplasms belonging to the former categories of "IPMN with low-grade dysplasia (LGD)" and "IPMN with intermediate-grade dysplasia" [1301,1306] are now categorized as low-grade IPMN. Those belonging to the former category of "IPMN with high-grade dysplasia (HGD)" are now categorized as high-grade IPMN [267].

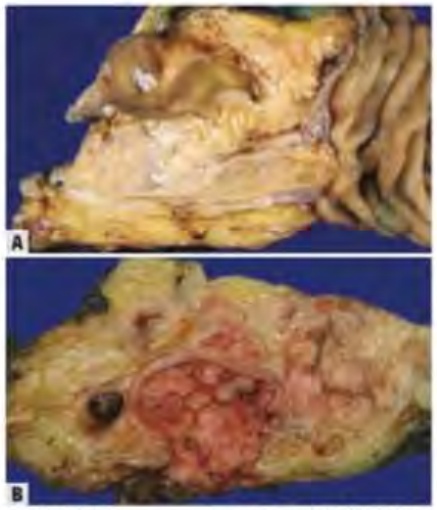


Fig. 10.XX Intraductal papillary mucinous neoplasm (IPMN). **A** Main duct-type IPMN; the duct is diffusely dilated and often filled with sticky mucin. **B** IPMN involving both the main and secondary pancreatic ducts; markedly dilated pancreatic ducts are filled with friable papillary formations.

Subtype(s)
Gastric-type intraductal papillary mucinous neoplasm; intestinal-type intraductal papillary mucinous neoplasm; pancreatobiliary-type intraductal papillary mucinous neoplasm.

Oncocytic-type intraductal papillary mucinous neoplasm is now recognized as a distinct entity [28,270,2048,265]. The designations "main duct-type intraductal papillary mucinous neoplasm", "branch duct-type intraductal papillary mucinous neoplasm", and "mixed duct-type intraductal papillary mucinous neoplasm" are imaging terms used by clinicians (see *Clinical features*, below) rather than pathological subtypes.

Localization
IPMNs can occur anywhere in the main pancreatic duct and/or its branches; however, most are located in the head of the pancreas [212,1663,266]. Multicentricity is observed in as many as 40% of cases [35,3241,1939,3091,2560,1423].

Clinical features
IPMNs are fairly common, particularly in elderly people. In consecutive CT scans, the prevalence was reported as 1.7%, rising to 6.7% in people in their eighth decade of life [563]. Patients with IPMNs with an associated invasive carcinoma are 3–5 years older than those without an associated invasive carcinoma, suggesting that progression occurs over a period of years [1689,3091]. Clinical symptoms include epigastric pain, chronic pancreatitis, weight loss, diabetes mellitus, and jaundice [3338,1649,3687,2837,3091]. Branch duct-type IPMNs are often detected incidentally [3240].

By imaging, three distinct types of IPMN can be discerned [1663,3239,3240,42]. Main duct-type IPMNs are characterized by primary involvement of the main pancreatic duct with segmental or diffuse dilatation. Branch duct-type IPMNs typically involve the smaller, secondary ducts without affecting the main pancreatic duct [2837,3170,3238,3239]. Mixed duct-type IPMN is a combination of the other two types [3239,3240,42,1640]. Mural nodules and/or irregularities in the duct contours may correspond to HGD or invasive carcinoma [995,1667].

D/Dx with PanIN

PanIN is a microscopic, usually < 5 mm in diameter (almost all gastric foveolar differentiation)

IPMNs are > 5 mm in diameter and can have varying differentiation

The term “incipient IPMN” or “incipient intraductal oncocytic papillary neoplasm” can be applied to lesions 0.5–1.0 cm in diameter with long finger-like papillae, intestinal or oncocytic differentiation, or a GNAS mutation.

Intraductal Papillary Mucinous Neoplasm (IPMN)

Pancreatic intraductal papillary mucinous neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Maitra A
Zamboni G

Definition
Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a grossly visible (typically ≥ 1.0 cm) intraductal epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct and/or its branches.

ICD-O coding
8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia
8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia

ICD-11 coding
2E92.8 & XH8MD2 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia
2E61.Y & XH3MB3 Carcinoma in situ of other specified digestive organs & Intraductal papillary mucinous neoplasm with high-grade dysplasia

Related terminology
High-grade IPMN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world).

Note: The current two-tiered grading system for IPMN recently replaced the former three-tiered grading scheme; neoplasms belonging to the former categories of "IPMN with low-grade dysplasia (LGD)" and "IPMN with intermediate-grade dysplasia" [1301,1306] are now categorized as low-grade IPMN. Those belonging to the former category of "IPMN with high-grade dysplasia (HGD)" are now categorized as high-grade IPMN [267].

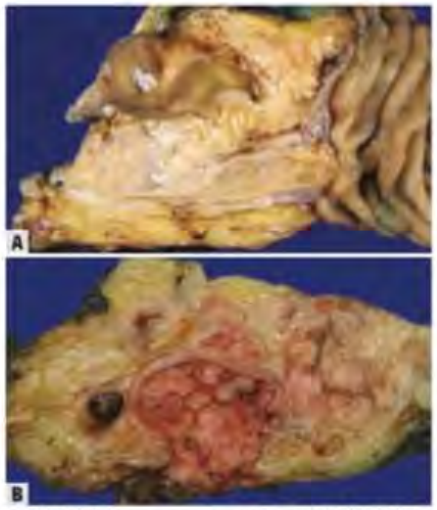


Fig. 10.XX Intraductal papillary mucinous neoplasm (IPMN). **A** Main duct-type IPMN; the duct is diffusely dilated and often filled with sticky mucin. **B** IPMN involving both the main and secondary pancreatic ducts; markedly dilated pancreatic ducts are filled with friable papillary formations.

Subtype(s)
Gastric-type intraductal papillary mucinous neoplasm; intestinal-type intraductal papillary mucinous neoplasm; pancreatobiliary-type intraductal papillary mucinous neoplasm.

Oncocytic-type intraductal papillary mucinous neoplasm is now recognized as a distinct entity [28,270,2048,265]. The designations "main duct-type intraductal papillary mucinous neoplasm", "branch duct-type intraductal papillary mucinous neoplasm", and "mixed duct-type intraductal papillary mucinous neoplasm" are imaging terms used by clinicians (see *Clinical features*, below) rather than pathological subtypes.

Localization
IPMNs can occur anywhere in the main pancreatic duct and/or its branches; however, most are located in the head of the pancreas [212,1663,266]. Multicentricity is observed in as many as 40% of cases [35,3241,1939,3091,2560,1423].

Clinical features
IPMNs are fairly common, particularly in elderly people. In consecutive CT scans, the prevalence was reported as 1.7%, rising to 6.7% in people in their eighth decade of life [563]. Patients with IPMNs with an associated invasive carcinoma are 3–5 years older than those without an associated invasive carcinoma, suggesting that progression occurs over a period of years [1689,3091]. Clinical symptoms include epigastric pain, chronic pancreatitis, weight loss, diabetes mellitus, and jaundice [3338,1649,3687,2837,3091]. Branch duct-type IPMNs are often detected incidentally [3240].

By imaging, three distinct types of IPMN can be discerned [1663,3239,3240,42]. Main duct-type IPMNs are characterized by primary involvement of the main pancreatic duct with segmental or diffuse dilatation. Branch duct-type IPMNs typically involve the smaller, secondary ducts without affecting the main pancreatic duct [2837,3170,3238,3239]. Mixed duct-type IPMN is a combination of the other two types [3239,3240,42,1640]. Mural nodules and/or irregularities in the duct contours may correspond to HGD or invasive carcinoma [995,1667].

Grade

IPMN with low-grade dysplasia (LGD)

IPMN with intermediate-grade dysplasia

Low grade IPMN

IPMN with high-grade dysplasia (HGD)

High grade IPMN

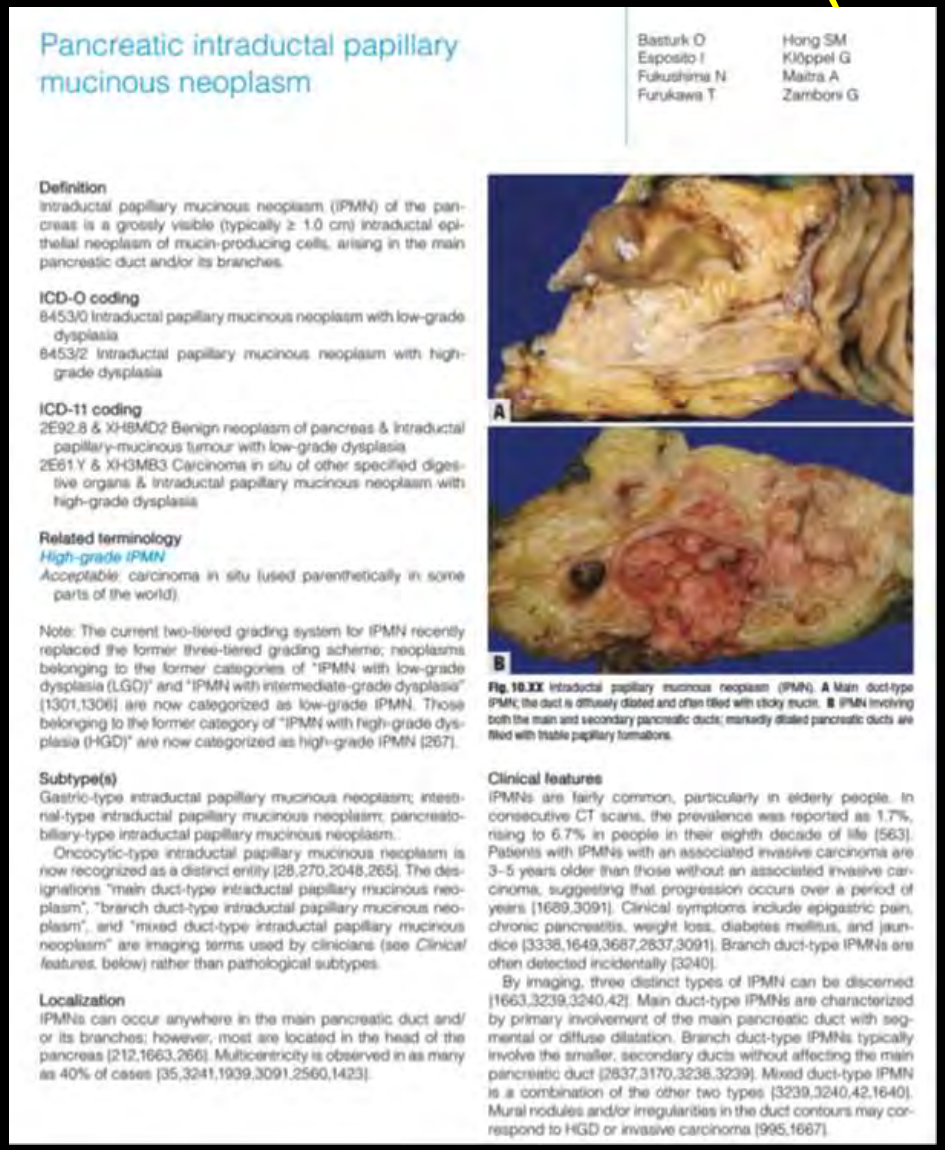
Intraductal Papillary Mucinous Neoplasm (IPMN)

Molecular Pathology

KRAS mutations in 60–80% of IPMNs

GNAS mutations 50–70% of IPMNs, particularly in the intestinal subtype (rare in PDAC)

RNF43 mutated in 50% of IPMN



Pancreatic intraductal papillary mucinous neoplasm

Basturk O, Esposito I, Fukushima N, Furukawa T, Hong SM, Klöppel G, Maitra A, Zamboni G

Definition
Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a grossly visible (typically ≥ 1.0 cm) intraductal epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct and/or its branches.

ICD-O coding
8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia
8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia

ICD-11 coding
2E92.8 & XH8MD2 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia
2E61.Y & XH3MB3 Carcinoma in situ of other specified digestive organs & Intraductal papillary mucinous neoplasm with high-grade dysplasia

Related terminology
High-grade IPMN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world).

Note: The current two-tiered grading system for IPMN recently replaced the former three-tiered grading scheme; neoplasms belonging to the former categories of "IPMN with low-grade dysplasia (LGD)" and "IPMN with intermediate-grade dysplasia" [1301,1306] are now categorized as low-grade IPMN. Those belonging to the former category of "IPMN with high-grade dysplasia (HGD)" are now categorized as high-grade IPMN [267].

Subtype(s)
Gastric-type intraductal papillary mucinous neoplasm; intestinal-type intraductal papillary mucinous neoplasm; pancreatobiliary-type intraductal papillary mucinous neoplasm.

Oncocytic-type intraductal papillary mucinous neoplasm is now recognized as a distinct entity [28,270,2048,265]. The designations "main duct-type intraductal papillary mucinous neoplasm", "branch duct-type intraductal papillary mucinous neoplasm", and "mixed duct-type intraductal papillary mucinous neoplasm" are imaging terms used by clinicians (see *Clinical features*, below) rather than pathological subtypes.

Localization
IPMNs can occur anywhere in the main pancreatic duct and/or its branches; however, most are located in the head of the pancreas [212,1663,266]. Multicentricity is observed in as many as 40% of cases [35,3241,1939,3091,2560,1423].

Fig. 10.XX Intraductal papillary mucinous neoplasm (IPMN). **A** Main duct-type IPMN; the duct is diffusely dilated and often filled with sticky mucin. **B** IPMN involving both the main and secondary pancreatic ducts; markedly dilated pancreatic ducts are filled with friable papillary formations.

Clinical features
IPMNs are fairly common, particularly in elderly people. In consecutive CT scans, the prevalence was reported as 1.7%, rising to 6.7% in people in their eighth decade of life [563]. Patients with IPMNs with an associated invasive carcinoma are 3–5 years older than those without an associated invasive carcinoma, suggesting that progression occurs over a period of years [1689,3091]. Clinical symptoms include epigastric pain, chronic pancreatitis, weight loss, diabetes mellitus, and jaundice [3338,1649,3687,2837,3091]. Branch duct-type IPMNs are often detected incidentally [3240].

By imaging, three distinct types of IPMN can be discerned [1663,3239,3240,42]. Main duct-type IPMNs are characterized by primary involvement of the main pancreatic duct with segmental or diffuse dilatation. Branch duct-type IPMNs typically involve the smaller, secondary ducts without affecting the main pancreatic duct [2837,3170,3238,3239]. Mixed duct-type IPMN is a combination of the other two types [3239,3240,42,1640]. Mural nodules and/or irregularities in the duct contours may correspond to HGD or invasive carcinoma [995,1667].

Intraductal Papillary Mucinous Neoplasm (IPMN)

Pancreatic intraductal papillary mucinous neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Maitra A
Zamboni G

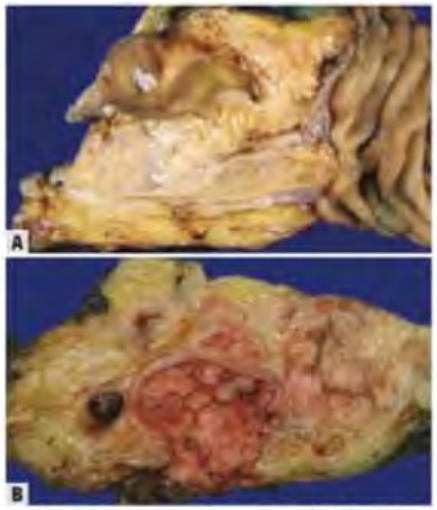
Definition
Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a grossly visible (typically ≥ 1.0 cm) intraductal epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct and/or its branches.

