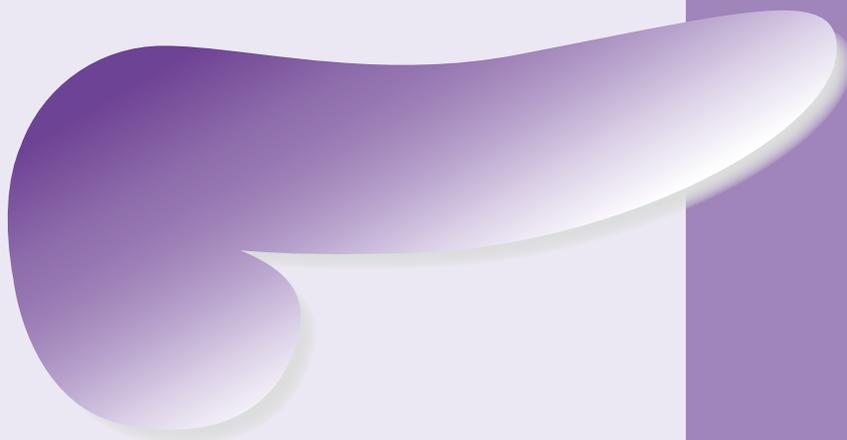


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Classification of Pancreatic Carcinoma

Japan Pancreas Society

Fourth English Edition



Kanehara & Co., Ltd.

Classification of Pancreatic Carcinoma

Japan Pancreas Society

Fourth English Edition

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Preface of the Fourth English Edition

The purpose of establishing cancer classification is to make rules and guidelines so that clinicians and pathologists can compare and discuss collected cancer data and clinical outcomes based on a common criteria. As for the classification of pancreatic cancer in Japan, the 1st Japanese edition of the *General Rules for the Study of Pancreatic Cancer* was released in 1980 by the Japan Pancreas Society (JPS). The 7th Japanese edition by JPS was published in 2016. During the interval, the English edition had been published: the 1st edition in 1996 as the 4th Japanese edition, the 2nd in 2003 as the 5th and the 3rd in 2011 as the 6th.

The 6th Japanese edition (2009) had been used widely in Japan, together with the Union for International Cancer Control (UICC) 7th edition (2009). Two classifications adopted TNM classification, but they were quite different in T category, N category, and Staging system, constituting obstacles to compare status and clinical outcomes of pancreatic cancer patients between Japan and western countries. Therefore, the revision committee of JPS started its work in April 2013, and the 7th Japanese edition has been published in July 2016. The current revision by JPS focuses on establishing consistency between the Japanese and UICC classifications; however, originality of JPS classification, which is more precise and contains more information, is maintained. In the 7th Japanese edition, major revisions have been carried out by comparing the 6th edition in the following points. (1) Definition of the portions of the pancreas: the border between the pancreatic body and tail is defined as the left side line of the abdominal aorta, (2) T category: consistency with that of the UICC 7th edition, (3) Reappraisal of anatomy of extrapancreatic nerve plexuses, (4) N category: new classification based on numbers of lymph nodal metastasis among the regional lymph nodes, (5) Stage grouping: consistency with UICC 7th staging system, and (6) Histopathological classification: consistency with the World Health Organization (WHO) classification. Furthermore, the following new items have been added: (1) criteria of diagnosis for T category based on multi-detector row computed tomography (MD-CT), (2) criteria of diagnosis for lymph nodal metastasis based on MD-CT, (3) criteria defining resectability, (4) cytopathology guideline, and (5) criteria of histological response to drug therapy and/or radiotherapy.

To assist in the dissemination of knowledge in the JPS classification of pancreatic cancer, the 7th Japanese edition is being published here as the fourth English edition. It is our hope that the new JPS classification will contribute to improvement of diagnosis as well as data analysis of pancreatic cancer.

July 2017

Shuji Isaji, MD, PhD

Chairman, Committee on General Rules for the Study of Pancreatic Cancer

Japan Pancreas Society

Preface of the Seventh Japanese Edition

The *General Rules of the Study of Pancreatic Cancer* (1st Japanese Edition) was published in Japan in October 1980 by the Japan Pancreas Society (JPS) as a means of recording surgical findings, pathological analysis, and histological classifications under standard criteria. Since then, there have been several revisions and in 1996, an English version entitled *Classification of Pancreatic carcinoma* was issued. It is now being used internationally. In Europe and America, TNM classification and staging for pancreatic cancer were established by the UICC in 1987, and the 7th Edition of UICC was published in 2009. Both classifications use the TNM system, but the Japanese classification emphasizes recording extensive clinical information whereas the UICC employs simple expression across organs. T and N classifications and staging differ significantly, creating significant obstacles to comparing outcomes for pancreatic cancer treatment between Japan and the West. Consequently, there have been demands for creating a new protocol that conforms to international standards, while retaining the advantages of the Japanese rules.

Discussion of revisions towards the 7th Edition of the General Rules started in April 2013 with a focus on the following four areas: 1) TNM classification and staging; 2) classifications for resectability (resectable, borderline resectable, unresectable); 3) diagnostic imaging criteria; and 4) histological classification in accordance to WHO. Considering the increasing preoperative therapy currently undertaken, new items were also added such as biopsy, cytology, and histological assessment of preoperative therapeutic effects. Consequently, the number of the 7th edition committee members was increased to 25 (12 surgeons, 4 gastroenterologists, 7 pathologists, 1 radiologist, and 1 anatomist). A total of 7 meetings were held to prepare the draft of the 7th Edition of the General Rules in October 2015. The draft was published on the website of the JPS with a call for public comment, and a public hearing was held in November (the 77th Annual Congress of Japan Surgical Association in Fukuoka), where a wide range of opinion was voiced. The 7th edition committee met again to consider the feedback, and convened a new extrapancreatic nerve plexus working group to conduct a fundamental review of the extrapancreatic nerve plexus including that in the head of the pancreas, a unique feature of the Japanese classification. These discussions resulted in the completion of the General Rules at the 8th committee meeting in March 2016.

This revision involved major changes and the addition of new items including CT imaging. The number of pages more than doubled from 57 in the 6th revised and expanded edition to 121 pages. The textbook begins with a summary of the rules for ease of use in clinical settings, with the details in the body of the volume. It also includes the various data at each stage, extrapolated from the nationwide pancreatic cancer case data of Japan Pancreatic Cancer Registry of Japan Pancreas Society. It is hoped that this General Rules will be used in daily clinical practice alongside the pancreatic cancer

treatment guidelines, and that research findings based on the JPS General Rules will be published globally.

The main revisions and new items are as follows.