ICD-O coding
8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia
8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia

ICD-11 coding
2E92.8 & XH8MD2 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia
2E61.Y & XH3MB3 Carcinoma in situ of other specified digestive organs & Intraductal papillary mucinous neoplasm with high-grade dysplasia

Related terminology
High-grade IPMN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world)

Note: The current two-tiered grading system for IPMN recently replaced the former three-tiered grading scheme; neoplasms belonging to the former categories of "IPMN with low-grade



Subtypes

Gastric

Intestinal

Pancreaticobiliary

Table 10.XX Immunohistochemical profile of intraductal papillary mucinous neoplasm (IPMN), intraductal oncocytic papillary neoplasm (IOPN), and intraductal tubulopapillary neoplasm (ITPN)

	CK7/CK8/CK18/CK19	CK20	EMA (MUC1)	MUC2	MUC5AC	MUC6	CDX2
IPMN							
Gastric	+	−	−	−	+	−/+	−
Pancreatobiliary	+	−	+	−	+	+	−
Intestinal	+	+	−	+	+	−	+
IOPN	+	+ in goblet cells	+	+ in goblet cells	+	+	+ in goblet cells
ITPN	+	−	+	−	−	+	−

Intraductal Papillary Mucinous Neoplasm (IPMN)

Pancreatic intraductal papillary mucinous neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Maitra A
Zamboni G

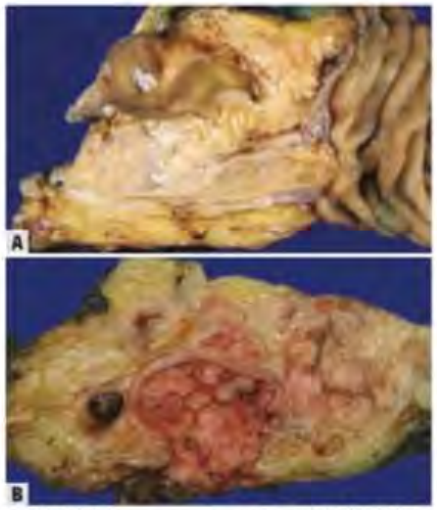
Definition
Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a grossly visible (typically ≥ 1.0 cm) intraductal epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct and/or its branches.

ICD-O coding
8453/0 Intraductal papillary mucinous neoplasm with low-grade dysplasia
8453/2 Intraductal papillary mucinous neoplasm with high-grade dysplasia

ICD-11 coding
2E92.8 & XH8MD2 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia
2E61.Y & XH3MB3 Carcinoma in situ of other specified digestive organs & Intraductal papillary mucinous neoplasm with high-grade dysplasia

Related terminology
High-grade IPMN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world)

Note: The current two-tiered grading system for IPMN recently replaced the former three-tiered grading scheme; neoplasms belonging to the former categories of "IPMN with low-grade



Subtypes

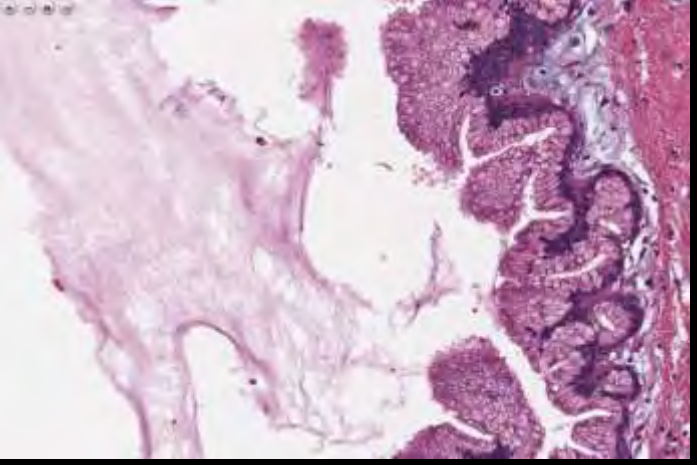
Gastric

Intestinal

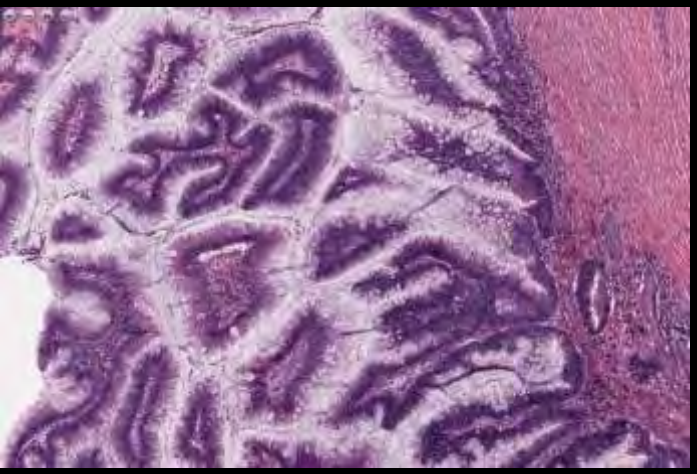
Pancreaticobiliary

Table 10.XX Immunohistochemical profile of intraductal papillary mucinous neoplasm (IPMN), intraductal oncocytic papillary neoplasm (IOPN), and intraductal tubulopapillary neoplasm (ITPN)

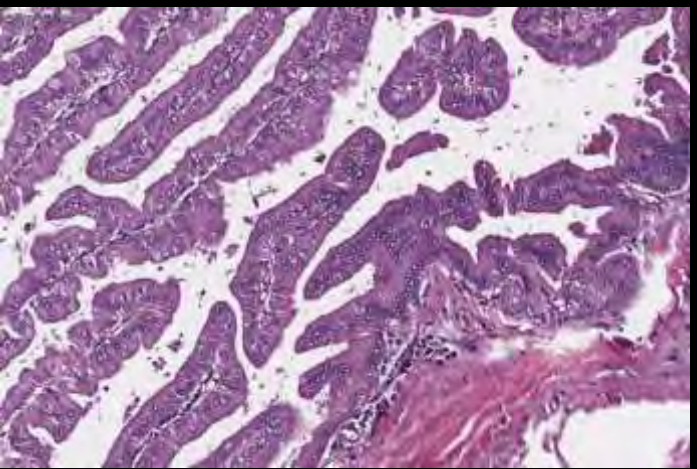
	CK7/CK8/CK18/CK19	CK20	EMA (MUC1)	MUC2	MUC5AC	MUC6	CDX2
IPMN							
Gastric	+	−	−	−	+	−/+	−
Pancreatobiliary	+	−	+	−	+	+	−
Intestinal	+	+	−	+	+	−	+
IOPN	+	+ in goblet cells	+	+ in goblet cells	+	+	+ in goblet cells
ITPN	+	−	+	−	−	+	−



Gastric -



Intestinal – MUC2/CDX2



Pancreaticobiliary - MUC1

Intraductal oncocytic papillary neoplasm (IOPN)

4.5% of intraductal neoplasms

Intraductal oncocytic papillary neoplasm (IOPN)

10.2.3

Pancreatic intraductal oncocytic papillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Maitra A
Zamboni G

Definition
Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is a grossly cystic epithelial neoplasm composed of exophytic nodular projections lined by oncocytic glandular epithelium, which grows within dilated pancreatic ducts. If there is a component of invasive carcinoma, the lesions are designated IOPN with an associated invasive carcinoma.

ICD-O coding
9453/0 Intraductal oncocytic papillary neoplasm

ICD-11 coding
2E92.5 & XH4MC2 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia

Related terminology
Acceptable: oncocytic subtype of intraductal papillary mucinous neoplasm

Subtype(s)
None

Localization
Approximately 70% of IOPNs occur in the head of the pancreas and involve the main duct. 10% diffusely involve the gland [28,2648,706].

Clinical features
IOPNs account for 4.5% of all intraductal neoplasms of the pancreas [706] and are more common in females. Patient age ranges from 36 to 87 years (mean: 68 years) [2620]. IOPNs either are incidentally discovered [706] or present with symptoms attributed to chronic pancreatitis and/or to the mass effect of the neoplasm, such as jaundice [28,2648]. Endoscopic biopsy or cytology may provide histological confirmation [3712,706,2690].

Epidemiology
Unknown

Etiology
Unknown

Pathogenesis
There are few data on pathogenesis. IOPNs typically lack the alterations reported to be related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm, such as mutations in *KRAS*, *GNAS* and *RNF43* [3622,265,2196,22927,3119]. In contrast, genes including *ARHGAP26*, *ASXL1*, *EPHA8*, and *ERBB4* are recurrently mutated in some IOPNs, but there are no entity-defining genomic alterations present in most cases [370].

Macroscopic appearance
Grossly, IOPNs typically form large (average size: 6.5 cm), tan-brown, friable papillary projections or solid nodules within cystically dilated pancreatic ducts, with little intraductal mucin accumulation [28,3487]. Occasionally, the connection of the cysts to the ductal system may not be apparent grossly.

Histopathology
Microscopically, the tumours form complex and arborizing papillae with delicate fibrovascular cores. Sometimes the intraductal growth may be difficult to recognize, but at least focal involvement of the ductal system can be demonstrated [28,30,3325].

A B

Fig. 10.2.3 Intraductal oncocytic papillary neoplasm. **A** These neoplasms are characterized by complex arborizing papillae with delicate fibrovascular cores. **B** The cells have distinctive oncocytic cytoplasm and nuclei with virgin, prominent nucleoli. Intraductal tumor are also seen.

Lack mutations in:

KRAS, GNAS, and RNF43

Frequent mutations in:

ARHGAP26, ASXL1, EPHA8, ERBB4

But no entity-defining genomic alterations present in most cases

Intraductal oncocytic papillary neoplasm (IOPN)

10.2.3

Pancreatic intraductal oncocytic papillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Maitra A
Zamboni G

Definition
Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is a grossly cystic epithelial neoplasm composed of exophytic nodular projections lined by oncocytic glandular epithelium, which grows within dilated pancreatic ducts. If there is a component of invasive carcinoma, the lesions are designated IOPN with an associated invasive carcinoma.

ICD-O coding
9453/0 Intraductal oncocytic papillary neoplasm

ICD-11 coding
2E92.5 & XH4MC2 Benign neoplasm of pancreas & Intraductal papillary-mucinous tumour with low-grade dysplasia

Related terminology
Acceptable: oncocytic subtype of intraductal papillary mucinous neoplasm

Subtype(s)
None

Localization
Approximately 70% of IOPNs occur in the head of the pancreas and involve the main duct. 10% diffusely involve the gland [28,2648,706].

Clinical features
IOPNs account for 4.5% of all intraductal neoplasms of the pancreas [706] and are more common in females. Patient age ranges from 36 to 87 years (mean: 68 years) [2620]. IOPNs either are incidentally discovered [706] or present with symptoms attributed to chronic pancreatitis and/or to the mass effect of the neoplasm, such as jaundice [28,2648]. Endoscopic biopsy or cytology may provide histological confirmation [3712,706,2690].

Epidemiology
Unknown

Etiology
Unknown

Pathogenesis
There are few data on pathogenesis. IOPNs typically lack the alterations reported to be related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm, such as mutations in *KRAS*, *GNAS* and *RNF43* [3622,265,2196,22927,3119]. In contrast, genes including *ARHGAP26*, *ASXL1*, *EPHA8*, and *ERBB4* are recurrently mutated in some IOPNs, but there are no entity-defining genomic alterations present in most cases [370].

Macroscopic appearance
Grossly, IOPNs typically form large (average size: 6.5 cm), tan-brown, friable papillary projections or solid nodules within cystically dilated pancreatic ducts, with little intraductal mucin accumulation [28,3487]. Occasionally, the connection of the cysts to the ductal system may not be apparent grossly.

Histopathology
Microscopically, the tumours form complex and arborizing papillae with delicate fibrovascular cores. Sometimes the intraductal growth may be difficult to recognize, but at least focal involvement of the ductal system can be demonstrated [28,30,3325].

A B

Fig. 10.2.3 Intraductal oncocytic papillary neoplasm. **A** These neoplasms are characterized by complex arborizing papillae with delicate fibrovascular cores. **B** The cells have distinctive oncocytic cytoplasm and nuclei with virgin, prominent nucleoli. Intraductal tumor are also seen.

Lack mutations in:

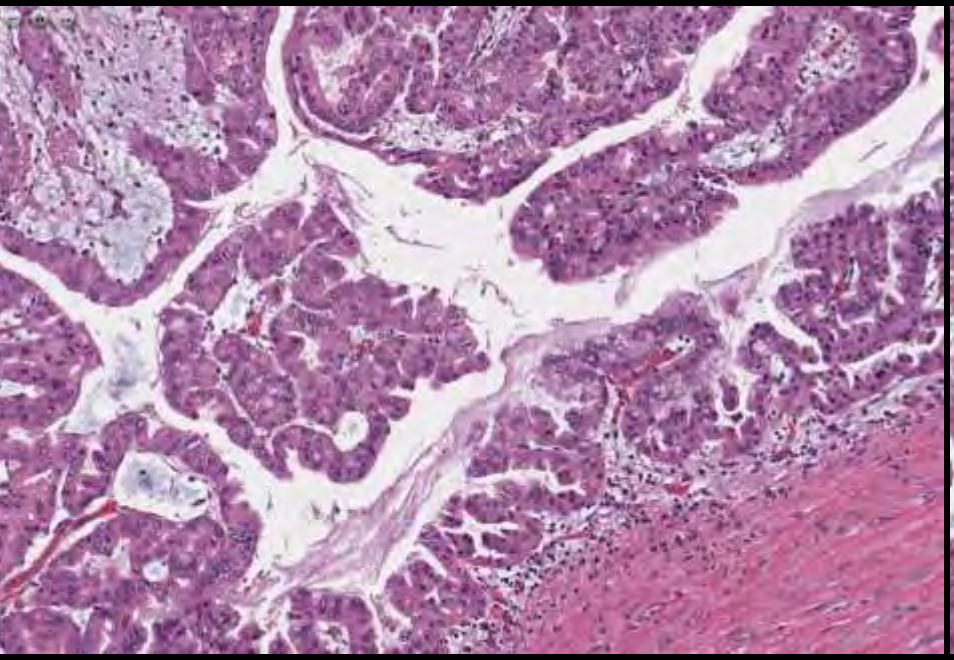
KRAS, GNAS, and RNF43

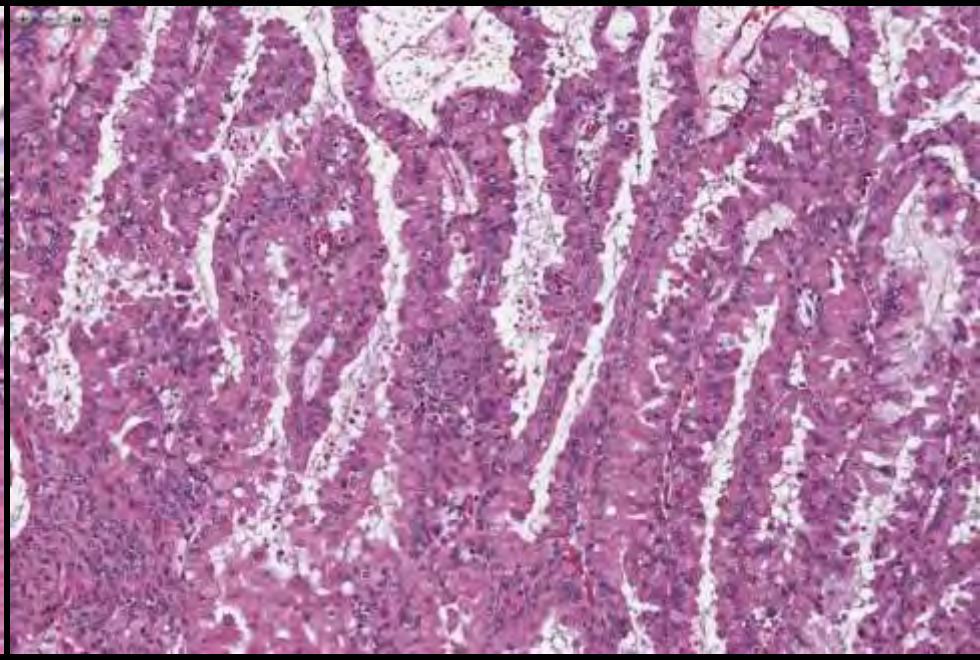
Frequent mutations in:

ARHGAP26, ASXL1, EPHA8, ERBB4

But no entity-defining genomic alterations present in most cases

Intraductal oncocytic papillary neoplasm (IOPN)





Oncocytic cytoplasm, Scattered goblet cells. Complex Cribriform architecture

MUC1+++, MUC6+++ (goblet cells MUC2, MUC5AC)

Intraductal tubulopapillary neoplasm (ITPN)

Pancreatic intraductal tubulopapillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Maitra A
Zamboni G

Definition
Intraductal tubulopapillary neoplasm (ITPN) of the pancreas is an intraductal, predominantly tubule-forming, epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin. Invasive carcinoma may occur, and these cases are designated ITPN with an associated invasive carcinoma.

ICD-O coding
8503/2 Intraductal tubulopapillary neoplasm
8503/3 Intraductal tubulopapillary neoplasm with associated invasive carcinoma

ICD-11 coding
2E81.Y & XH6437 Carcinoma in situ of other specified digestive organs & Intraductal tubular-papillary neoplasm, high grade
2C10.0 & XH8GW1 Adenocarcinoma of pancreas & Intraductal papillary neoplasm with associated invasive carcinoma

Related terminology
Not recommended: Intraductal tubular carcinoma

Subtype(s)
None

Localization
About half of all ITPNs occur in the head of the pancreas and a third involve the gland diffusely [263].

Clinical features
ITPNs account for < 1% of all pancreatic exocrine neoplasms and 3% of intraductal neoplasms of the pancreas [3643]. ITPNs are slightly more common in females. Patient age ranges from 25 to 84 years (mean, 65 years [263]. Patients present with non-specific symptoms including abdominal pain, vomiting, weight loss, steatorrhoea, and diabetes mellitus. Obstructive jaundice is uncommon. Some ITPNs are detected incidentally [263].

Epidemiology
Unknown

Etiology
Unknown

Pathogenesis
There are few data on pathogenesis. The genetic features of ITPNs differ from those of ductal adenocarcinomas and other intraductal neoplasms of the pancreas. Most of the reported alterations related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm (IPMN), including *KRAS* mutations, are absent in ITPNs [3643,3841,3842,120]. However, certain chromatin remodelling genes (*KMT2A* [*MLL1*], *KMT2B* [*MLL2*], *KMT2C* [*MLL3*], *BAP1*) and PI3K pathway genes (*PIK3CA*, *PTEN*) can be mutated. A subset of cases harbour *FGFR2* fusions [264], which might be targetable.

Macroscopic appearance
ITPNs form solid, fleshy to rubbery, nodular masses within dilated pancreatic ducts [879,1244,3180,3643], but the intraductal growth may be difficult to recognize. Cyst formation is often less evident than in IPMNs. Mucinous secretions are not present. The average ITPN is 4.5 cm in diameter (range: 0.5–15.0 cm).

Histopathology
Microscopically, ITPNs form nodules of back-to-back tubular glands, resulting in large cribriform structures [263,3209,3643]. The intraductal location of at least some of the nodules is evidenced by continuity of the neoplastic epithelium with non-neoplastic ductal epithelium. However, most intraductal tumour nodules obliterate the ductal lumen, appearing as sharply circumscribed nests surrounded by fibrotic stroma. Although most ITPNs are predominantly tubular, papillae may be seen [3643]. ITPNs are architecturally complex and typically have high-grade dysplasia. The tumour cells are predominantly cuboidal, with modest amounts of eosinophilic to amphophilic and rarely clear cytoplasm [57,263]. In some cases, intraluminal extensions may be seen. However, intracellular mucin is typically not detectable or is minimal [1743,3643]. The nuclei are round to oval and atypical but uniform. Mitotic figures are often readily identifiable [3643]. Most cases show foci of necrosis within the nodules, often with a comedo-like pattern.

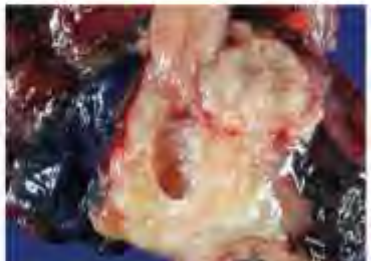


Fig. 10.XX Intraductal tubulopapillary neoplasm. Gross appearance, with the polypoid component within the dilated main pancreatic duct.

Intraductal tubulopapillary neoplasm (ITPN)

Pancreatic intraductal tubulopapillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T

Hong SM
Klöppel G
Mishra A
Zamboni G

Definition
Intraductal tubulopapillary neoplasm (ITPN) of the pancreas is an intraductal, predominantly tubule-forming, epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin. Invasive carcinoma may occur, and these cases are designated ITPN with an associated invasive carcinoma.

ICD-O coding
8503/2 Intraductal tubulopapillary neoplasm
8503/3 Intraductal tubulopapillary neoplasm with associated invasive carcinoma

ICD-11 coding
2E91.Y & XH6437 Carcinoma in situ of other specified digestive organs & Intraductal tubular papillary neoplasm, high grade
2C10.0 & XH3DW1 Adenocarcinoma of pancreas & Intraductal papillary neoplasm with associated invasive carcinoma

Related terminology
Not recommended: intraductal tubular carcinoma

Subtype(s)
None

Localization
About half of all ITPNs occur in the head of the pancreas and a third involve the gland diffusely (263).

Clinical features
ITPNs account for < 1% of all pancreatic exocrine neoplasms and 3% of intraductal neoplasms of the pancreas (3643). ITPNs are slightly more common in females. Patient age ranges from 25 to 84 years (mean, 55 years) (263). Patients present with nonspecific symptoms including abdominal pain, vomiting, weight loss, steatorrhoea, and diabetes mellitus. Obstructive jaundice is uncommon. Some ITPNs are detected incidentally (263).

Epidemiology
Unknown.

Etiology
Unknown.

Pathogenesis
There are few data on pathogenesis. The genetic features of ITPNs differ from those of ductal adenocarcinomas and other intraductal neoplasms of the pancreas. Most of the reported alterations related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm (IPMN), including *KRAS* mutations, are absent in ITPNs (3643,3841,3842,120). However, certain chromatin remodelling genes (*KMT2A* [*MLL1*], *KMT2B* [*MLL2*], *KMT2C* [*MLL3*], *IAP1* and PI3K pathway genes (*PIK3CA*, *PTEN*) can be mutated. A subset of cases harbour *FGFR2* fusions (264), which might be targetable.

Macroscopic appearance
ITPNs form solid, fleshy to rubbery, nodular masses within dilated pancreatic ducts (879,1844,3160,3643), but the intraductal growth may be difficult to recognize. Cyst formation is often less evident than in IPMNs. Mucinous secretions are not present. The average ITPN is 4.5 cm in diameter (range 0.5–15.0 cm).

Histopathology
Microscopically, ITPNs form nodules of back-to-back tubular glands resulting in large cribriform structures (3643,3208,3643). The intraductal location of at least some of the nodules is evidenced by continuity of the neoplastic epithelium with non-neoplastic ductal epithelium. However, most intraductal tumour nodules obliterate the ductal lumen, appearing as sharply circumscribed nests surrounded by fibrotic stroma. Although most ITPNs are predominantly tubular, papillae may be seen (3643). ITPNs are architecturally complex and typically have high-grade dysplasia. The tumour cells are predominantly cuboidal, with modest amounts of eosinophilic to amphophilic and rarely clear cytoplasm (57,363). In some cases, intraluminal extrusions may be seen. However, intracellular mucin is typically not detectable or is minimal (1743,3643). The nuclei are round to oval and atypical but uniform. Mitotic figures are often readily identifiable (3643). Most cases show foci of necrosis within the nodules, often with a comedo-like pattern.

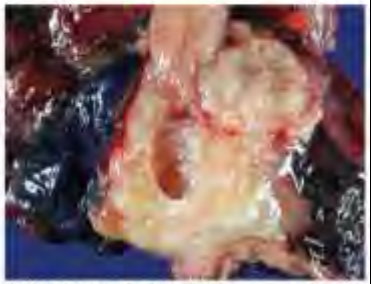


Fig. 10.XX Intraductal tubulopapillary neoplasm. Gross appearance, note the polypoid component within the dilated main pancreatic duct.

Intraductal tubulopapillary neoplasm (ITPN)

Pancreatic intraductal tubulopapillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Heng SM
Klöppel G
Mishra A
Zamboni G

Definition
Intraductal tubulopapillary neoplasm (ITPN) of the pancreas is an intraductal, predominantly tubule-forming, epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin. Invasive carcinoma may occur, and these cases are designated ITPN with an associated invasive carcinoma.

ICD-O coding
8503/2 Intraductal tubulopapillary neoplasm
8503/3 Intraductal tubulopapillary neoplasm with associated invasive carcinoma

ICD-11 coding
2E91Y & XH6437 Carcinoma in situ of other specified digestive organs & Intraductal tubular papillary neoplasm, high grade
2C10.0 & XH3DW1 Adenocarcinoma of pancreas & Intraductal papillary neoplasm with associated invasive carcinoma

Related terminology
Not recommended: intraductal tubular carcinoma

Subtype(s)
None

Localization
About half of all ITPNs occur in the head of the pancreas and a third involve the gland diffusely (263).

Clinical features
ITPNs account for < 1% of all pancreatic exocrine neoplasms and 3% of intraductal neoplasms of the pancreas (3643). ITPNs are slightly more common in females. Patient age ranges from 25 to 84 years (mean, 55 years) (263). Patients present with non-specific symptoms including abdominal pain, vomiting, weight loss, steatorrhoea, and diabetes mellitus. Obstructive jaundice is uncommon. Some ITPNs are detected incidentally (263).

Epidemiology
Unknown.

Etiology
Unknown.

Pathogenesis
There are few data on pathogenesis. The genetic features of ITPNs differ from those of ductal adenocarcinomas and other intraductal neoplasms of the pancreas. Most of the recurrent alterations related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm (IPMN), including *KRAS* mutations, are absent in ITPNs (3643,3841,3842,120). However, certain chromatin remodelling genes (*KMT2A* [*MLL1*], *KMT2B* [*MLL2*], *KMT2C* [*MLL3*], *IAP1* and PI3K pathway genes (*PIK3CA*, *PTEN*) can be mutated. A subset of cases harbour *FGFR2* fusions (264), which might be targetable.

Macroscopic appearance
ITPNs form solid, fleshy to rubbery, nodular masses within dilated pancreatic ducts (879,1844,3160,3643), but the intraductal growth may be difficult to recognize. Cyst formation is often less evident than in IPMNs. Mucinous secretions are not present. The average ITPN is 4.5 cm in diameter (range 0.5–15.0 cm).

Histopathology
Microscopically, ITPNs form nodules of back-to-back tubular glands resulting in large cribriform structures (3643,3208,3643). The intraductal location of at least some of the nodules is evidenced by continuity of the neoplastic epithelium with non-neoplastic ductal epithelium. However, most intraductal tumour nodules obliterate the ductal lumen, appearing as sharply circumscribed nests surrounded by fibrotic stroma. Although most ITPNs are predominantly tubular, papillae may be seen (3643). ITPNs are architecturally complex and typically have high-grade dysplasia. The tumour cells are predominantly cuboidal, with modest amounts of eosinophilic to amphophilic and rarely clear cytoplasm (57,363). In some cases, intraluminal necrosis may be seen. However, intracellular mucin is typically not detectable or is minimal (1743,3643). The nuclei are round to oval and atypical but uniform. Mitotic figures are often readily identifiable (3643). Most cases show foci of necrosis within the nodules, often with a comedo-like pattern.

Fig. 10.XX Intraductal tubulopapillary neoplasm. Gross appearance, note the polypoid component within the dilated main pancreatic duct.

< 1% of all pancreatic exocrine neoplasms

< 3% of intraductal neoplasms of the pancreas

Intraductal tubulopapillary neoplasm (ITPN)

Pancreatic intraductal tubulopapillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T

Hong SM
Klöppel G
Maitra A
Zamboni G

Definition
Intraductal tubulopapillary neoplasm (ITPN) of the pancreas is an intraductal, predominantly tubule-forming, epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin. Invasive carcinoma may occur, and these cases are designated ITPN with an associated invasive carcinoma.

ICD-O coding
8503/2 Intraductal tubulopapillary neoplasm
8503/3 Intraductal tubulopapillary neoplasm with associated invasive carcinoma

ICD-11 coding
2E91.Y & XH6437 Carcinoma in situ of other specified digestive organs & Intraductal tubular papillary neoplasm, high grade
2C10.0 & XH3DW1 Adenocarcinoma of pancreas & Intraductal papillary neoplasm with associated invasive carcinoma

Related terminology
Not recommended: Intraductal tubular carcinoma

Subtype(s)
None

Localization
About half of all ITPNs occur in the head of the pancreas and a third involve the gland diffusely (263).

Clinical features
ITPNs account for < 1% of all pancreatic exocrine neoplasms and 3% of intraductal neoplasms of the pancreas (3643). ITPNs are slightly more common in females. Patient age ranges from 25 to 84 years (mean, 55 years) (263). Patients present with nonspecific symptoms including abdominal pain, vomiting, weight loss, steatorrhoea, and diabetes mellitus. Obstructive jaundice is uncommon. Some ITPNs are detected incidentally (263).

Epidemiology
Unknown.

Etiology
Unknown.

Pathogenesis
There are few data on pathogenesis. The genetic features of ITPNs differ from those of ductal adenocarcinomas and other intraductal neoplasms of the pancreas. Most of the recurrent alterations related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm (IPMN), including *KRAS* mutations, are absent in ITPNs (3643,3841,3842,120). However, certain chromatin remodelling genes (*KMT2A* [*MLL1*], *KMT2B* [*MLL2*], *KMT2C* [*MLL3*], *BAP1*) and PI3K pathway genes (*PIK3CA*, *PTEN*) can be mutated. A subset of cases harbour *FGFR2* fusions (264), which might be targetable.

Macroscopic appearance
ITPNs form solid, fleshy to rubbery, nodular masses within dilated pancreatic ducts (879,1844,3160,3643), but the intraductal growth may be difficult to recognize. Cyst formation is often less evident than in IPMNs. Mucinous secretions are not present. The average ITPN is 4.5 cm in diameter (range, 0.5–15.0 cm).

Histopathology
Microscopically, ITPNs form nodules of back-to-back tubular glands resulting in large cribriform structures (3643,3208,3643). The intraductal location of at least some of the nodules is evidenced by continuity of the neoplastic epithelium with non-neoplastic ductal epithelium. However, most intraductal tumour nodules obliterate the ductal lumen, appearing as sharply circumscribed nests surrounded by fibrotic stroma. Although most ITPNs are predominantly tubular, papillae may be seen (3643). ITPNs are architecturally complex and typically have high-grade dysplasia. The tumour cells are predominantly cuboidal, with modest amounts of eosinophilic to amphophilic and rarely clear cytoplasm (57,363). In some cases, intraluminal extrusions may be seen. However, intracellular mucin is typically not detectable or is minimal (1743,3643). The nuclei are round to oval and atypical but uniform. Mitotic figures are often readily identifiable (3643). Most cases show foci of necrosis within the nodules, often with a comedo-like pattern.

Fig. 10.XX Intraductal tubulopapillary neoplasm. Gross appearance, note the polypoid component within the dilated main pancreatic duct.

Lack KRAS mutations

Mutations in:

Chromatin remodelling genes

KMT2A [MLL1], KMT2B [MLL2], KMT2C [MLL3], BAP1

And

PI3K pathway genes (PIK3CA, PTEN)

And

FGFR2 fusions

Intraductal tubulopapillary neoplasm (ITPN)

Pancreatic intraductal tubulopapillary neoplasm

Basturk O
Esposito I
Fukushima N
Furukawa T
Heng SM
Klöppel G
Maitra A
Zamboni G

Definition
Intraductal tubulopapillary neoplasm (ITPN) of the pancreas is an intraductal, predominantly tubule-forming, epithelial neoplasm with high-grade dysplasia and ductal differentiation without overt production of mucin. Invasive carcinoma may occur, and these cases are designated ITPN with an associated invasive carcinoma.

ICD-O coding
8503/2 Intraductal tubulopapillary neoplasm
8503/3 Intraductal tubulopapillary neoplasm with associated invasive carcinoma

ICD-11 coding
2E91.Y & XH6437 Carcinoma in situ of other specified digestive organs & Intraductal tubular papillary neoplasm, high grade
2C10.0 & XH3DW1 Adenocarcinoma of pancreas & Intraductal papillary neoplasm with associated invasive carcinoma

Related terminology
Not recommended: intraductal tubular carcinoma

Subtype(s)
None

Localization
About half of all ITPNs occur in the head of the pancreas and a third involve the gland diffusely [263].