[Revisions]

- Tumor lesion sites: Changed the boundary of the pancreas body and tail to the left margin of the aorta.
- T classification: The T3 and T4 classifications were determined by the degree of infiltration into the superior mesenteric artery (SMA) and celiac artery (CA) in accordance with the UICC TNM classifications (7th Edition). The T1 classification was sub-classified as T1a, T1b, and T1c according to the size of the tumor, in view of future application to intraductal papillary mucinous neoplasms (IPMNs).
 - New figures were prepared based on review of the anatomy of the extrapancreatic nerve plexus, and intraoperative photographs were included.
- N classification: Changed from classification by metastatic lymph node group to classification by the number of metastases in the regional lymph nodes. 1 to 3 metastases to the regional lymph nodes are sub-classified as N1a and 4 or more as N1b.
- Staging: We focused on consistency with UICC staging (7th Edition) and comparison with resectability classifications rather than prognostic stratification to assist in creating treatment plans. Pancreatic cancer to Stage II is resectable (R) or borderline resectable (BR-PV), Stage III is borderline resectable (BR-A) or locally advanced unresectable pancreatic cancer (UR-LA), and Stage IV is metastasis to distant organs (UR-M).
- Creation and revision of the recording method
 - The method of notation for the presence of cancer was changed from (–) or (+) to 0 or 1.
 - For assessment of residual tumor (R), we recommend noting the distance from the cut end margin in the case of R0.
 - For pancreatic cut end margin (PCM) and bile duct cut end margin (BCM) positive, (e) is written for carcinoma in situ only and (i) for invasive carcinoma.
 - The notation for infiltrating tumors was changed from $INF\alpha, \beta, \gamma$ to $INF\alpha, b, c$.
- Histopathological classification
 - We aimed for consistency with the WHO classification of Tumors of the digestive system (2010).
 - Pancreatic duct tumors are classified as intraductal papillary mucinous neoplasms (IPMNs), intraductal tubulopapillary neoplasm (ITPNs), and pancreatic intraepithelial neoplasia (PanIN).
 - We changed the notation for invasive pancreatic cancer from morphological notation (papillary adenocarcinoma: pap, tubular adenocarcinoma: tub) to differentiation (well differentiated:

wel, moderately differentiated: mod, poorly differentiated: por).

[New items]

- CT diagnostic imaging: CT diagnostic guidelines and an evaluation method for local invasion of pancreatic cancer are presented. Representative CT imaging examples by T factor and resectability are presented. CT image and histopathological images are compared.
- Resectability classifications: We formulated resectability classifications consisting solely of anatomical findings obtained based on CT images. Resectable (R), borderline resectable (BR: BR-PV, BR-A), unresectable (UR: UR-LA, UR-M).
- We developed biopsy, cytology, and histological assessment of preoperative therapeutic effects.

June 2016

Shuji Isaji

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Masamichi Mizuma

Preface of the Third English Edition

The Japanese edition of the *General Rules for the Study of Pancreatic Cancer* by the Japan Pancreas Society (JPS) has undergone several revisions since the publication of the 1st edition in 1980, and the 6th edition was released in 2009. During the interval, the 1st English edition was published in 1996, and the 2nd English edition was published in 2003. Today, the JPS' *General Rules for the Study of Pancreatic Cancer* is widely used, together with the UICC classifications, not only in Japan, but around the world. In addition, in 2006, the JPS published the first *Guidelines for the Diagnosis and Treatment of Pancreatic Cancer*. These two volumes are the twin pillars for the treatment of pancreatic cancer in Japan. The Pancreatic Cancer Registry was established by the JPS in 1981, and is also used as a source of valuable data.

Following the publication of the 5th Japanese edition, the Committee on General Rules for the Study of Pancreatic Cancer repeatedly reviewed the organization of surgical procedures and T, N, and M staging in the 5th edition based on the data compiled in the JPS' Pancreatic Cancer Registry. The pathological classifications, mainly of IPMN and MCN, were also reviewed, and the 6th edition was published in July 2009. We believe that the JPS' General Rules have advantages over the UICC classification in their characterization of the T classification, and especially the N classification, and both classifications have been continued unchanged. Problems remain in regard to the definitions of RP and PL, the definition of "minimal invasion" in MCC and IPMC, and establishing General Rules that are common to all countries. To assist in the dissemination and more widespread use of the JPS' General Rules, the 6th edition is being published here as the 3rd English edition.

It is our hope that wider use of the JPS' General Rules will be beneficial in improving the results of regular diagnosis and treatment of pancreatic cancer.

June 2011

Akimasa Nakao
Chairman, Committee on General Rules for the Study of Pancreatic Cancer
Japan Pancreas Society

Preface of the Second English Edition

The Japan Pancreas Society published the 1st English edition of the *Classification of Pancreatic Carcinoma* in 1996. It was based on the 4th Japanese edition of the *General Rules for the Study of Pancreatic Cancer* published in 1993.

In July 1997, the Review Committee of the General Rules for the Study of Pancreatic Cancer began comparing the Japanese classification with the 5th edition of the UICC classification (1997) and identified the advantages and disadvantages of the two classification schemes. The Committee also carefully reviewed the validity of each factor used in the 4th edition of the General Rules based on the data from 18,629 cases of carcinoma of the pancreas (1981–1996) in the National Pancreatic Cancer Registry of the Japan Pancreas Society.

In late 1997, using the 5th edition of the UICC classification scheme for reference, the Committee commenced preparation of the 5th edition of the General Rules with the goal of making the General Rules simple, easy to understand, and acceptable by international standards, while not sacrificing any of the merits of the Japanese classification scheme. Unfortunately, the 5th edition of the General Rules was published in 2002, the same year that the UICC published its 6th edition. Since the UICC publication was unexpected and there was not enough time to incorporate the changes made in the 6th UICC edition in this English edition based on the 5th edition of the General Rules, mutual discussion is needed before preparing future editions.

May 2003

Yoshifumi Kawarada
Chairman, Committee of General Rules for Study of Pancreatic Cancer
Japan Pancreas Society

Preface of the First English Edition

To make it possible to compare the incidence and therapeutic outcome of pancreatic cancer in different institutions based on common criteria and terminology, the Japan Pancreas Society published the 1st Japanese-language edition of the General Rules for the Study of Pancreatic Cancer in 1980. Improvements in diagnostic and treatment methods since that time have led to repeated revisions, and the 4th edition is currently in use. Because the Japan Pancreas Society believes that these general rules, which are anatomy-based and practical, will not be of much benefit unless their concepts become widely accepted, it has decided to make them available in English. The publication of this *Classification of Pancreatic Carcinoma* represents the first English edition of the *General Rules for the Study of Pancreatic Cancer*, and is based on the 4th Japanese edition, with full illustrations and detailed descriptions.

This manual is composed of the following three parts: “Clinical, Surgical, and Comprehensive Findings,” “Handling of the Specimen,” and “Histological Findings.”

We hope that this 1st English edition will be of great service to those in the field throughout the world.

March 1996

Ryuji Mizumoto

Chairman, Committee of General Rules for Study of Pancreatic Cancer

Japan Pancreas Society

Conflicts of Interest

In preparation of the 7th edition of the Classification of Pancreatic Carcinoma, the Japan Pancreas Society applied the following criteria regarding the economic interests of relationships with corporations related to the contents of the Classification of Pancreatic Carcinoma, to request the relevant committee members to declare relationships with financial interests.

The names of the declared corporates are listed below (in the period between January 1, 2013 and December 31, 2015). Non-profit organizations are not included.

1. Corporation/organization where a member, their spouse, first-degree family member, or income/property sharer received some personal consideration
Board member/advisor with compensation $\geq 1,000,000$ yen; stock compensation $\geq 1,000,000$ yen; or 5% of the issued stocks.
2. Corporation/organization where a member received some personal consideration
Lecture fee $\geq 500,000$ yen; manuscript fee $\geq 500,000$ yen; other remuneration $\geq 50,000$ yen
3. Corporation/organization having academic-industrial alliance with the department a committee member belongs to
Research fund $\geq 1,000,000$ yen; scholarship fund $\geq 1,000,000$ yen; endowed chair/contribution $\geq 2,000,000$ yen.