Clinical features
ITPNs account for < 1% of all pancreatic exocrine neoplasms and 3% of intraductal neoplasms of the pancreas [3643]. ITPNs are slightly more common in females. Patient age ranges from 25 to 84 years (mean, 55 years) [263]. Patients present with nonspecific symptoms including abdominal pain, vomiting, weight loss, steatorrhoea, and diabetes mellitus. Obstructive jaundice is uncommon. Some ITPNs are detected incidentally [263].

Epidemiology
Unknown.

Etiology
Unknown.

Pathogenesis
There are few data on pathogenesis. The genetic features of ITPNs differ from those of ductal adenocarcinomas and other intraductal neoplasms of the pancreas. Most of the recorded alterations related to ductal adenocarcinoma and intraductal papillary mucinous neoplasm (IPMN), including *KRAS* mutations, are absent in ITPNs [3643,3841,3842,120]. However, certain chromatin remodelling genes (*KMT2A* [*MLL1*], *KMT2B* [*MLL2*], *KMT2C* [*MLL3*], *IAP1* and PI3K pathway genes (*PIK3CA*, *PTEN*) can be mutated. A subset of cases harbour *FGFR2* fusions [264], which might be targetable.

Macroscopic appearance
ITPNs form solid, fleshy to rubbery, nodular masses within dilated pancreatic ducts [879,1844,3160,3643], but the intraductal growth may be difficult to recognize. Cyst formation is often less evident than in IPMNs. Mucinous secretions are not present. The average ITPN is 4.5 cm in diameter (range 0.5–15.0 cm).

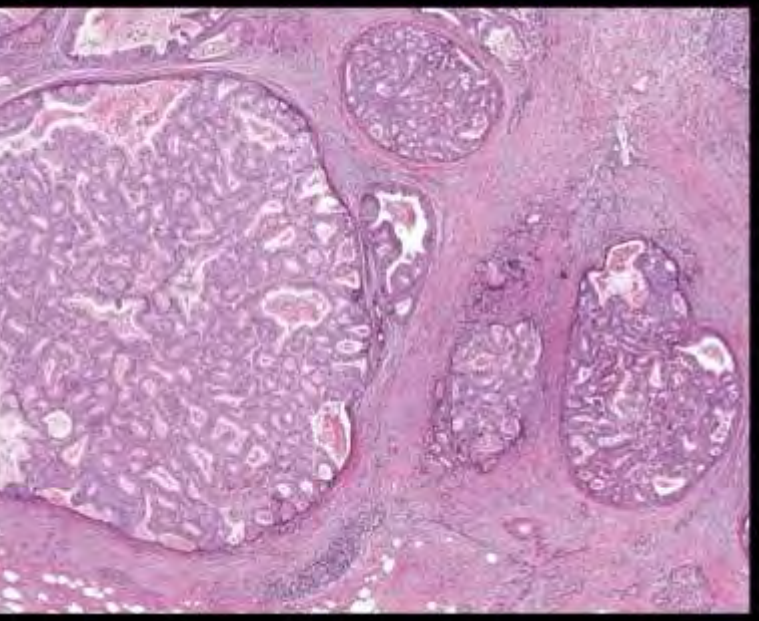
Histopathology
Microscopically, ITPNs form nodules of back-to-back tubular glands resulting in large cribriform structures [263,3208,3643]. The intraductal location of at least some of the nodules is evidenced by continuity of the neoplastic epithelium with non-neoplastic ductal epithelium. However, most intraductal tumour nodules obliterate the ductal lumen, appearing as sharply circumscribed nests surrounded by fibrotic stroma. Although most ITPNs are predominantly tubular, papillae may be seen [3643]. ITPNs are architecturally complex and typically have high-grade dysplasia. The tumour cells are predominantly cuboidal, with modest amounts of eosinophilic to amphophilic and rarely clear cytoplasm [57,263]. In some cases, intraluminal extrusions may be seen. However, intracellular mucin is typically not detectable or is minimal [1743,3643]. The nuclei are round to oval and atypical but uniform. Mitotic figures are often readily identifiable [3643]. Most cases show foci of necrosis within the nodules, often with a comedo-like pattern.

Fig. 10.XX Intraductal tubulopapillary neoplasm. Gross appearance, note the polypoid component within the dilated main pancreatic duct.

Do not produce mucin

Completely fill the ducts (do not appear cystic) so in-situ nature is often not apparent

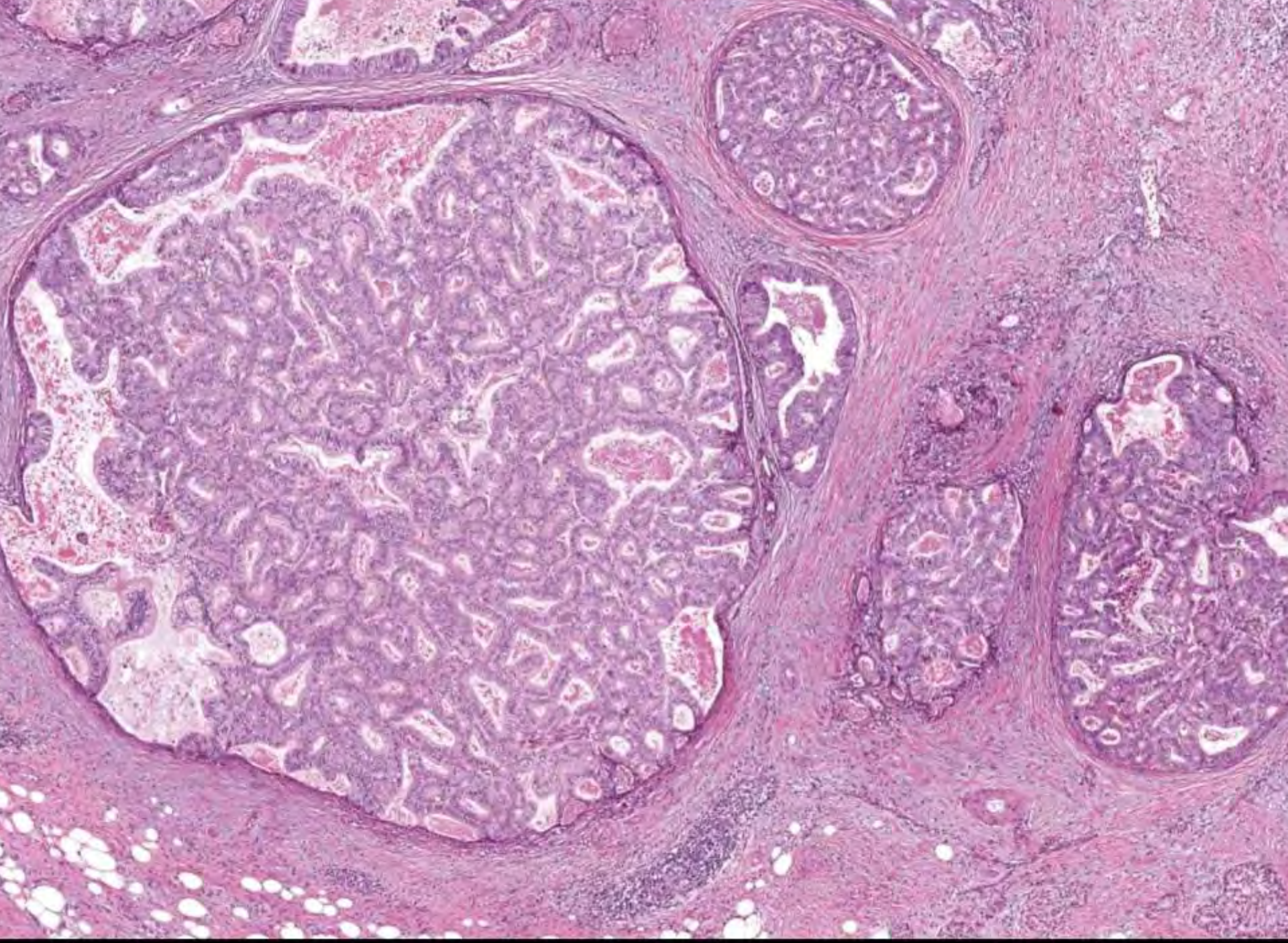
Intraductal tubulopapillary neoplasm (ITPN)

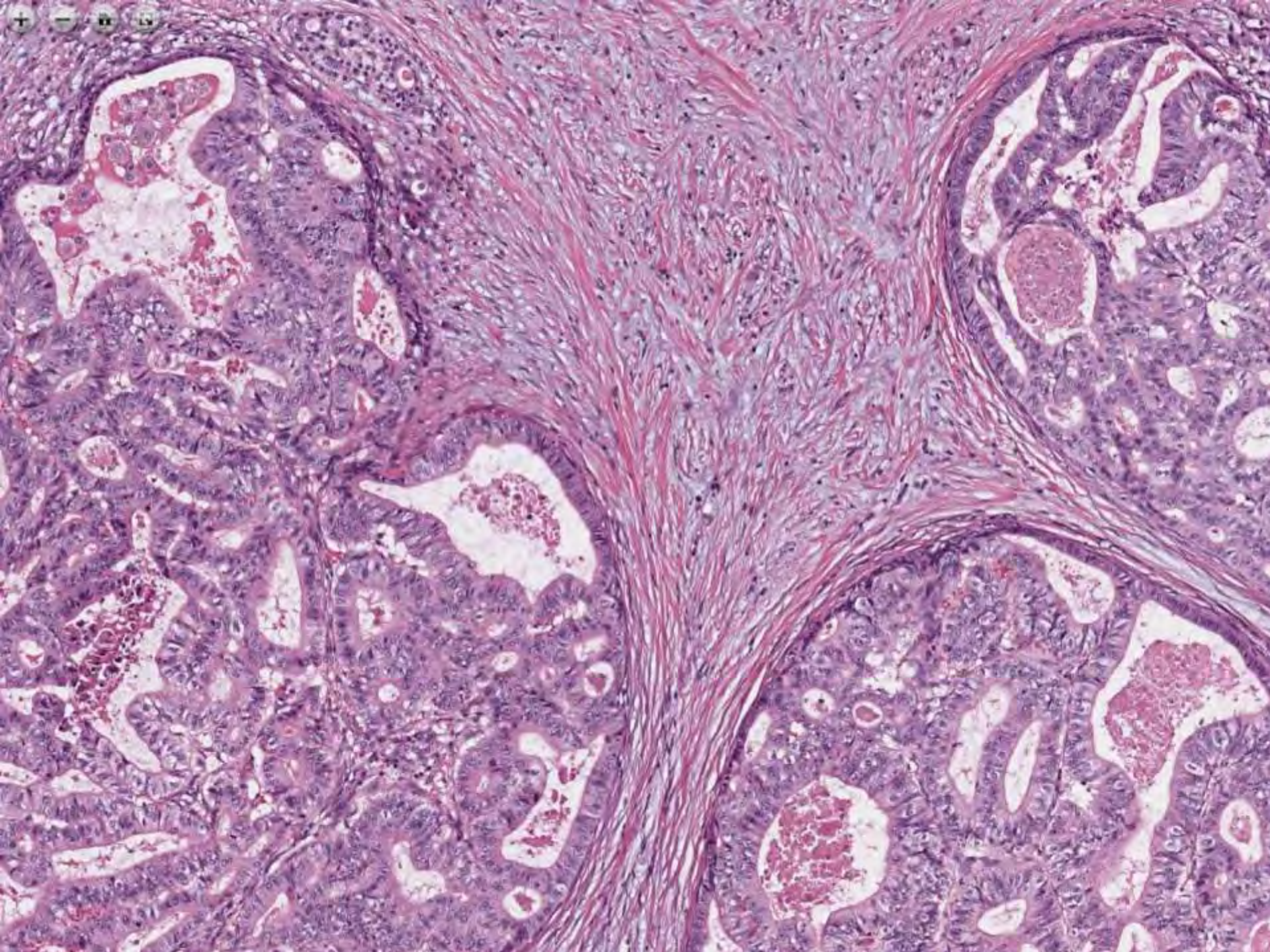


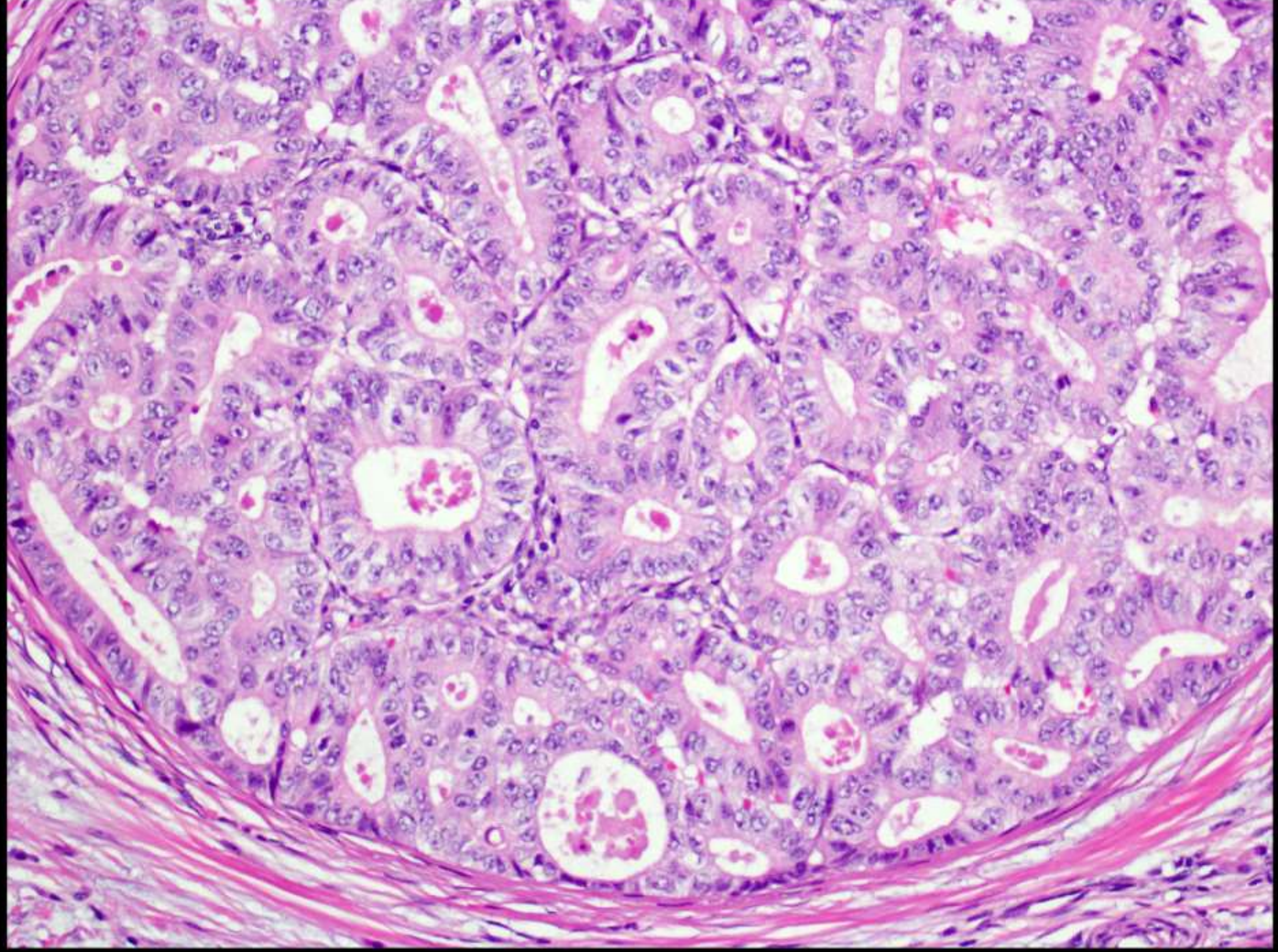
Typically homogeneous

70% have invasive carcinoma

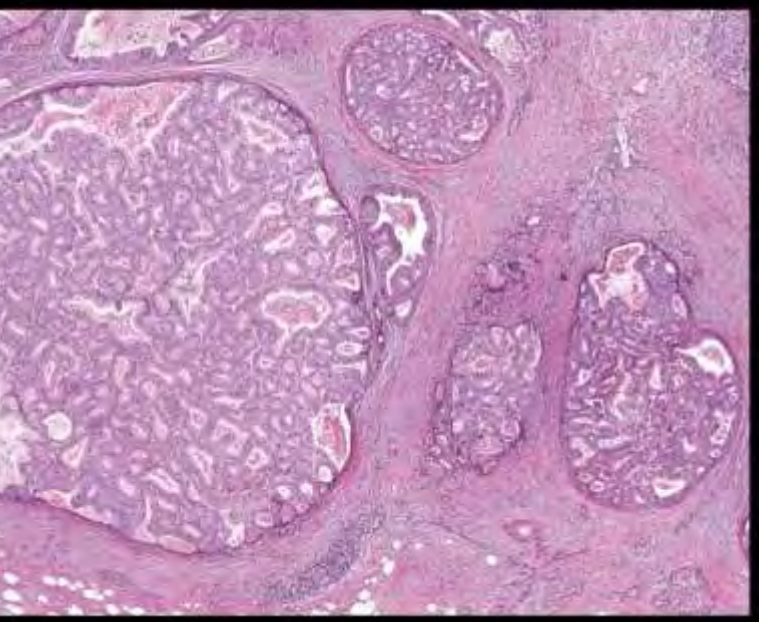
However invasion is hard to appreciate







Intraductal tubulopapillary neoplasm (ITPN)



Typically homogeneous

MUC2 negative

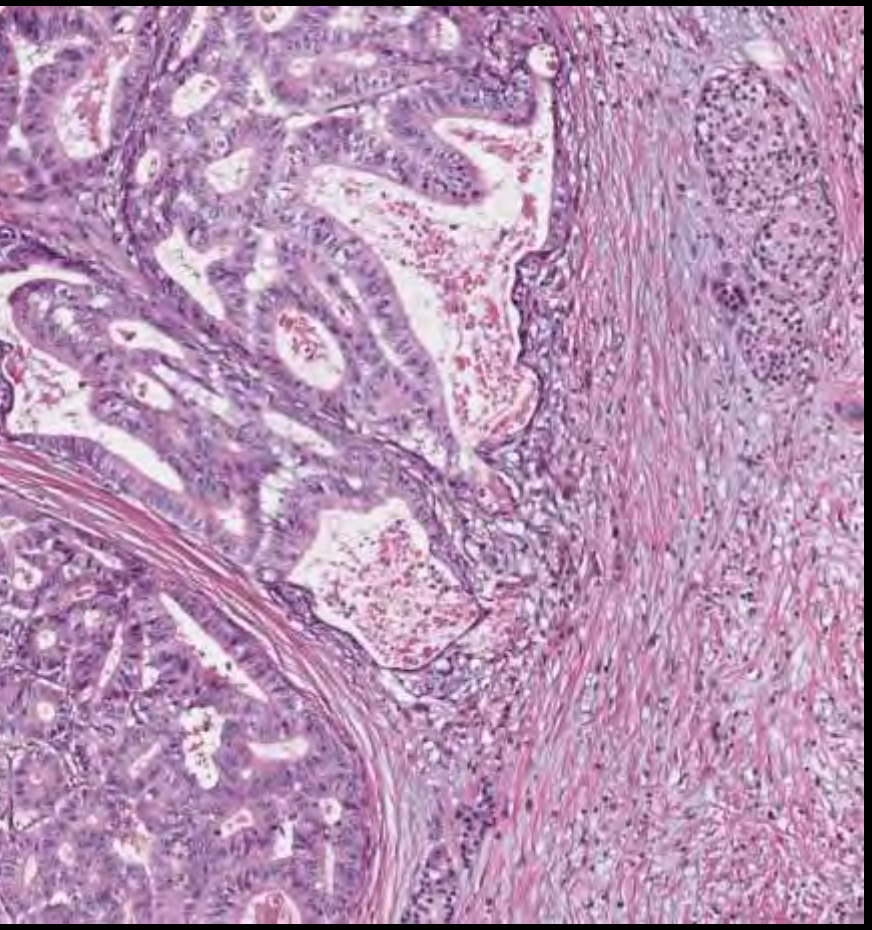
MUC5AC is negative

BCL10,Trypsin negative

Table 10.XX Immunohistochemical profile of intraductal papillary mucinous neoplasm (IPMN), intraductal oncocytic papillary neoplasm (IOPN), and intraductal tubulopapillary neoplasm (ITPN)

	CK7/CK8/CK18/CK19	CK20	EMA (MUC1)	MUC2	MUC5AC	MUC6	CDX2
IPMN							
Gastric	+	–	–	–	+	–/+	–
Pancreatobiliary	+	+	+	–	+	+	–
Intestinal	+	+	–	+	+	–	+
IOPN	+	+ in goblet cells	+	+ in goblet cells	+	+	+ in goblet cells
ITPN	+	–	+	–	–	+	–

Intraductal tubulopapillary neoplasm (ITPN)

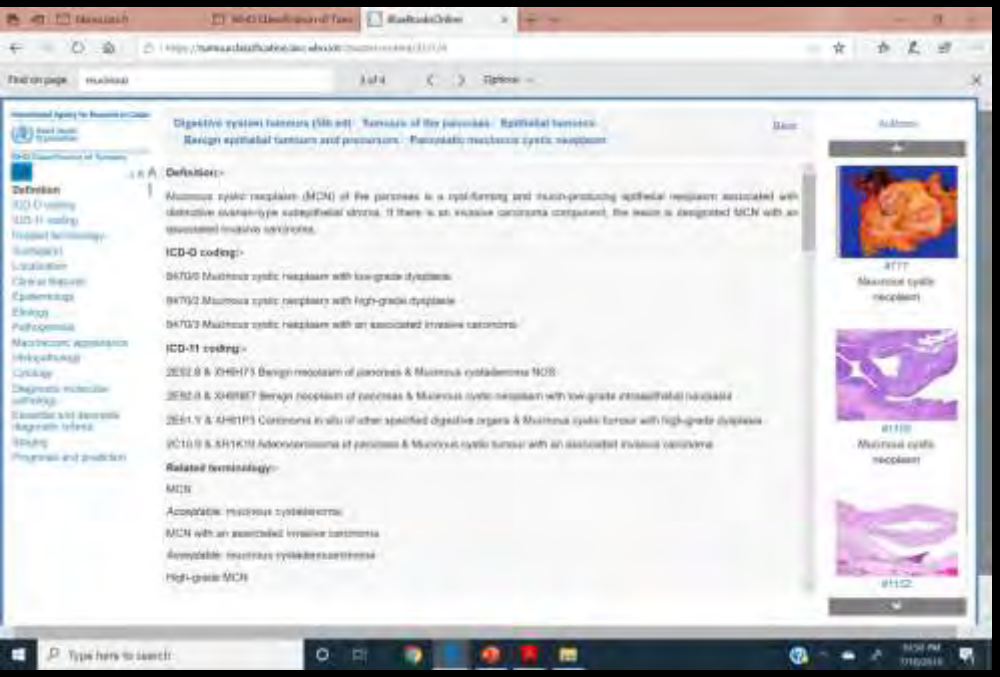


70% have invasive carcinoma

However invasion is hard to appreciate

Even when only the ITPNs with invasive carcinoma are considered, the 5-year survival rate is 71%

Mucinous Cystic Neoplasm (MCN)



Pancreatic mucinous cystic neoplasm

Bentrem D
Esposito I
Fukushima N
Furukawa T
Hong SM
Kloppel G
Matos A
Zamboni G

Definition

Mucinous cystic neoplasm (MCN) of the pancreas is a cyst-forming and mucin-producing epithelial neoplasm associated with distinctive ovarian-type subepithelial stroma. If there is an invasive carcinoma component, the lesion is designated MCN with an associated invasive carcinoma.

ICD-O coding

8470/0 Mucinous cystic neoplasm with low-grade dysplasia
8470/2 Mucinous cystic neoplasm with high-grade dysplasia
8470/3 Mucinous cystic neoplasm with an associated invasive carcinoma

ICD-11 coding

2E92.8 & XH8H73 Benign neoplasm of pancreas & Mucinous cystadenoma NOS
2E92.8 & XH0NK7 Benign neoplasm of pancreas & Mucinous cystic neoplasm with low-grade intraepithelial neoplasia
2E61.Y & XH81P3 Carcinoma in situ of other specified digestive organs & Mucinous cystic tumour with high-grade dysplasia
2C10.0 & XH1K39 Adenocarcinoma of pancreas & Mucinous cystic tumour with an associated invasive carcinoma

Related terminology

MCN

Acceptable: mucinous cystadenoma; mucinous cystadenocarcinoma

High-grade MCN

Acceptable: carcinoma in situ (used parenthetically in some parts of the world)

Subtype(s)

None

Localization

The majority (> 99%) of MCNs occur in the body or tail of the pancreas [3733,3302,3655,1424].

Clinical features

MCNs account for about 8% of resected cystic lesions of the pancreas [1689,563]. The vast majority of MCNs (> 98%) occur in women, and the average age at diagnosis is 46 years (range 14–95 years) [3733,3302,3655,1424]. Patients with an invasive carcinoma component are 5–10 years older than patients with a non-invasive MCN, suggesting that progression occurs over a period of years [1689].

Small tumours (< 3 cm) are usually found incidentally. Larger tumours may produce symptoms due to compression of adjacent structures, often accompanied by a palpable abdominal mass. Imaging studies reveal a large well-defined cystic lesion with thick-walled locations without connection to the pancreatic ducts [266,1689,3655]. Features suggestive of an associated invasive carcinoma include large tumour size (> 5 cm), irregular thickening of the cyst wall, intracystic mural nodules, and elevated serum CA19-9 level (> 37 KU/L) [3655,1434]. Preoperative cyst fluid CEA levels (≥ 192) [266,2203,3277] and molecular analysis [2360,2594,3018] may also supplement other findings in assessing the risk of carcinoma in MCNs.

Fig. 10.33 Mucinous cystic neoplasm. Macroscopically, mucinous cystic neoplasms are typically single unilocular or multilocular cysts containing thick mucin (a haemorrhagic material).

Epidemiology

There are no known geographical variations in the occurrence of MCNs.

Etiology

Unknown.

Pathogenesis

Pancreatic MCNs share many clinicopathological features with their counterparts in the hepatobiliary tract, ovary, and other organs [3022,3733]. It is conceivable that ectopic ovarian stroma incorporated during embryogenesis in the pancreas and other organs may become activated in the setting of a hormonal imbalance, releasing hormones and growth factors and causing nearby ductal epithelium to proliferate and form cystic neoplasms [3733,1415]. This hypothesis cannot account for MCNs in males. Another possibility is that the ovarian-type stroma represents persistent fetal pericystic mesenchyme, which may respond and proliferate in response to hormonal stimulation [1304].

The epithelial component of MCNs harbours activating mutations in codon 12 of *KRAS* in 50–66% of cases, as well as loss-of-function alterations in *RNF43* [3617,22927,3116]. Mutations of *TP53* are rare. Because *TP53* mutations are often associated

Mucinous Cystic Neoplasm (MCN)

Pancreatic mucinous cystic neoplasm

Bertelli G
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Matos A
Zamboni G

Definition
Mucinous cystic neoplasm (MCN) of the pancreas is a cyst-forming and mucin-producing epithelial neoplasm associated with distinctive ovarian-type subepithelial stroma. If there is an invasive carcinoma component, the lesion is designated MCN with an associated invasive carcinoma.

ICD-O coding
8470/0 Mucinous cystic neoplasm with low-grade dysplasia
8470/2 Mucinous cystic neoplasm with high-grade dysplasia
8470/3 Mucinous cystic neoplasm with an associated invasive carcinoma

ICD-11 coding
2E92.8 & XH8HR3 Benign neoplasm of pancreas & Mucinous cystadenoma NOS
2E92.8 & XH0NK7 Benign neoplasm of pancreas & Mucinous cystic neoplasm with low-grade intraepithelial neoplasia
2E61.Y & XH81P3 Carcinoma in situ of other specified digestive organs & Mucinous cystic tumour with high-grade dysplasia
2C10.0 & XH1H39 Adenocarcinoma of pancreas & Mucinous cystic tumour with an associated invasive carcinoma

Related terminology
MCN
Acceptable: mucinous cystadenoma; mucinous cystadenocarcinoma.

High-grade MCN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world).

Subtype(s)
None

Localization
The majority (> 98%) of MCNs occur in the body or tail of the pancreas [3733,3302,3655,1424].

Clinical features
MCNs account for about 8% of resected cystic lesions of the pancreas [1689,563]. The vast majority of MCNs (> 98%) occur in women, and the average age at diagnosis is 46 years (range: 14–95 years) [3733,3302,3655,1424]. Patients with an invasive carcinoma component are 5–10 years older than patients with a non-invasive MCN, suggesting that progression occurs over a period of years [1689].

Small tumours (< 3 cm) are usually found incidentally. Larger tumours may produce symptoms due to compression of adjacent structures, often accompanied by a palpable abdominal mass. Imaging studies reveal a large well-defined cystic lesion with thick-walled locations without connection to the pancreatic ducts [266,1689,3655]. Features suggestive of an associated invasive carcinoma include large tumour size (> 5 cm), irregular thickening of the cyst wall, intracystic mural nodules, and mmatent serum CA19-9 level (> 37 KU/L) [3655,1434]. Preoperative cyst fluid CEA levels (1240,2220,3277) and molecular analysis [2260,2594,1014] may also supplement other findings in assessing the risk of carcinoma in MCNs.

Fig. 10.33 Mucinous cystic neoplasm. Macroscopically, mucinous cystic neoplasms are typically single unilocular or multilocular cysts containing thick mucin or haemorrhagic material.

Epidemiology
There are no known geographical variations in the occurrence of MCNs.

Etiology
Unknown.

Pathogenesis
Pancreatic MCNs share many clinicopathological features with their counterparts in the hepatobiliary tract, ovary, and other organs [3022,3733]. It is conceivable that ectopic ovarian stroma incorporated during embryogenesis in the pancreas and other organs may become activated in the setting of a hormonal imbalance, releasing hormones and growth factors and causing nearby ductal epithelium to proliferate and form cystic neoplasms [2733,1415]. This hypothesis cannot account for MCNs in males. Another possibility is that the ovarian-type stroma represents persistent fetal periductal mesenchyme, which may respond and proliferate in response to hormonal stimulation [1304].

The epithelial component of MCNs harbours activating mutations in codon 12 of *KRAS* in 50–68% of cases, as well as loss-of-function alterations in *RNF43* [3617,2927,3116]. Mutations of *TP53* are rare. Because *TP53* mutations are often associated

Mucinous Cystic Neoplasm (MCN)

Pancreatic mucinous cystic neoplasm

Bertelli G
Esposito I
Fukushima N
Furukawa T
Hong SM
Klöppel G
Matsui A
Zamboni G

Definition
Mucinous cystic neoplasm (MCN) of the pancreas is a cyst-forming and mucin-producing epithelial neoplasm associated with distinctive ovarian-type subepithelial stroma. If there is an invasive carcinoma component, the lesion is designated MCN with an associated invasive carcinoma.

ICD-O coding
8470/0 Mucinous cystic neoplasm with low-grade dysplasia
8470/2 Mucinous cystic neoplasm with high-grade dysplasia
8470/3 Mucinous cystic neoplasm with an associated invasive carcinoma

ICD-11 coding
2E92.8 & XH8HR3 Benign neoplasm of pancreas & Mucinous cystadenoma NOS
2E92.8 & XH0NK7 Benign neoplasm of pancreas & Mucinous cystic neoplasm with low-grade intraepithelial neoplasia
2E61.Y & XH8YP3 Carcinoma in situ of other specified digestive organs & Mucinous cystic tumour with high-grade dysplasia
2C10.0 & XH1H39 Adenocarcinoma of pancreas & Mucinous cystic tumour with an associated invasive carcinoma

Related terminology
MCN
Acceptable: mucinous cystadenoma; mucinous cystadenocarcinoma.

High-grade MCN
Acceptable: carcinoma in situ (used parenthetically in some parts of the world).