Financial relationships between the relevant member and corporations

1. N/A
2. Eizai Co., Ltd., Taiho Pharmaceutical Co, Ltd.
3. Ajinomoto Co., Inc., AstraZeneca K. K., Eizai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., OncoTherapy Science, Inc., Kyowa Hakko Kirin Co., Ltd., GlaxoSmithKline K. K., Kowa Company, Ltd., Shionogi & Co., Ltd., JUNKEN MEDICAL Co., Ltd., Zeria Pharmaceutical Co., Ltd., Century Medical, Inc., Sumitomo Dainippon Pharma Co., Ltd., Taiho Pharmaceutical Co, Ltd., Takeda Bio Development Center Limited, Chugai Pharmaceutical Co., Ltd., NanoCarrier Co., Ltd., Eli Lilly Japan K. K., Zeon Corporation, Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K. K., Bayer Yakuhin, Ltd., Piolax Medical Devices, Inc., Hitachi Medical Corporation, Pfizer Japan Inc., Fujifilm Corporation., Boston Scientific Japan K. K., Merck Serono Co., Ltd., Yakult Honsha Co., Ltd.

Note: Conflicts of interest issues are now under discussion both within and outside of Japan, and their policies and forms will be reviewed in the future.

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Abbreviations

Ao	aorta
ASPDA	anterior superior pancreaticoduodenal artery
CA	celiac artery
CBD	common bile duct
CHA	common hepatic artery
CHD	common hepatic duct
DPA	dorsal pancreatic artery
Du	duodenum
GCT	gastrocolic trunk
GDA	gastroduodenal artery
GEPV	gastroepiploic vein
IMA	inferior mesenteric artery
IMV	inferior mesenteric vein
IPDA	inferior pancreaticoduodenal artery
IVC	inferior vena cava
J1A	artery of the first jejunum/first jejunal artery
J2A	artery of the second jejunum/second jejunal artery
J1V	first jejunal vein
LGA	left gastric artery
LGV	left gastric vein
LHA	left hepatic artery
LN	lymph node
LRA	left renal artery
LRV	left renal vein
MCA	middle colic artery
MCV	middle colic vein
MPD	main pancreatic duct
Pb	pancreatic body
Ph	pancreatic head
PHA	proper hepatic artery
PIPDA	posterior inferior pancreatoduodenal artery
PLph I	pancreatic head plexus I
PLph II	pancreatic head plexus II
Pt	pancreatic tail
PV	portal vein
RCV	right colic vein
RGEA	right gastroepiploic artery
RGV	right gastric vein
RHA	right hepatic artery
RRA	right renal artery
RRV	right renal vein
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SP	splenic plexus
SPA	splenic artery
SPV	splenic vein
UP	uncinate process

Synopsis

II. Principles of Recording Findings (refer to p.10)

The main disease covered is primary pancreatic carcinoma. Therefore, cancers occurring in the pancreatic bile duct, duodenum or duodenal papilla are not covered, but if differentiation is difficult, they can be handled according to this classification.

T category clinical findings, surgical findings, pathological findings, final findings

N category clinical findings, surgical findings, pathological findings, final findings

M category clinical findings, surgical findings, pathological findings, final findings

III. Description of Findings

1. Primary tumor

1) Tumor location (refer to p.12)

The pancreas is anatomically divided into three main portions: the head, the body, and the tail. The border between pancreatic body and tail is defined as left side line of abdominal aorta. The uncinata process is included as part of the head of the pancreas. When lesions are present in two or more adjacent portions of the pancreas, the abbreviation of the part in which the primary tumor is located should be recorded first, followed by the part (s) involved as a result of infiltration.

Sample notation: Phb, Pbht

4) Grade of local invasion (T category) (refer to p.14)

The grade of local invasion of the pancreas by the primary tumor should be recorded as the T category and be further specified by using the local invasion factors^[1]: Abbreviations CH, DU, S, RP, PV, A, PL, and OO are used.

TX: Local invasion cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: Tumor limited to the pancreas, 20 mm or less in the greatest dimension

 T1a: Tumor 5 mm or less in greatest dimension

 T1b: Tumor greater than 5 mm and less than 10 mm in greatest dimension

 T1c: Tumor greater than 10 mm but no more than 20 mm in greatest dimension

T2: Tumor limited to the pancreas, more than 20 mm in greatest dimension

T3: Tumor extends beyond the pancreas, but without involvement of CA or SMA.

T4: Tumor involves CA or SMA

NOTE 1: Local invasion factors

- Bile duct invasion CH0: absent CH1: present* CHX: cannot be assessed
*Histologically, invasion into the fibromuscular layer of the bile duct or further into the inner side of the bile duct.
- Duodenal invasion DU0: absent DU1: present* DUX: cannot be assessed
*Histologically, invasion into the muscular layer of the duodenum or further into the inner side of the duodenum.
- Serosal side of the anterior pancreatic tissue invasion
S0: absent S1: present* SX: cannot be assessed
*Invasion into the serosal tissue (e. g. fibrous connective tissue, adipose tissue) : Invasion exposed on the serous surface, or adhesion of the greater and lesser omentum or mesocolon, due to invasion are also classified as S1 with a note of that effect.
- Retropancreatic tissue invasion RP0: absent RP1: present* RPX: cannot be assessed
*Invasion into the retropancreatic tissue (e. g. fibrous connective tissue, adipose tissue)
Note: S and RP are the factors to evaluate the presence of extrapancreatic invasion to define T3. When differentiation between S1 and RP1 is challenging, classify the case as RP1 for descriptive purposes.
- Portal venous system invasion PV0: absent PV1: present* PVX: cannot be assessed
*Histologically, invasion into the vein wall, including the outer layer
Note: The portal venous system consists of the portal vein (PVp), superior mesenteric vein (PVsm), and splenic vein (PVsp).
- Arterial system invasion AO: absent A1: present* AX: cannot be assessed
*Histologically, invasion into the artery wall, including the outer layer
Note: The artery system consists of the superior mesenteric artery (Asm), celiac artery (Ace), common hepatic artery (Ach), and splenic artery (Asp).
- Extrapancreatic nerve plexus invasion PL0: absent PL1: present PLX: cannot be assessed
Note: When the extrapancreatic nerve plexus is difficult to identify, classify the case as PLX.
- Invasion of other organs OO0: absent OO1: present OOX: cannot be assessed
Note: Other organs consist of the adrenal gland, stomach, large intestine, spleen, renal vein, kidney, inferior vena cava, aorta, and others. The invaded organ name should be clearly indicated.

2. Lymph node metastases

2) Regional lymph nodes (refer to p.41)

Lymph node numbers 5, 6, 7, 8a, 8p, 9, 10, 11p, 11d, 12a, 12b, 12p, 13a, 13b, 14p, 14d, 17a, 17b, and 18 are defined as pancreatic regional lymph nodes irrespective of the tumor location. Metastasis to any lymph node other than those mentioned above, including numbers 1, 2, 3, 4, 15, 16a1, 16a2, 16b1, and 16b2, should be classified as M1.

3) Recording lymph node metastases (N) (refer to p.41)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Regional lymph node metastasis

N1a: Metastasis in one to three regional lymph nodes

N1b: Metastasis in four or more regional lymph nodes

3. Distant metastases (M) (refer to p.48)

M0: No distant metastasis

M1: Distant metastasis

The M1 site should be recorded using the following codes:

PUL: pulmonary MAR: bone marrow OSS: osseous PLE: pleura
 HEP: hepatic PER: peritoneum BRA: brain ADR: adrenals
 LYM: lymph nodes SKI: skin OTH: others

Note 1: Lymph node metastasis outside the regional nodes should be recorded as M1.

Specifically, peritoneal and hepatic metastases classified as M1 should be recorded as follows:

1) Peritoneal metastasis (P, M1 PER in the UICC TNM classification system) (refer to p.48)

P0: No peritoneal metastasis

P1: Peritoneal metastasis

2) Hepatic metastasis (H, M1 HEP in the UICC TNM classification system) (refer to p.48)

H0: No hepatic metastasis

H1: Hepatic metastasis

Recording peritoneal washing cytology (CY) (refer to p.48)

CYX: Peritoneal washing cytology not performed

CY0: Peritoneal washing cytology negative for carcinoma cells

CY1: Peritoneal washing cytology positive for carcinoma cells

Note: The CY1 category is not considered as M1 in this Classification, but further discussion on this issue is expected to continue in the future.