Subtype(s)
None

Localization
The majority (> 98%) of MCNs occur in the body or tail of the pancreas (3733,3302,3655,1424).

Clinical features
MCNs account for about 8% of resected cystic lesions of the pancreas (1689,563). The vast majority of MCNs (> 98%) occur in women, and the average age at diagnosis is 46 years (range: 14–95 years) (3733,3302,3655,1424). Patients with an invasive carcinoma component are 5–10 years older than patients with a non-invasive MCN, suggesting that progression occurs over a period of years (1689).

Small tumours (< 3 cm) are usually found incidentally. Larger tumours may produce symptoms due to compression of adjacent structures, often accompanied by a palpable abdominal mass. Imaging studies reveal a large well-defined cystic lesion with thick-walled loculations without connection to the pancreatic ducts (266,1689,3655). Features suggestive of an associated invasive carcinoma include large tumour size (> 5 cm), irregular thickening of the cyst wall, intracystic mural nodules, and mmatent serum CA19-9 level (> 37 KU/L) (3655,1434). Preoperative cyst fluid CEA levels (1260,2220,3277) and molecular analysis (2260,2594,1014) may also supplement other findings in assessing the risk of carcinoma in MCNs.

Fig. 10.33 Mucinous cystic neoplasm. Macroscopically, mucinous cystic neoplasms are typically single unilocular or multilocular cysts containing thick mucin or haemorrhagic material.

Epidemiology
There are no known geographical variations in the occurrence of MCNs.

Etiology
Unknown.

Pathogenesis
Pancreatic MCNs share many clinicopathological features with their counterparts in the hepatobiliary tract, ovary, and other organs (3022,3733). It is conceivable that ectopic ovarian stroma incorporated during embryogenesis in the pancreas and other organs may become activated in the setting of a hormonal imbalance, releasing hormones and growth factors and causing nearby ductal epithelium to proliferate and form cystic neoplasms (2733,1415). This hypothesis cannot account for MCNs in males. Another possibility is that the ovarian-type stroma represents persistent fetal periductal mesenchyme, which may respond and proliferate in response to hormonal stimulation (1304).

The epithelial component of MCNs harbours activating mutations in codon 12 of *KRAS* in 50–68% of cases, as well as loss-of-function alterations in *RNF43* (3617,2927,3116). Mutations of *TP53* are rare. Because *TP53* mutations are often associated

Two tiered grading:

Low grade

High grade

No communication to the ductal system

Ovarian-like stroma

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

- Benign epithelial tumours and precursors
  - Acinar cystic transformation
  - Serous neoplasms
  - Intraepithelial neoplasia
  - Intraductal papillary mucinous neoplasm
  - Intraductal oncocytic papillary neoplasm
  - Intraductal tubulopapillary neoplasm
  - Mucinous cystic neoplasm
- Malignant epithelial tumours
  - Ductal adenocarcinoma
  - Acinar cell carcinoma
  - Pancreatoblastoma
  - Solid pseudopapillary neoplasm
- Neuroendocrine neoplasms
  - Non-functioning neuroendocrine tumours
  - Functioning neuroendocrine tumours
    - Insulinoma
    - Gastrinoma
    - VIPoma
    - Glucagonoma
    - Somatostatinoma
    - ACTH-producing neuroendocrine tumour
    - Serotonin-producing neuroendocrine tumour
  - Neuroendocrine carcinoma
  - MiNENs

Solid Pseudopapillary Neoplasm (SPN)

10.3.5:

Solid pseudopapillary neoplasm of the pancreas

Klöppel G
Basturk O
Klimstra DS
Notohara K

Definition
Solid pseudopapillary neoplasm (SPN) of the pancreas is a low-grade malignant pancreatic tumour composed of poorly cohesive epithelial cells forming solid and pseudopapillary structures that lack a specific line of pancreatic epithelial differentiation.

ICD-O coding
8452/3 Solid pseudopapillary neoplasm

ICD-11 coding
2C10.Y & XH3FD4 Other specified malignant neoplasms of pancreas & Solid pseudopapillary tumour

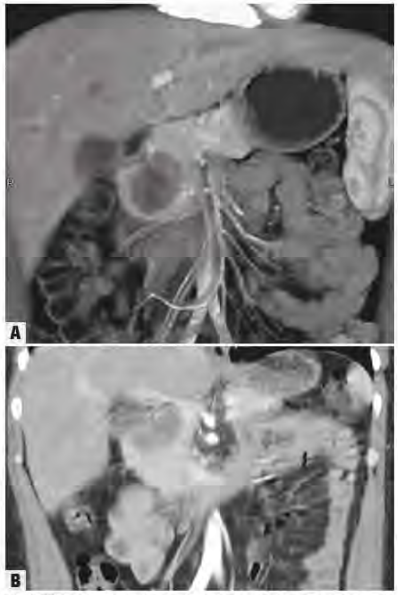


Fig. 10.XX Solid pseudopapillary neoplasm. **A** Coronal CT revealing a solid pseudopapillary neoplasm in the head of the pancreas. **B** Coronal CT demonstrating a solid pseudopapillary neoplasm in the head of the pancreas.

Related terminology
Acceptable: solid-pseudopapillary tumour; solid-cystic tumour; papillary-cystic tumour; solid and papillary epithelial neoplasm; Frantz's tumour (964).

Subtype(s)
Solid pseudopapillary neoplasm with high-grade carcinoma (8452/3)

Localization
SPNs have a slight preference for the tail region (2005,2100). Extrapancreatic SPNs have been reported in retropancreatic tissue, ovary, and testis (1645,1671,3279,2135,1304).

Clinical features
They occur predominantly (90%) in adolescent girls and young women (mean age: 28 years; range: 7–79 years), are rare in men (mean age: 35 years; range: 25–72 years) (1646,3279), and account for 30% of all pancreatic neoplasms in patients aged < 40 years (1980).

SPNs are often found incidentally by imaging or present with abdominal discomfort and pain (1304). Intratumoural haemorrhage after abdominal trauma can produce acute abdomen. All known tumour markers are normal, and the neoplasms are not associated with a functional endocrine syndrome. The diagnosis is established by imaging (ultrasonography, CT, MRI), which reveals a well-demarcated, variably solid and pseudocystic mass, occasionally with calcifications.

Epidemiology
SPNs are rare, accounting for 0.9–2.7% of all exocrine pancreatic neoplasms and only 5% of cystic neoplasms (1689,1304). There is no apparent ethnic predilection.

Etiology
Rare cases have been reported in the setting of familial adenomatous polyposis (2802,1377).

Pathogenesis
The striking sex and age distribution suggests a role for hormonal factors, but no association with endocrine disturbances has been noted to date. The somatic mutation of *CTNNB1* (encoding β-catenin), which most likely occurs early in life, results in a protein that has lost its function as an adhesion molecule at the cell membrane and might be a cause of the tumour cell dyscohesion that is typical of SPNs. Because SPNs identical to those in the pancreas have also been described in the ovary and testis (1671,3047,2135), it is possible that the cells giving rise to SPNs occur in the genital ridges and may be translocated into pancreatic parenchyma during embryogenesis (1690).

The mutation leads to a β-catenin protein that escapes intracytoplasmic phosphorylation and forms complexes with the

Solid Pseudopapillary Neoplasm (SPN)

10.3.5:

Solid pseudopapillary neoplasm of the pancreas

Klöppel G
Basturk O
Klimstra DS
Notohara K

Definition
Solid pseudopapillary neoplasm (SPN) of the pancreas is a low-grade malignant pancreatic tumour composed of poorly cohesive epithelial cells forming solid and pseudopapillary structures that lack a specific line of pancreatic epithelial differentiation.

ICD-O coding
8452/3 Solid pseudopapillary neoplasm

ICD-11 coding
2C10.Y & XH3FD4 Other specified malignant neoplasms of pancreas & Solid pseudopapillary tumour

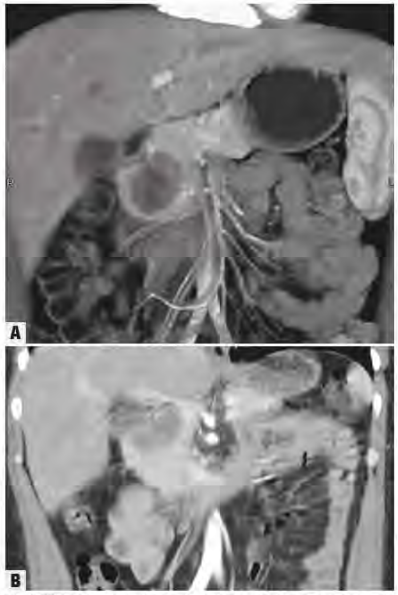


Fig. 10.XX Solid pseudopapillary neoplasm. **A** Coronal CT revealing a solid pseudopapillary neoplasm in the head of the pancreas. **B** Coronal CT demonstrating a solid pseudopapillary neoplasm in the head of the pancreas.

Related terminology
Acceptable: solid-pseudopapillary tumour; solid-cystic tumour; papillary-cystic tumour; solid and papillary epithelial neoplasm; Frantz's tumour (964).

Subtype(s)
Solid pseudopapillary neoplasm with high-grade carcinoma (8452/3)

Localization
SPNs have a slight preference for the tail region (2005,2100). Extrapancreatic SPNs have been reported in retropancreatic tissue, ovary, and testis (1645,1671,3279,2135,1304).

Clinical features
They occur predominantly (90%) in adolescent girls and young women (mean age: 28 years; range: 7–79 years), are rare in men (mean age: 35 years; range: 25–72 years) (1646,3279), and account for 30% of all pancreatic neoplasms in patients aged < 40 years (1980).

SPNs are often found incidentally by imaging or present with abdominal discomfort and pain (1304). Intratumoural haemorrhage after abdominal trauma can produce acute abdomen. All known tumour markers are normal, and the neoplasms are not associated with a functional endocrine syndrome. The diagnosis is established by imaging (ultrasonography, CT, MRI), which reveals a well-demarcated, variably solid and pseudocystic mass, occasionally with calcifications.

Epidemiology
SPNs are rare, accounting for 0.9–2.7% of all exocrine pancreatic neoplasms and only 5% of cystic neoplasms (1689,1304). There is no apparent ethnic predilection.

Etiology
Rare cases have been reported in the setting of familial adenomatous polyposis (2802,1377).

Pathogenesis
The striking sex and age distribution suggests a role for hormonal factors, but no association with endocrine disturbances has been noted to date. The somatic mutation of *CTNNB1* (encoding β-catenin), which most likely occurs early in life, results in a protein that has lost its function as an adhesion molecule at the cell membrane and might be a cause of the tumour cell discohesion that is typical of SPNs. Because SPNs identical to those in the pancreas have also been described in the ovary and testis (1671,3047,2135), it is possible that the cells giving rise to SPNs occur in the genital ridges and may be translocated into pancreatic parenchyma during embryogenesis (1690).

The mutation leads to a β-catenin protein that escapes intracytoplasmic phosphorylation and forms complexes with the

Solid Pseudopapillary Neoplasm (SPN)

10.3.5:

Solid pseudopapillary neoplasm of the pancreas

Klöppel G
Basturk O
Klimstra DS
Notohara K

Definition
Solid pseudopapillary neoplasm (SPN) of the pancreas is a low-grade malignant pancreatic tumour composed of poorly cohesive epithelial cells forming solid and pseudopapillary structures that lack a specific line of pancreatic epithelial differentiation.

ICD-O coding
8452/3 Solid pseudopapillary neoplasm

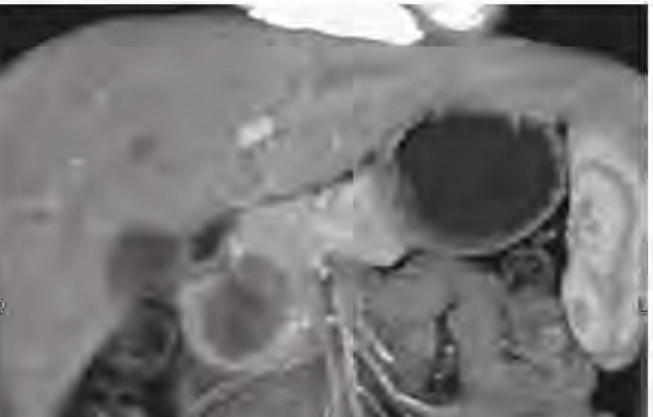
ICD-11 coding
2C10.Y & XH3FD4 Other specified malignant neoplasm of pancreas & Solid pseudopapillary tumour

Related terminology
Acceptable: solid-pseudopapillary tumour; solid papillary-cystic tumour; solid and papillary plasm; Frantz's tumour {964}.

Subtype(s)
Solid pseudopapillary neoplasm with high-g (8452/3)

/3 means malignant

ail region {2005,2100}.
ted in retropancreatic tissue, ovary, and testis {1645,1671,3279,2135,1304}.



Clinical features
They occur predominantly (90%) in adolescent girls and young women (mean age: 28 years; range: 7–79 years), are rare in men (mean age: 35 years; range: 25–72 years) {1646,3279}, and account for 30% of all pancreatic neoplasms in patients aged < 40 years {1980}.

SPNs are often found incidentally by imaging or present with abdominal discomfort and pain {1304}. Intratumoural haemorrhage after abdominal trauma can produce acute abdomen. All known tumour markers are normal, and the neoplasms are not associated with a functional endocrine syndrome. The diagnosis is established by imaging (ultrasonography, CT, MRI), which reveals a well-demarcated, variably solid and pseudocystic mass, occasionally with calcifications.

The long-term prognosis is generally excellent for localized, metastatic, and recurrent disease, with long disease-free periods after complete surgical resection
Only a few patients have died of a metastasizing SPN, mostly patients whose tumours harboured an undifferentiated component

Solid Pseudopapillary Neoplasm (SPN)

10.3.5:

Solid pseudopapillary neoplasm of the pancreas

Klöppel G
Basturk O
Klimstra DS
Notohara K

Definition
Solid pseudopapillary neoplasm (SPN) of the pancreas is a low-grade malignant pancreatic tumour composed of poorly cohesive epithelial cells forming solid and pseudopapillary structures that lack a specific line of pancreatic epithelial differentiation.

ICD-O coding
8452/3 Solid pseudopapillary neoplasm

ICD-11 coding
2C10.Y & XH3FD4 Other specified malignant neoplasm of pancreas & Solid pseudopapillary tumour

Related terminology
Acceptable: solid-pseudopapillary tumour; solid papillary-cystic tumour; solid and papillary neoplasm; Frantz's tumour [964].

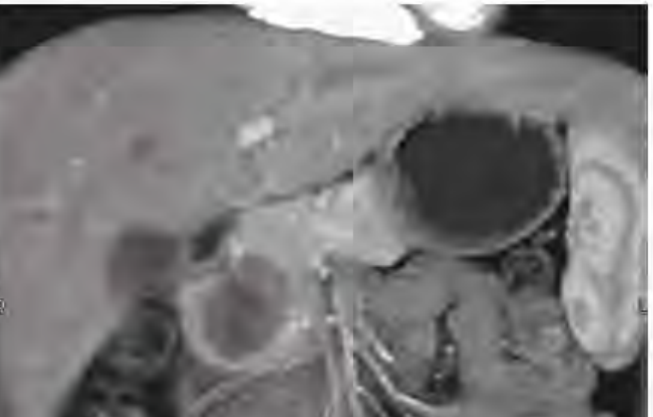
Subtype(s)
Solid pseudopapillary neoplasm with high-grade (8452/3)

/3 means malignant

...ail region [2005,2100].
...ted in retropancreatic tissue, ovary, and testis [1645,1671,3279,2135,1304].

Clinical features
They occur predominantly (90%) in adolescent girls and young women (mean age: 28 years; range: 7–79 years) and in young men (mean age: 35 years; range: 25–72 years) and account for 30% of all pancreatic neoplasms in patients aged < 40 years [1980].

SPNs are often found incidentally by imaging. Patients with abdominal discomfort and pain [1304]. Intratumoral haemorrhage after abdominal trauma can produce acute pancreatitis. Well-known tumour markers are normal, and there is no syndrome associated with a functional endocrine syndrome. Diagnosis is established by imaging (ultrasonography, CT, MRI) which reveals a well-demarcated, variably solid and cystic mass, occasionally with calcifications.