4. Staging (refer to p.49)

Stage 0	Tis	N0	M0
Stage IA	T1 (T1a, T1b, T1c)	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1 (T1a, T1b, T1c), T2, T3	N1 (N1a, N1b)	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

5. Resectability classification (refer to p.53)

Resectable: R

No tumor contact with SMV or PV or less than 180 contact or invasion without occlusion. Clear fat planes around SMA, CA, and CHA, showing no contact or invasion.

Borderline resectable: BR

Subclassified according to SMV/PV invasion alone or arterial invasion.

BR-PV (SMV/PV invasion alone)

No findings of contact and invasion of SMA, CA, and CHA. Tumor contact or invasion of the SMV/PV of 180 or more degrees or occlusion of the SMV/PV, not exceeding the inferior border of the duodenum.^[1]

BR-A (Arterial invasion)

Tumor contact or invasion of SMA and/or CA of less than 180 degrees without showing stenosis or deformity. Tumor contact or invasion of CHA without showing tumor contact or invasion of PHA and/or CA.^[2]

Note 1: Reconstruction is challenging when images show SMV/PV having contact with/invasion of the tumor or an occlusion, or display tumor invasion beyond the lower margin of the duodenum.

Note 2: Cases of contact or invasion are classified as BR-A for both the portal venous and arterial systems.

Unresectable: UR

Subclassified according to the status of distant metastasis.

UR-LA (Locally advanced)

Tumor contact or invasion of SMV/PV of 180 or more degree or occlusion of SMV/PV, exceeding the inferior border of the duodenum. Tumor contact or invasion of SMA and/or CA of 180 or more degree. Tumor contact or invasion of CHA showing tumor contact or invasion of the PHA and/or CA. Tumor contact or invasion of the aorta.

UR-M (Tumor with distant metastasis)

Distant metastasis including non-regional lymph node metastasis.

IV. Surgical Treatment

4. Assessment of residual tumor (R) (refer to p.61)

RX: Presence of residual tumor cannot be assessed

R0: No residual tumor

R1: Microscopic residual tumor

R2: Macroscopic residual tumor

For R0, it is desirable to record the shortest distance (mm) from the cut-end margin to the invasion site.

Note: the presence/absence of invasion at the cut-end and dissected margins should be recorded as below.

1) Pancreatic cut-end margin (PCM)

PCM0: No cancer infiltration

PCM1: Cancer infiltration present*

PCMX: Cancer infiltration cannot be assessed.

*Only PCM1 with carcinoma in situ should be recorded as PCM1e (epithelium), while PCM1 with invasive carcinoma or with both cancer in situ and invasive carcinoma should be recorded as PCM1i (invasive).

2) Bile duct cut-end margin (BCM)

BCM0: No cancer infiltration

BCM1: Cancer infiltration present*

BCMx: Cancer infiltration cannot be assessed.

*BCM1 with carcinoma in situ only is recorded as BCM1e (epithelium), while BCM1 with invasive carcinoma or with both cancer in situ and invasive carcinoma is recorded as BCM1i (invasive).

3) Dissected peripancreatic tissue margin (DPM)

DPM0: No cancer infiltration

DPM1: Cancer infiltration present

DCMX: Cancer infiltration cannot be assessed.

Summary

Pancreas	
T1	Limited to pancreas ≤ 20 mm
	T1a ≤ 5 mm
	T1b > 5 mm to 10 mm
	T1c > 10 mm to 20 mm
T2	Limited to pancreas > 20 mm
T3	Beyond pancreas
T4	Involves CA or SMA
N1	Regional lymph node (s)
	N1a 1–3
	N1b 4 or more
M1	Distant organ or non-regional lymph node (s) (CY1 is not considered as M1)

Dataset for histopathological reports for pancreatic cancer

Category	Grading/classification	Refer to
Tumor location	Ph, Pb, Pt, Phb, Pbt, Phbt, others	p.12
Size and number of the tumors	TS1 [≤ 20 mm], TS2 [20 mm<, ≤ 40 mm], TS3 [40 mm<, ≤ 60 mm], TS4 [> 60 mm], i-TS. Number of tumors and greatest diameter (mm) should be recorded.	p.12
Macroscopic type	masked, type, nodular type, infiltrative type, cystic type, ductectatic type, mixed type, unclassifiable type	p.13
Histopathological diagnosis	serous neoplasms, mucinous cystic neoplasms, intraductal neoplasms, invasive ductal carcinoma, acinar cell neoplasms, neuroendocrine neoplasms, solid-pseudopapillary neoplasms, pancreatoblastoma, others	p.70
T category	pTX pT0 pTis pT1a [≤ 5 mm], pT1b [5 mm<, ≤ 10 mm], pT1c [10 mm<, ≤ 20 mm] pT2 [tumor limited to the pancreas, > 20 mm] pT3 [tumor extends beyond the pancreas, but without involvement of CA or SMA] pT4 [Tumor involves CA or SMA]	p.14
Cancer-stroma relationship	med, int, sci	p.71
Growth patterns of neoplasms infiltrating surrounding tissue	INFa, INFb, INFc	p.71
Lymphatic invasion	ly0, ly1, ly2, ly3	p.72
Venous invasion	v0, v1, v2, v3	p.72
Nerve invasion	ne0, ne1, ne2, ne3	p.72
Intraductal spread in MPD	mpd0, mpd1: the distance beyond the area of the invasive tumor should be recorded (mm), mpdx	p.72
Bile duct invasion	pCH0, pCH1, pCHX	p.14
Duodenal invasion	pDU0, pDU1, pDUX	p.14
Serosal side of the anterior pancreatic tissue invasion	pS0, pS1, pSX	p.14
Retropancreatic tissue invasion	pRP0, pRP1, pRPX	p.14
Portal venous system invasion	pPV0, pPV1 (PVp, PVsm, PVsp), pPVX	p.14
Arterial invasion	pA0, pA1 (Asm, Ace, Ach, Asp), pAX	p.14
Extrapancreatic nerve plexus invasion	pPL0, pPL1, pPLX	p.14
Invasion of other organs*	pOO0, pOO1: the invaded organ name should be recorded, pOOX	p.14
Pancreatic cut-end margin	pPCM0, pPCM1e, pPCM1i, pPCMX	p.61

Category	Grading/classification	Refer to
Bile duct cut-end margin	pBCM0, pBCM1e, pBCM1i, pBCMx	p.62
Dissected peripancreatic tissue margin	pDPM0, pDPM1, pDPMx	p.62
Regional lymph node metastases [†]	pNX, pN0, pN1a [1–3], pN1b [≥4]	p.41
Distant metastases [‡]	M0, M1: metastatic organ should be recorded	p.48
Peritoneal washing cytology	CYX, CY0, CY1	p.48
Staging [§]	pStage 0, pStage IA, pStage IB, pStage IIA, pStage IIB, pStage III, pStage IV	p.49
Residual tumor	R0: it is desirable to record shortest distance (mm) from the cut-end margin to the invasion site, R1, R2	p.61
Histological response to preoperative therapy	Grade 1a [estimated residual rate ≥90%] Grade 1b [50% ≤ estimated residual rate <90%] Grade 2 [10% ≤ estimated residual rate <50%] Grade 3 [estimated residual rate <10%] Grade 4 [no viable cancer cells are found]: the presence of intraductal components should be noted in remarks.	p.117

*Invasion of other organs (refer to p.14)

Other organs consist of the adrenal gland, stomach, large intestine, spleen, renal vein, kidney, inferior vena cava, aorta, and others. The invaded organ name should be clearly indicated.

[†]Regional lymph nodes (refer to p.41)

No. 5, 6, 7, 8a, 8p, 9, 10, 11p, 11d, 12a, 12b, 12p, 13a, 13b, 14p, 14d, 17a, 17b, 18

[‡]Metastatic organ (refer to p.48)

Pulmonary: PUL	Bone marrow: MAR	Osseous: OSS	Pleura: PLE
Hepatic: HEP	Peritoneum: PER	Brain: BRA	Adrenals: ADR
Lymph nodes: LYM	Skin: SKI	Others: OTH	

[§]Staging (refer to p.49)

Stage 0	Tis	N0	M0
Stage IA	T1 (T1a, T1b, T1c)	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1 (T1a, T1b, T1c), T2, T3	N1 (N1a, N1b)	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

I. Introduction (purpose and the main disease covered)

The 1st Japanese Edition of the *General Rules for the Study of Pancreatic Cancer* was published in 1980. In 1993, the 4th Japanese Edition of the General Rules was produced in Japan incorporating the UICC TNM classification. Based on the 4th edition, in 1996, the 1st Edition of the English version entitled “*Classification of Pancreatic Carcinoma*” (hereafter “the Classification”) was published. In 1997, the 5th Edition of the UICC TNM classification was published. It was pointed out that the Japanese 4th Edition and UICC 5th Edition had few points in common, and that the Japanese classification was complex and lacked international applicability. Therefore, the 5th Japanese Edition published in 2002 was prepared aiming to achieve a protocol that maintained the advantages of the previous versions, that was clear, simple and internationally applicable, based on results tabulated nationwide and at various facilities. The 6th Japanese Edition reorganized the surgical procedure and the pathological classifications of IPMN, and MCN of the 5th Japanese Edition while inheriting the outline of the 5th Japanese Edition.

The 7th Japanese Edition saw major new revisions. The main revisions are as follows: 1. Tumor lesion sites (changed the boundary between the body and tail of the pancreas to the left margin of the aorta); 2. T classification (achieves consistency with UICC 7th Edition); 3. Review of the anatomy of the extrapancreatic nerve plexus; 4. N classification (changed from classification by metastatic lymph node group to classification by the number of metastases to the regional lymph nodes), 5. Staging (places importance on the treatment plan, achieves consistency with UICC 7th Edition), 6. Histopathological classification (achieves consistency with the WHO classifications). The newly added content includes; 1. CT diagnostic imaging guidelines for T factor notation, 2. CT diagnostic guidelines for lymph node metastasis, 3. Resectability classifications using CT imaging, 4. Biopsy, 5. Cytology, 6. Histological assessment of preoperative therapeutic effects.

The purpose of this Classification is to establish clinical and pathological handling methods to enable comparison of materials based on common standards, with the ultimate goal of contributing to improving the treatment outcomes of pancreatic cancer. The main disease covered is primary pancreatic carcinoma. Therefore, cancers occurring in the pancreatic bile duct, duodenum or duodenal papilla are not covered, but if differentiation is difficult, they can be handled according to this classification. It is desirable to follow the notation in the Classification for metastatic cancer or tumor other than carcinoma.

II. Principles of Recording Findings

Categories of findings are abbreviated by using uppercase letters: “T” for the extent of invasion by the primary tumor, “N” for lymph node metastasis, and “M” for distant metastasis. The grade of each finding is indicated by Arabic numerals following the uppercase letter for each category, and “X” is used when the finding is unknown. The stage is recorded by using combinations of the T, N, and M findings. The findings at the time of diagnosis, that is, the clinical findings, surgical findings, pathological findings, and final findings, are indicated by the lower case letters “c,” “s,” “p,” and “f,” respectively, and these letters are placed before the finding notation. The “f” for “final findings” may be omitted.

The symbols “m,” “y,” “r,” and “a” may also be used to identify special cases in the TNM or pTNM classification systems. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

Symbol “m”(multiple)

The suffix “m,” in parentheses, is used to indicate the presence of multiple primary tumors at a single site. This corresponds to multiple tumors, similar to T2 (m) or T3 (2).

Symbol “y”(yield to treatment)

In cases in which classification is performed during or following multimodality therapy, the cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM designation categorizes the extent of tumor present at the time of that examination. The “y” categorization is not an estimate of the extent of tumor prior to multimodality therapy.

Symbol “r”(recurrent)

Recurrent tumors, when classified after a disease-free interval, are identified by the prefix “r”.

Symbol “a”(autopsy)

The prefix “a” indicates that classification is determined for the first time at autopsy.

Local extension and the presence of malignant infiltration at surgical margins are recorded by placing “s” or “p” before the surgical and pathological finding notation.

Table 1 Principles of recording findings

Clinical findings	Surgical findings	Pathological findings	Final findings
<ul style="list-style-type: none"> ● Physical findings ● Imaging findings ● Endoscopic findings ● Biopsy/cytology ● Biochemical/biological examination ● Others (e. g. Gene test) 	<ul style="list-style-type: none"> ● Intraoperative findings (laparotomy) ● Intraoperative imaging findings ● Cytology ● Frozen section 	<ul style="list-style-type: none"> ● Pathological findings of resected specimen 	<ul style="list-style-type: none"> ● Overall findings of clinical, surgical, and pathological findings

Note: Laparoscopic findings are “clinical findings”; findings obtained by examination of specimens resected during laparoscopic surgery are “surgical findings.”

Examples of recording:

[Clinical findings (PDAC: pancreatic ductal adenocarcinoma)]

Clinical diagnosis: PDAC

Cytodiagnosis: Malignant (presumptive diagnosis: Invasive ductal carcinoma)

Ph, TS2 (30 mm), infiltrative type, cT2, cCH0, cDU0, cS0, cRP0, cPV0, cA0, cPL0, cOO0, cN0, cM0, (P0, H0), CYX

TNM Classification (JPS 7th/UICC 8th): cT2 cN0 cM0 cStage IB/cT2 cN0 cM0 cStage IB

Resectability: Resectable

[Clinical findings (IPMN: intraductal papillary mucinous neoplasm)]

Clinical diagnosis: IPMN

Cytodiagnosis: Malignancy suspected/low or higher malignant potential (presumptive diagnosis: IPMN (high-grade dysplasia or more serious)

Pb, TS2 (35 mm), cystic type, cTis, cCH0, cDU0, cS0, cRP0, cPV0, cA0, cPL0, cOO0, cN0, cM0 (P0, H0), CYX

TNM Classification (JPS 7th/UICC 8th): cTis cN0 cM0 cStage 0/cTis cN0 cM0 cStage 0

[Surgical findings]

SSPPD-II-A-1, D2, Ph, TS2 (30 mm), infiltrative type, sT3, sCH0, sDU0, sS0, sRP0, sPV1 (PVp), sA0, sPL0, sOO0, sPCM0, sBCM0, sDPM0, R0, sN1a, sM0 (P0, H0), CY1

TNM Classification (JPS 7th/UICC 8th): sT3 sN1a sM0 sStage IIB/cT3 cN1 cM0 sStage IIB

[Pathological findings]

Pancreas, pancreatoduodenectomy: Invasive ductal carcinoma, mod>por, Ph, TS2 (35 mm), infiltrative type, int, INFb, ly0, v1, ne2, mpd (-)

pT3, pCH1, pDU0, pS0, pRP1, pPV1 (PVsm), pA0, pPL1, pOO0, pPCM0, pBCM0, pDPM1, R1, pN1b (4/14) M0