The long-term prognosis is generally excellent for localized, metastatic, and recurrent disease, with long disease-free periods after complete surgical resection
Only a few patients have died of a metastasizing SPN, mostly patients whose tumours harboured an undifferentiated component

Metastatic behaviour cannot be predicted by perineural invasion, angioinvasion, and/or deep infiltration of surrounding structures. Consequently, all SPNs are currently classified as low-grade malignant neoplasms.

Solid Pseudopapillary Neoplasm (SPN)

10.3.5:

Solid pseudopapillary neoplasm of the pancreas

Klöppel G
Basturk O
Klimstra DS
Notohara K

Definition
Solid pseudopapillary neoplasm (SPN) of the pancreas is a low-grade malignant pancreatic tumour composed of poorly cohesive epithelial cells forming solid and pseudopapillary structures that lack a specific line of pancreatic epithelial differentiation.

ICD-O coding
8452/3 Solid pseudopapillary neoplasm

ICD-11 coding
2C10.Y & XH3FD4 Other specified malignant neoplasms of pancreas & Solid pseudopapillary tumour

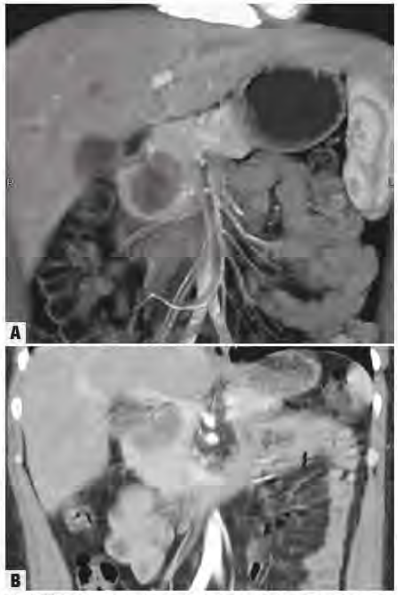


Fig. 10.XX Solid pseudopapillary neoplasm. **A** Coronal CT revealing a solid pseudopapillary neoplasm in the head of the pancreas. **B** Coronal CT demonstrating a solid pseudopapillary neoplasm in the head of the pancreas.

Related terminology
Acceptable: solid-pseudopapillary tumour; solid-cystic tumour; papillary-cystic tumour; solid and papillary epithelial neoplasm; Frantz's tumour (964).

Subtype(s)
Solid pseudopapillary neoplasm with high-grade carcinoma (8452/3)

Localization
SPNs have a slight preference for the tail region (2005,2100). Extrapancreatic SPNs have been reported in retropancreatic tissue, ovary, and testis (1645,1671,3279,2135,1304).

Clinical features
They occur predominantly (90%) in adolescent girls and young women (mean age: 28 years; range: 7–79 years), are rare in men (mean age: 35 years; range: 25–72 years) (1646,3279), and account for 30% of all pancreatic neoplasms in patients aged < 40 years (1980).

SPNs are often found incidentally by imaging or present with abdominal discomfort and pain (1304). Intratumoural haemorrhage after abdominal trauma can produce acute abdomen. All known tumour markers are normal, and the neoplasms are not associated with a functional endocrine syndrome. The diagnosis is established by imaging (ultrasonography, CT, MRI), which reveals a well-demarcated, variably solid and pseudocystic mass, occasionally with calcifications.

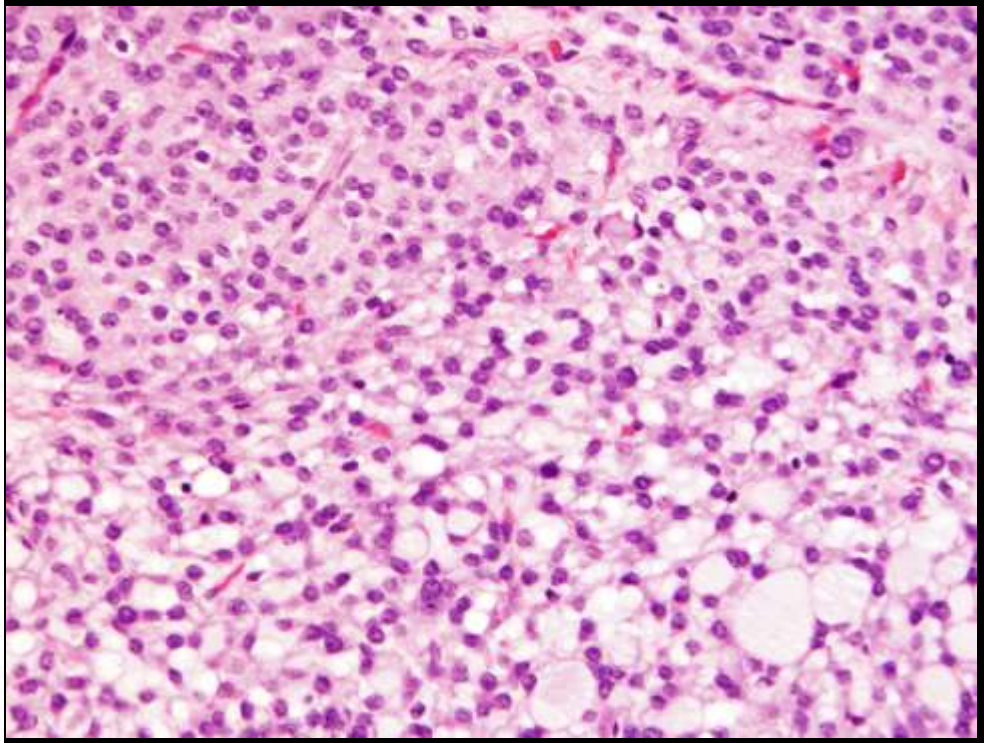
Epidemiology
SPNs are rare, accounting for 0.9–2.7% of all exocrine pancreatic neoplasms and only 5% of cystic neoplasms (1689,1304). There is no apparent ethnic predilection.

Etiology
Rare cases have been reported in the setting of familial adenomatous polyposis (2802,1377).

Pathogenesis
The striking sex and age distribution suggests a role for hormonal factors, but no association with endocrine disturbances has been noted to date. The somatic mutation of *CTNNB1* (encoding β-catenin), which most likely occurs early in life, results in a protein that has lost its function as an adhesion molecule at the cell membrane and might be a cause of the tumour cell discohesion that is typical of SPNs. Because SPNs identical to those in the pancreas have also been described in the ovary and testis (1671,3047,2135), it is possible that the cells giving rise to SPNs occur in the genital ridges and may be translocated into pancreatic parenchyma during embryogenesis (1690).

The mutation leads to a β-catenin protein that escapes intracytoplasmic phosphorylation and forms complexes with the

Ovarian Microcystic Stromal Tumour



10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

Benign epithelial tumours and precursors
- Acinar cystic transformation
- Serous neoplasms
- Intraepithelial neoplasia
- Intraductal papillary mucinous neoplasm
- Intraductal oncocytic papillary neoplasm
- Intraductal tubulopapillary neoplasm
- Mucinous cystic neoplasm

Malignant epithelial tumours
- Ductal adenocarcinoma
- Acinar cell carcinoma
- Pancreatoblastoma
- Solid pseudopapillary neoplasm

Neuroendocrine neoplasms
- Non-functioning neuroendocrine tumours
- Functioning neuroendocrine tumours
  - Insulinoma
  - Gastrinoma
  - VIPoma
  - Glucagonoma
  - Somatostatinoma
  - ACTH-producing neuroendocrine tumour
  - Serotonin-producing neuroendocrine tumour
- Neuroendocrine carcinoma
- MiNENs

Pancreatoblastoma vs Acinar Cell Carcinoma

Pancreatoblastoma

Ohike N
La Rosa S

Definition
Pancreatoblastoma is a malignant epithelial neoplasm of the pancreas showing predominantly acinar differentiation with squamoid nests.

ICD-O coding
8971/3 Pancreatoblastoma

ICD-11 coding
2C10.Y & XH27L6 Other specified malignant neoplasms of pancreas & Pancreatoblastoma

Related terminology
None

Subtype(s)
None

Localization
Pancreatoblastoma has no preferential location within the pancreas.

Clinical features
The presenting features of pancreatoblastoma are nonspecific, and many cases are discovered incidentally. Common symptoms include abdominal pain, weight loss, nausea, and diarrhoea. Jaundice is uncommon. An abdominal mass is often palpable, especially in children. Isolated case reports have described patients with Cushing syndrome as a result of the inappropriate secretion of ACTH by the tumour (2632,1627,2542). Serum AFP, which can be used to monitor the effectiveness of therapy, is elevated in two thirds of children, with levels often in excess of 1000 µg/L (634), but it is not consistently elevated in adults (2647). CEA may be elevated in children.

Epidemiology
Although pancreatoblastoma is a rare neoplasm, with approximately 200 cases reported, it is one of the most frequent pancreatic neoplasms in childhood, accounting for approximately 25% of pancreatic neoplasms occurring in the first decade of life (median age: ~4–6 years) (3034,2259). Approximately 40 cases have been reported in patients of between 18 and 78 years of age (2396). No sex predominance is seen.

Etiology
The precise etiology is unknown. Although most cases are sporadic, there are associations with genetic syndromes (Beckwith–Wiedemann syndrome and familial adenomatous polyposis) and with the corresponding genetic mutations.

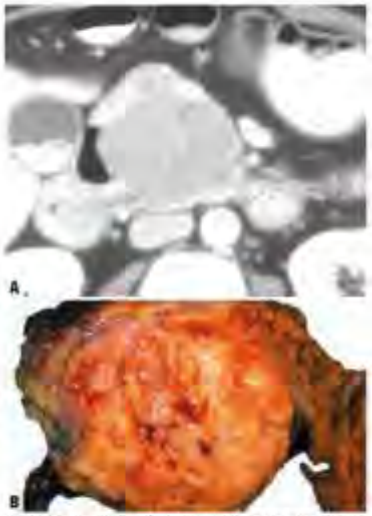


Fig. 10.XX Pancreatoblastoma. **A** CT of a pancreatoblastoma in the head of the pancreas. **B** The cut section of the neoplasm reveals multilobated surfaces.

Pathogenesis
Unknown.

Macroscopic appearance
Pancreatoblastomas are usually large at presentation, ranging from 1.5 to 20 cm in size (mean: 10 cm) (3425). Most are solitary, at least partially well-circumscribed or encapsulated, solid masses. Sectioning reveals tan to whitish-yellow soft lobules separated by fibrous stromal bands. Some may contain cystic spaces due to haemorrhagic necrosis and cystic degeneration, which appear as a heterogeneous or multiloculated mass on radiological imaging. Congenital cases in association with Beckwith–Wiedemann syndrome may be predominantly cystic (813). Biliary and pancreatic ductal dilatation may be present.

Pancreatic acinar cell carcinoma

La Rosa S
Klimstra DS
Wood LD

Definition
Acinar cell carcinoma of the pancreas is a malignant pancreatic epithelial neoplasm showing acinar cell differentiation.

ICD-O coding
8550/3 Acinar cell carcinoma

ICD-11 coding
2C10.0 & XH0PG8 Adenocarcinoma of pancreas & Acinar cell carcinoma

Related terminology
None

Subtype(s)
Acinar cell cystadenocarcinoma (8551/3); mixed acinar-ductal carcinoma (8552/3); mixed acinar neuroendocrine carcinoma (8154/3); mixed acinar-ductal neuroendocrine carcinoma (8154/3)

Localization
Acinar cell carcinomas may arise in any portion of the pancreas, but they are most frequent in the head, followed by the tail and the body (1748,1628).

Clinical features
Presenting symptoms are usually related to tumour growth and/or metastatic spread and include weight loss, abdominal pain, vomiting, and nausea. Jaundice can be present but is rare. Patients with extensive metastatic disease may show symptoms due to lipase hypersecretion, which include subcutaneous fat necrosis and polyarthralgia (1629,1748,1628,1757). Rare patients, especially when young, can show increased blood levels of AFP (640,2045).

Epidemiology
Acinar cell carcinomas account for about 1–2% of pancreatic neoplasms in adults and about 15% in children (1628). The average age of adult patients is approximately 60 years (range: 20–88 years). Males are more commonly affected, with an M:F ratio of 2.3:1 (1748,1628,1257).

Etiology
Although most acinar cell carcinomas are sporadic, rare cases diagnosed in the context of Lynch syndrome, Carney complex, or familial adenomatous polyposis have been documented (1017,1748,1522,1931,2931).

Pathogenesis
Little is known about the pathogenesis. Although some cytogenetic similarities between acinar cell carcinomas and ductal adenocarcinomas have been observed, the cytogenetic profile is globally different between the two entities. Acinar cell carcinomas show a mutation signature associated with tobacco use and defective DNA repair (1496). Acinar cell carcinomas show chromosomal instability characterized by high degrees of allelic loss and gains. The regions more frequently involved by losses included 1p, 3p, 5q, 6q, 8p, 9p, 11, 17p, and 18q, whereas the gained regions were mainly 1q, 7, 8q, 12, 17q, and 20q (1464,1270,3264,306). Interestingly, a hierarchical clustering of comparative genomic hybridization findings did not find differences between pure acinar cell carcinomas, cystic acinar cell carcinomas, and mixed acinar-neuroendocrine carcinomas, indicating that these subtypes have the same cytogenetic background (306). *MYC* alterations, including gene amplification and/or chromosome 8 polysomy, have been described in a subset of acinar cell carcinomas and in all mixed acinar-neuroendocrine carcinomas investigated, but they were not associated with a different prognostic signature (306,1750). Loss of 18q has been correlated with loss or substantial reduction of

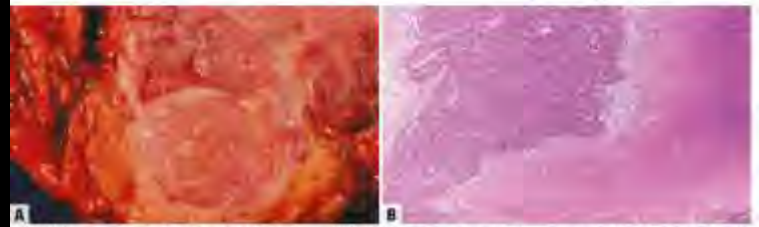
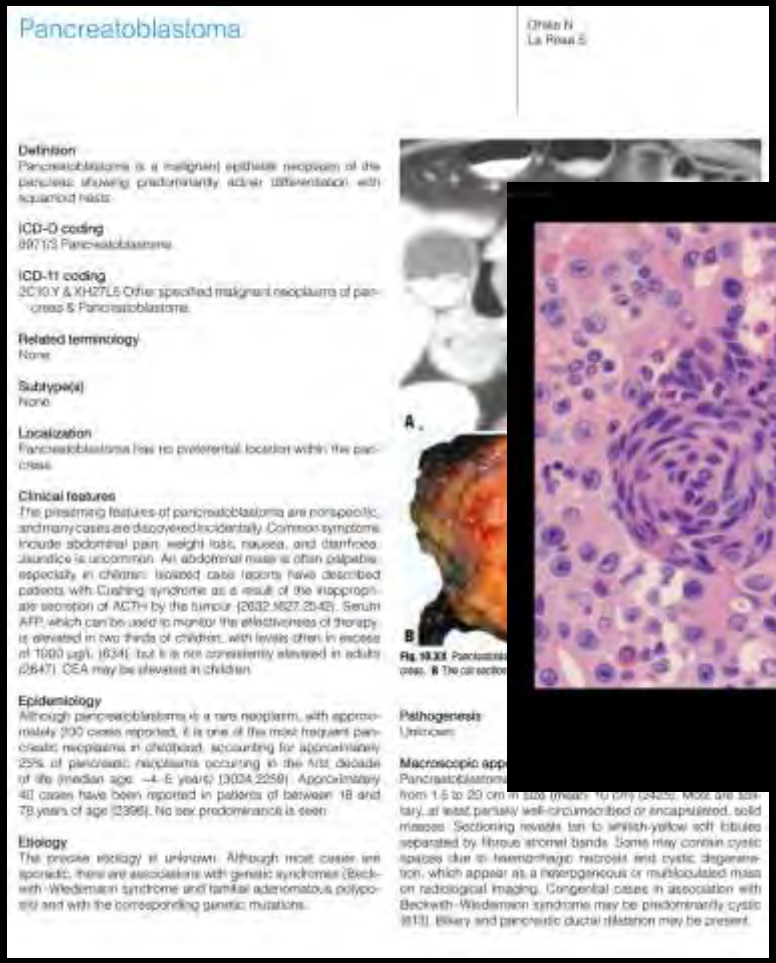


Fig. 10.XX Acinar cell carcinoma. **A** The cut surface shows a well circumscribed, encapsulated, solid tumour with a homogeneous pink surface. **B** At low power, acinar cell carcinoma appears as a highly cellular tumour with scant fibrous stroma showing a lobular pattern of growth and necrosis.