TNM Classification (JPS 7th/UICC 8th): pT3 pN1b M0 pStage IIB/pT3 pN1 M0 pStage IIB

[Pathological findings (post-chemoradiation therapy)]

Pancreas, pancreatoduodenectomy: Invasive ductal carcinoma, mod>por, Ph, TS1 (17 mm), infiltrative type, int, INFb, ly0, v1, ne2, mpd1 (1 mm, 5 mm to the stump)

ypT1c, ypCH0, ypDU0, ypS0, ypRP0, ypPV0, ypA0, ypPL1, ypOO0, ypPCM0, ypBCM0, ypDPM0, R0 (1 mm), ypN1a (1/9) M0

TNM Classification (JPS 7th/UICC 8th): ypT3 ypN1a M0 ypStage IIB/ypT1 ypN1 yM0 ypStage IIB

Histological assessment of therapeutic response: Grade 2

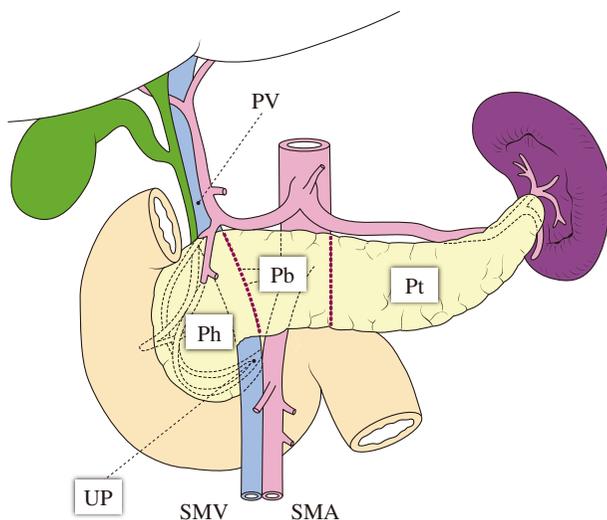
III. Description of Findings

1. Primary tumor

1) Tumor location

The pancreas is anatomically divided into three main portions: the head, the body, and the tail (Fig. 1). The uncinate process is included as part of the head of the pancreas. When lesions are present in two or more adjacent portions of the pancreas, the abbreviation of the part in which the primary tumor is located should be recorded first, followed by the part (s) involved as a result of infiltration.

Sample notation: Phb, Pbht



Ph: head of pancreas, Pb: body of pancreas, Pt: tail of pancreas

PV: portal vein, SMA: superior mesenteric artery, SMV: superior mesenteric vein

UP: uncinate process

Fig. 1 Parts of the pancreas

The border between pancreatic head and body is defined as the left side of SMV and PV. The neck of the pancreas (a part anterior to SMV and PV) and uncinate process are included in the pancreatic head. The border between pancreatic body and tail is defined as left border of the abdominal aorta.

2) Size and number of the tumors

The greatest diameter (mm) of the primary tumor is recorded as the tumor size (TS). Based on this, the tumor size is coded further as follows:

Tumor 20 mm or less in greatest dimension (TS1 \leq 20 mm)

Tumor more than 20 mm but no more than 40 mm in greatest dimension (20 mm < TS2 \leq 40 mm)

Tumor more than 40 mm but no more than 60 mm in greatest dimension (40 mm < TS3 \leq 60 mm)

Tumor more than 60 mm (TS4 > 60 mm)

For multiple tumors, the number of tumors, the location, and the greatest diameter of each are recorded.

In case of MCC (mucinous cystadenocarcinoma), the greatest diameter of the cyst is recorded as the TS, and in case of intraductal papillary-mucinous carcinoma (IPMC) or intraductal tubulopapillary carcinoma (ITPC) (including non-infiltrative types; p.70), the greatest distance of extension within the main pancreatic duct (main pancreatic duct type) or the size of the dilated pancreatic duct (branch type) is recorded as the TS. Moreover, if there is an area of invasion, the greatest diameter of the invaded area is measured separately and recorded as “i: invasive area.”

Sample notation for an IPMC: TS2 (35 mm), i-TS (15 mm)

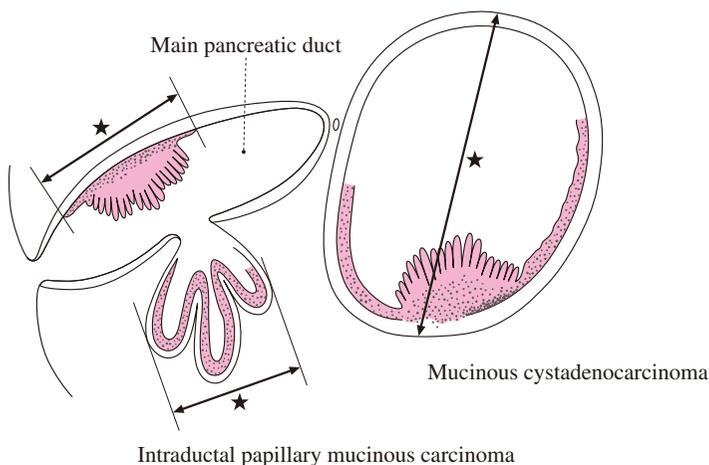


Fig. 2 Measurement of the size of MCC and IPMC
Measure the distances marked with a star (★).

3) Macroscopic type

Masked type	No macroscopic evidence of tumor
Nodular type	Tumor with a clearly defined border
Infiltrative type	Tumor with a poorly defined border and diffuse infiltration into surrounding tissue
Cystic type	Cystic tumor, such as cystadenocarcinoma (excluding secondary cysts due to central necrosis in a solid tumor, and excluding retention cysts or pseudocysts accompanying a tumor)
Ductectatic type	Tumor with pancreatic duct dilatation (due to mucus retention, etc.) as a dominant feature
Mixed type	A mixture of 2 or more macroscopic types
Unclassified type	Tumor that cannot be classified into any of the above types

4) Grade of local invasion

(1) T category

The grade of local invasion of the pancreas by the primary tumor should be recorded as the T category and be further specified by using the local invasion factors^[1]: Abbreviations CH, DU, S, RP, PV, A, PL, and OO are used.

TX: Local invasion cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ^[2]

T1: Tumor limited to the pancreas, 20 mm or less in greatest dimension^[3]

T1a: Tumor 5 mm or less in greatest dimension

T1b: Tumor greater than 5 mm and less than 10 mm in greatest dimension

T1c: Tumor greater than 10 mm but no more than 20 mm in greatest dimension

T2: Tumor limited to the pancreas, more than 20 mm in greatest dimension

T3: Tumor extends beyond the pancreas^[4], but without involvement of CA or SMA.

T4: Tumor involves CA or SMA^[5]

NOTE 1: Local invasion factors

- Bile duct invasion CH0: absent CH1: present* CHX: cannot be assessed
*Histologically, invasion into the fibromuscular layer of the bile duct or further into the inner side of the bile duct.
- Duodenal invasion DU0: absent DU1: present* DUX: cannot be assessed
*Histologically, invasion into the muscular layer of the duodenum or further into the inner side of the duodenum.
- Serosal side of the anterior pancreatic tissue invasion
S0: absent S1: present* SX: cannot be assessed
*Invasion into the serosal tissue (e. g. fibrous connective tissue, adipose tissue) : Invasion exposed on the serous surface, or adhesion of the greater and lesser omentum or mesocolon, due to invasion are also classified as S1 with a note of that effect.
- Retropancreatic tissue invasion RP0: absent RP1: present* RPX: cannot be assessed
*Invasion into the retropancreatic tissue (e. g. fibrous connective tissue, adipose tissue)
Note: S and RP are the factors to evaluate the presence of extrapancreatic invasion to define T3. When differentiation between S1 and RP1 is challenging, classify the case as RP1 for descriptive purposes.
- Portal venous system invasion PV0: absent PV1: present* PVX: cannot be assessed
*Histologically, invasion into the vein wall, including the outer layer
Note: The portal venous system consists of the portal vein (PVp), superior mesenteric vein (PVsm), and pancreatic vein (PVsp).
- Arterial system invasion A0: absent A1: present* AX: cannot be assessed
*Histologically, invasion into the artery wall, including the outer layer
Note: The artery system consists of the superior mesenteric artery (Asm), celiac artery (Ace), common hepatic artery (Ach), and splenic artery (Asp).
- Extrapancreatic nerve plexus invasion PLO: absent PL1: present PLX: cannot be assessed
Note: When the extrapancreatic nerve plexus is difficult to identify, classify the case as PLX.
- Invasion of other organs OO0: absent OO1: present OOX: cannot be assessed

Note: Other organs consist of the adrenal gland, stomach, large intestine, spleen, renal vein, kidney, inferior vena cava, aorta, and others. The invaded organ name should be clearly indicated.

NOTE 2: Carcinoma in situ includes non-invasive mucinous cystadenocarcinoma, IPMC, and high-grade pancreatic intraepithelial neoplasia (high-grade PanIN).

NOTE 3: The degree of local extension of a case satisfying this condition is T1, even if the invasion beyond the pancreatic duct wall is over 20 mm. Microinvasive carcinoma is also classified as T1. IPMC, ITPN, and mucinous cystadenocarcinoma are classified as T1a, T1b, or T1c, depending on the size of invasion.

NOTE 4: Invasion reaches either the bile duct (CH), duodenum (DU), serosal tissue (S), retropancreatic tissue (RP), portal venous system (PV), common hepatic artery (Ach), splenic artery (Asp), extrapancreatic nerve plexus (PL), or other organs (OO).

NOTE 5: CA and SMA invasion should be equivalent to abutment/contact on images.

[Anatomical reconsideration of the extrapancreatic nerve plexus]

The definition and classification in the 3rd to 6th edition of the Classification of Pancreatic Cancer (1st to 3rd edition of the English version) used seven categories for the nerve plexus in accordance with the report by Yoshioka et al.¹⁾²⁾: pancreatic head nerve plexus I, or PLph I; pancreatic head nerve plexus II, or PLph II; superior mesenteric nerve plexus, or PLsma; common hepatic artery nerve plexus, or PLcha; hepatoduodenal ligament nerve plexus, or PLhdl; splenic artery nerve plexus, or PLspa; and celiac plexus, or PLce.

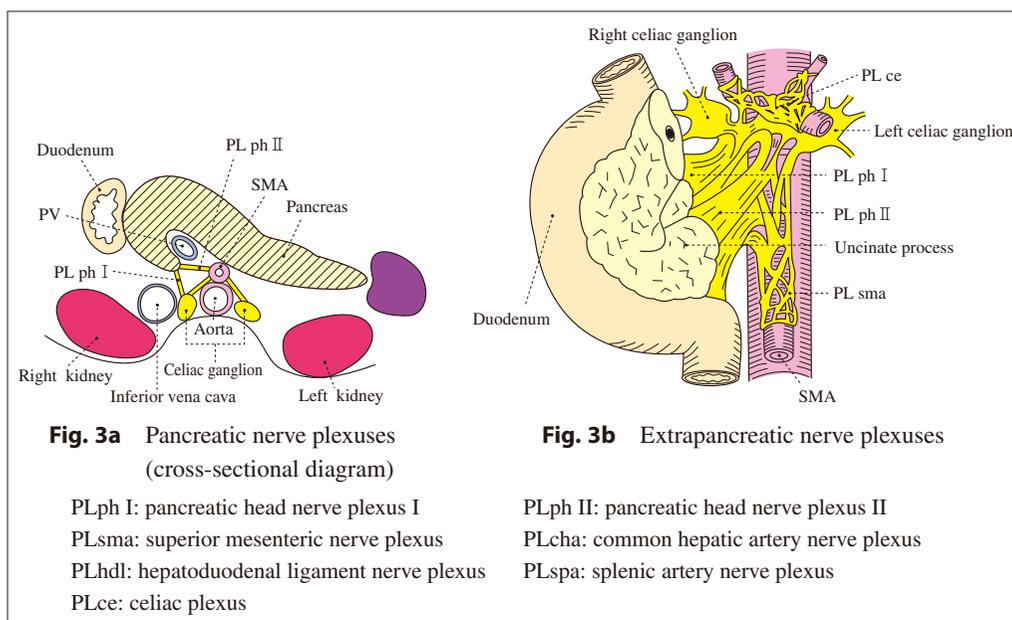


Fig. 3 Extrapancreatic nerve plexus in the 6th Japanese edition

Regarding the figures used in the 6th or earlier Japanese editions (Figs. 3a and 3b), the following issues have been pointed out and reconsidered by the anatomical classification committee (extrapan-

creatic nerve plexus working group) from anatomical and surgical points of view, focusing on the pancreatic head nerve plexus.

(1) In Fig. 3a, the pancreatic nerve plexus (cross-sectional diagram), PLph I and II are depicted on the same cross section. In the surgical findings, however, the former is located in the cranial side and the former in the caudal side, and placing them on the same cross section seems inappropriate.

(2) In Fig. 3b, the extrapancreatic nerve plexuses, PLph I and II are depicted as thick nerve bundle. In the anatomical reconsideration at this time, PLph I and II are considered as a plexus in the sense that they are where the sympathetic nerves mix with the parasympathetic nerves from the vagal nerve, but the thickness and number of the nerves are likely to be smaller. We found that the parts indicated previously as PLph I and II represented a thick part, including not only the nerve structures but also the fiber tissue, vessels, and adipose tissues. Considering the anatomical and surgical findings, PLph I is supposed to be a region principally for the nerves distributing from PLce to the posterior side of the pancreatic head, and PLph II is principally for the nerves distributing from PLsma to the uncinat process of pancreas. In addition, Fig. 3b in the 6th Japanese edition shows the third and fourth portions of duodenum on the right side of SMA, which is not correct in regard to real anatomical findings.

Therefore, we created a new figure (Fig. 4), and added intraoperative images with corresponding schemes (Fig. 5).

- 1) Yoshioka H, Wakabayashi T. Procedure of neurotomy on the head of the pancreas. *Operation*. 1957; 11: 849–57 (in Japanese).
- 2) Yoshioka H, Wakabayashi T. Therapeutic neurotomy on the head of the pancreas for relief of pain due to chronic pancreatitis; a new technical procedure and its results. *AMA Arch Surg*. 1958; 76: 546–54.