Pancreatoblastoma vs Acinar Cell Carcinoma



Pancreatoblastoma

Ohike N
La Rosa S

Definition
Pancreatoblastoma is a malignant epithelial neoplasm of the pancreas showing predominantly acinar differentiation with squamoid nests.

ICD-O coding
8971/3 Pancreatoblastoma

ICD-11 coding
2C10.Y & XH27L6 Other specified malignant neoplasms of pancreas & Pancreatoblastoma

Related terminology
None

Subtype(s)
None

Localization
Pancreatoblastoma has no preferential location within the pancreas.

Clinical features
The presenting features of pancreatoblastoma are nonspecific, and many cases are discovered incidentally. Common symptoms include abdominal pain, weight loss, nausea, and diarrhoea. Jaundice is uncommon. An abdominal mass is often palpable, especially in children. Isolated case reports have described patients with Cushing syndrome as a result of the inappropriate secretion of ACTH by the tumour (2632,1627,2542). Serum AFP, which can be used to monitor the effectiveness of therapy, is elevated in two thirds of children, with levels often in excess of 1000 µg/L (634), but it is not consistently elevated in adults (2647). CEA may be elevated in children.

Epidemiology
Although pancreatoblastoma is a rare neoplasm, with approximately 200 cases reported, it is one of the most frequent pancreatic neoplasms in childhood, accounting for approximately 25% of pancreatic neoplasms occurring in the first decade of life (median age: ~4–5 years) (3034,2259). Approximately 40 cases have been reported in patients of between 18 and 78 years of age (2396). No sex predominance is seen.

Etiology
The precise etiology is unknown. Although most cases are sporadic, there are associations with genetic syndromes (Beckwith-Wiedemann syndrome and familial adenomatous polyposis) and with the corresponding genetic mutations.

Pathogenesis
Unknown

Macroscopic app
Pancreatoblastoma
from 1.5 to 20 cm in size (mean: 10 cm) (2425). Most are solitary, at least partially well-circumscribed or encapsulated, solid masses. Sectioning reveals tan to whitish-yellow soft lobules separated by fibrous stromal bands. Some may contain cystic spaces due to haemorrhagic necrosis and cystic degeneration, which appear as a heterogeneous or multiloculated mass on radiological imaging. Congenital cases in association with Beckwith-Wiedemann syndrome may be predominantly cystic (813). Biliary and pancreatic ductal dilatation may be present.

Pancreatic acinar cell carcinoma

La Rosa S
Klimstra DS
Wood LD

Definition
Acinar cell carcinoma of the pancreas is a malignant pancreatic epithelial neoplasm showing acinar cell differentiation.

Epidemiology
Acinar cell carcinomas account for about 1–2% of pancreatic neoplasms in adults and about 15% in children (1625). The age of adult patients is approximately 60 years (range: ...years). Males are more commonly affected, with an ... of 2.3:1 (1748,1628,1257).

...t most acinar cell carcinomas are sporadic, rare cases ...ed in the context of Lynch syndrome, Carney complex, ...ial adenomatous polyposis have been documented ...48,1520,1931,2931).

...nesis
...known about the pathogenesis. Although some cytoge... ...milarities between acinar cell carcinomas and ductal ...arcinomas have been observed, the cytogenetic profile ...ly different between the two entities. Acinar cell car... ...show a mutation signature associated with tobacco ...defective DNA repair (1490). Acinar cell carcinomas ...romosomal instability characterized by high degrees ... loss and gains. The regions more frequently involved ...es included 1p, 3p, 5q, 6q, 8p, 9p, 11, 17p, and 18q. ...the gained regions were mainly 1q, 7, 8q, 12, 17q, and ...54,1270,3264,306). Interestingly, a hierarchical cluster... ...omparative genomic hybridization findings did not find ...ces between pure acinar cell carcinomas, cystic acinar ...rcinomas, and mixed acinar-neuroendocrine carcino... ...ggesting that these subtypes have the same cytogenetic ...und (306). *MYC* alterations, including gene amplifica... ...or chromosome 8 polysomy, have been described in ...t of acinar cell carcinomas and in all mixed acinar-neu... ...rine carcinomas investigated, but they were not associ... ...h a different prognostic signature (306,1750). Loss of ... been correlated with loss or substantial reduction of

Pancreatic Acinar Cell Carcinoma

Pancreatic acinar cell carcinoma

La Rosa S
Adsmona DS
Woodi LD

Definition
Acinar cell carcinoma of the pancreas is a malignant pancreatic epithelial neoplasm showing acinar cell differentiation.

ICD-O coding
8550/3 Acinar cell carcinoma

ICD-11 coding
2C10.0 & XH3PG9 Adenocarcinoma of pancreas & Acinar cell carcinoma

Related terminology
None

Subtype(s)
Acinar cell cystadenocarcinoma (8551/3); mixed acinar-ductal carcinoma (8552/3); mixed acinar neuroendocrine carcinoma (8154/3); mixed acinar-ductal neuroendocrine carcinoma (8154/3)

Localization
Acinar cell carcinomas may arise in any portion of the pancreas, but they are most frequent in the head, followed by the tail and the body (1748,1628)

Clinical features
Presenting symptoms are usually related to tumour growth and to metastatic spread and include weight loss, abdominal pain, vomiting, and nausea. Jaundice can be present but is rare. Patients with extensive metastatic disease may show symptoms due to lipase hypersecretion, which include subcutaneous fat necrosis and polyarthralgia (1629,1748,1638,1757). Rare patients, especially when young, can show increased blood levels of AFP (640,2045).

Epidemiology
Acinar cell carcinomas account for about 1–2% of pancreatic neoplasms in adults and about 15% in children (1629). The average age of adult patients is approximately 60 years (range, 20–86 years). Males are more commonly affected, with an M:F ratio of 2:1:1 (1748,1628,1257).

Etiology
Although most acinar cell carcinomas are sporadic, rare cases diagnosed in the context of Lynch syndrome, Carney complex, or familial adenomatous polyposis have been documented (1017,1748,1522,1931,2931).

Pathogenesis
Little is known about the pathogenesis. Although some cytogenetic similarities between acinar cell carcinomas and ductal adenocarcinomas have been observed, the cytogenetic profile is globally different between the two entities. Acinar cell carcinomas show a mutation signature associated with tobacco use and defective DNA repair (1490). Acinar cell carcinomas show chromosomal instability characterized by high degrees of allelic loss and gains. The regions more frequently involved by losses included 1p, 3p, 5q, 6q, 8p, 9p, 11, 13p, and 18q, whereas the gained regions were mainly 1q, 7, 8q, 12, 17q, and 20q (1464,1270,3264,308). Interestingly, a hierarchical clustering of comparative genomic hybridization findings did not find differences between pure acinar cell carcinomas, cystic acinar cell carcinomas, and mixed acinar-neuroendocrine carcinomas, indicating that these subtypes have the same cytogenetic background (306). *MYC* alterations, including gene amplification and/or chromosome 8 polysomy, have been described in a subset of acinar cell carcinomas and in all mixed acinar-neuroendocrine carcinomas investigated, but they were not associated with a different prognostic signature (606,1750). Loss of 18q has been correlated with loss or substantial reduction of

A B

Fig. 10.33 Acinar cell carcinoma. **A** The cut surface shows a well-circumscribed, encapsulated, solid tumour with a homogeneous pink surface. **B** At low power, acinar cell carcinoma appears as a highly cellular tumour with scant fibrous stroma showing a lobular pattern of growth and necrosis.

Lack KRAS/GNAS mutations

Frequent fusions

BRAF

RET

RAF1

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

10

Tumours of the pancreas

Edited by: Gill AJ, Klimstra DS, Lam AK, Washington MK

- Benign epithelial tumours and precursors
  - Acinar cystic transformation
  - Serous neoplasms
  - Intraepithelial neoplasia
  - Intraductal papillary mucinous neoplasm
  - Intraductal oncocytic papillary neoplasm
  - Intraductal tubulopapillary neoplasm
  - Mucinous cystic neoplasm
- Malignant epithelial tumours
  - Ductal adenocarcinoma
  - Acinar cell carcinoma
  - Pancreatoblastoma
  - Solid pseudopapillary neoplasm
- Neuroendocrine neoplasms
  - Non-functioning neuroendocrine tumours
  - Functioning neuroendocrine tumours
    - Insulinoma
    - Gastrinoma
    - VIPoma
    - Glucagonoma
    - Somatostatinoma
    - ACTH-producing neuroendocrine tumour
    - Serotonin-producing neuroendocrine tumour
  - Neuroendocrine carcinoma
  - MiNENs

Pancreatic Ductal Adenocarcinoma

10.3.1

Pancreatic ductal adenocarcinoma

Hruban RH
Adsay NV
Esposito I
Fukushima N
Fukayama T
Klöppel G
Maitra A
Nicolaides K
Offerhaus GJA
Ohike N
Pilman MB
Zamboni G

Definition

Pancreatic ductal adenocarcinoma (PDAC) is an invasive pancreatic epithelial neoplasm with glandular (ductal) differentiation usually demonstrating luminal and/or intracellular mucin production, without a substantial component of any other histological type.

ICD-O coding

8140/3 Ductal adenocarcinoma

ICD-11 coding

2C10.0 Adenocarcinoma of pancreas

Related terminology

Ductal adenocarcinoma

Acceptable: duct cell adenocarcinoma; infiltrating duct carcinoma; tubular adenocarcinoma; adenocarcinoma

Adenosquamous carcinoma

Acceptable: Mucoepidermoid carcinoma

Colloid carcinoma

Acceptable: mucinous non-cystic carcinoma

Undifferentiated carcinoma, anaplastic type

Acceptable: giant cell carcinoma; anaplastic carcinoma; pleomorphic large cell carcinoma

Undifferentiated carcinoma, sarcomatoid type

Acceptable: spindle cell carcinoma; sarcomatoid carcinoma

Undifferentiated carcinoma with osteoclast-like giant cells

Acceptable: osteoclastic giant cell carcinoma

Subtype(s)

Adenosquamous carcinoma (8560/3); colloid carcinoma (8480/3); hepatoid carcinoma (8576/3); medullary carcinoma (8510/3); poorly cohesive carcinoma, with or without signet-ring cells (8490/3); undifferentiated carcinoma (8020/3); undifferentiated carcinoma with osteoclast-like giant cells (8035/3); undifferentiated carcinoma with rhabdoid cells (8014/3)

Localization

Two-thirds of ductal adenocarcinomas arise in the head of the pancreas, and the remainder in the body or tail of the gland (1304). The vast majority of ductal adenocarcinomas are solitary, but multifocal disease can occur (1304,2503). Very rarely, ectopic pancreatic tissue can give rise to pancreatic intraepithelial neoplasia (PanIN) lesions and even to an invasive carcinoma (1062,3260,1488,3754).

Clinical features

Clinical features include decreased appetite and indigestion, changes in bowel habits, fatigue, back pain, unexplained weight loss, and jaundice (3505). New-onset diabetes (type II) may be the first manifestation of pancreatic cancer (1175,2973). Depression may be a presenting symptom (3569). Symptoms of advanced disease are related to liver metastases and/or invasion of adjacent organs (e.g. the duodenum) or of the peritoneal cavity (ascites). Patients occasionally present with migratory thrombophlebitis (1706) or rarely with acute pancreatitis (1887).

Multidetector CT with dual-phase or multiphase dynamic contrast using early arterial, pancreatic, and late venous phases is one of the best imaging modalities for the pancreas and the surrounding vasculature (3589). PDAC usually appears as an irregular solid hypodense or hypoenhancing mass with abrupt cut-off and upstream dilatation of the pancreatic duct. The double-duct sign (dilatation of both the biliary and the pancreatic ducts) is virtually pathognomonic of carcinoma of the head of the pancreas. MRI may be more sensitive than CT for the detection and evaluation of liver metastases (2532), and magnetic resonance cholangiopancreatography provides excellent evaluation of the duct system. EUS allows high-resolution imaging of the pancreas and surrounding lymph nodes and vessels; it also allows tissue sampling, which remains the gold standard for diagnosis. PET may have diagnostic value, especially in cases with enlarged lymph nodes or of pancreatic masses after therapy (3520). The cancer markers CA19-9 and CEA are not useful for screening of asymptomatic individuals but can be used to monitor established disease (2906).

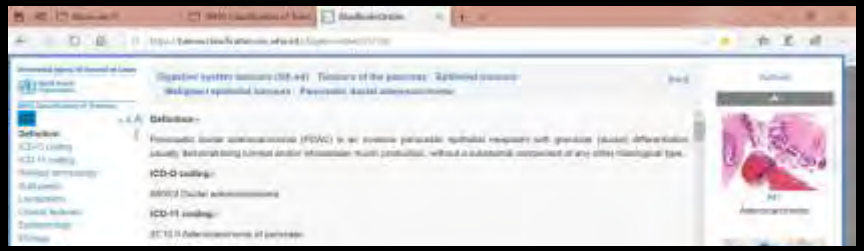
Epidemiology

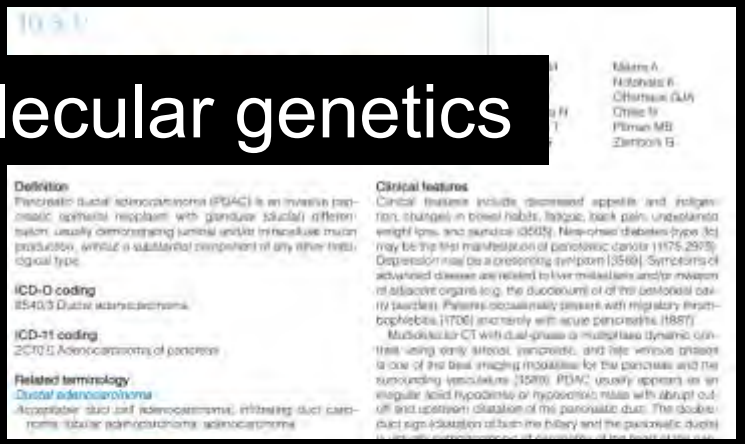
The epidemiological study of PDAC is complicated by substantial geographical and temporal variations in the sensitivity and specificity of clinical diagnosis and in the proportion of cases that are histologically verified. Differences in access to health care (e.g. across different social classes or age groups) can affect the reported incidence and mortality rates.

Worldwide, 458 918 new cases of PDAC were estimated in 2018, with an age-adjusted incidence rate among both sexes of 6.2 cases per 100 000 person-years in higher-income countries and 1.5 cases per 100 000 person-years in lower-income countries (359). The highest rates have been recorded among black people in the USA (about 17 cases per 100 000 person-years among men and 14 cases per 100 000 person-years among women (3043)) and in indigenous populations in Oceania. The lowest rates (< 2 cases per 100 000 person-years among men and 1 case per 100 000 person-years among women), which may be partially attributable to underdiagnosis, have been recorded in India, northern and central Africa, and south-eastern Asia. Most patients are diagnosed at an age of 55–85 years (median age at diagnosis in the USA: 70 years). Globally, the M:F ratio is 1.1:1. Because of the very poor survival, mortality

Pancreatic Ductal Adenocarcinoma

Increased discussion of molecular genetics





Invasive micropapillary carcinoma

Invasive micropapillary carcinoma is an adenocarcinoma in which ≥ 50% of the neoplasm consists of small solid nests of cells suspended within stromal lacunae. Micropapillary carcinomas behave more aggressively.

WHO 5th edition 2019 GIT Blue Book

E-format and uniformity

Two tiered grading (PanIN,IPMN, MCN)

IOPN and ITPN separated from IPMN