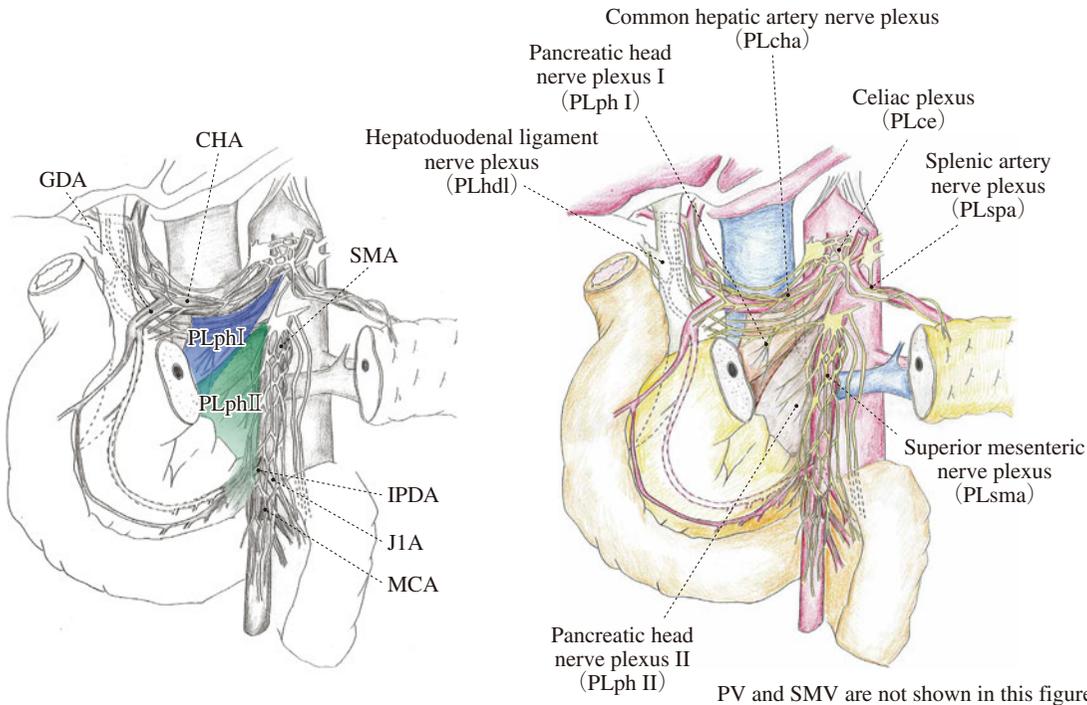


Fig. 4 Extrapancreatic nerve plexus

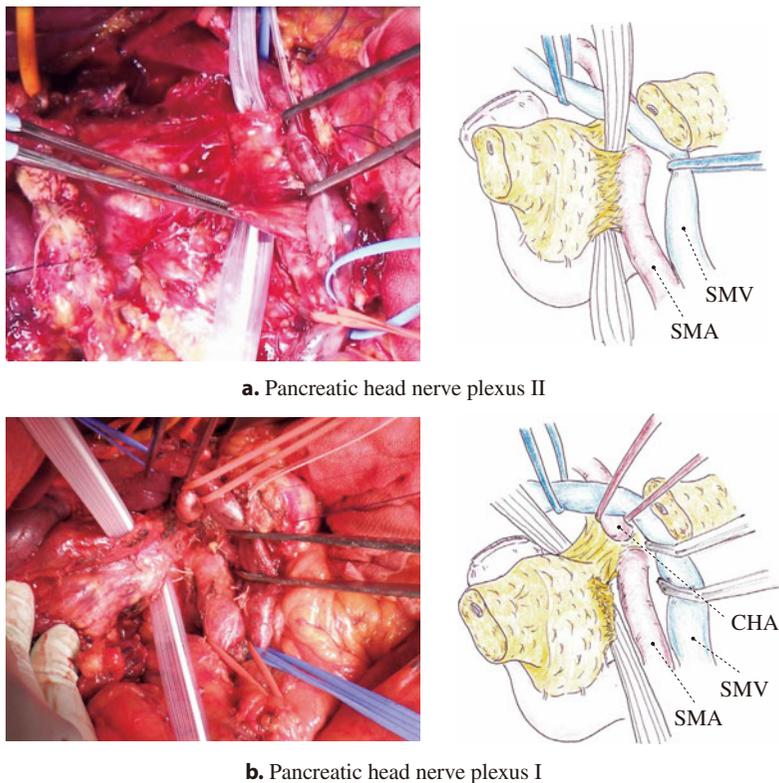


Fig. 5 Intraoperative images and corresponding schemes

■ Regarding the mesopancreas

The boundary and concept of the mesopancreas are vague at present. Gockel et al.¹⁾ have defined the membranous structure between SMA and the pancreatic head as the mesopancreas, which contains nerve tissue, capillaries, fibrous tissue, and fat tissue. The mesopancreas seems to correspond to PLph II, while PLph I has not been mentioned previously²⁾. The term “meso” is not a proper word, because the mesentery and mesocolon contain blood vessels and lymphatics with peritoneal attachment³⁾. There is no consensus of whether PLph I or II should be called the mesopancreas; therefore, the term is not used in this classification.

- 1) Gockel I, Domeyer M, Wolloscheck T, et al. Resection of the mesopancreas (RMP) : a new surgical classification of a known anatomical space. *World J Surg Oncol.* 2007; 5: 44.
- 2) Isaji S. Do you know mesopancreas? *Therapeutic Research for Hepato-Biliary-Pancreatic Diseases.* 2008. 6: 82–4 (in Japanese).
- 3) Sharma D, Isaji S. Mesopancreas is a misnomer: time to correct the nomenclature. *J Hepatobiliary Pancreat Sci.* 2016; 23: 745–9.

Extrapancreatic nerve plexus working group committee members:

Keiichi Akita, Shuang-Qin Yi (Chief), Katsunori Uchida, Masashi Kishiwada, Hirohisa Kitagawa, Yuichi Nagakawa, Tsutomu Fujii

(2) Diagnostic imaging guidance for T category

i) Dynamic CT for pancreatic carcinoma

Dynamic contrast-enhanced multidetector CT (MDCT) is required to detect lesions and accurately determine the extension of the pancreatic neoplasm. A ductal carcinoma, which is characterized by abundant fibrillary stroma, often shows hypovascularity in the arterial phase and delayed enhancement from the venous to equilibrium phases. Therefore, if an arterial phase image is not obtained and only contrast-enhanced equilibrium-phase views are available, tumors show the same level of enhancement as surrounding tissues and may be missed (Fig. 6).



Fig. 6 Carcinoma in the body of the pancreas showing the same level of enhancement as the surrounding tissues in the equilibrium phase of dynamic CT

An ischemic tumor can be detected in the body of the pancreas (arrow head) in the arterial phase of dynamic CT (a). However, the tumor shows delayed enhancement similar to that of the surrounding pancreatic parenchyma. Thus, tumors may be missed if only contrast-enhanced equilibrium-phase images are used.

Parameters for preoperative CT of pancreatic neoplasms are exemplified in Table 2. High-concentration non-ionic contrast medium (350 mg/mL or 370 mg/mL, 100–135 mL) is used for dynamic CT. The contrast medium injection time is fixed at 30 seconds (fixed contrast medium injection time method)^{1,2}. Dynamic CT is performed at a dose of 1.8 mL/kg (108 mL and 126 mL for patients weighing 60 kg and 70 kg, respectively); the injection rate is the dose/30 seconds (3.6 mL/s and 4.2 mL/s for patients weighing 60 kg and 70 kg, respectively). At least four phases of dynamic CT are required: early arterial phase (25 seconds after media injection), late arterial phase (40 seconds), venous phase (70 seconds), and equilibrium phase (180 seconds). Using the volume rendering (VR) technique, early arterial phase data can be used to construct 3D images that allow evaluation of arterial anatomy and venous invasion (Fig. 7). It is also important to evaluate tumor extension and invasion of the blood vessels from perspectives other than those of transverse images; coronal, axial, or even oblique views parallel to the head or tail sections can be reconstructed from pancreatic parenchyma phase data (Fig. 8). In addition, a slab maximum intensity projection (MIP) image can be generated in dynamic CT by superimposing four or seven 2.5 mm-thick slices (10 mm or 17.5 mm in

total thickness, respectively) in arterial and parenchymal, or portal phase. As an MIP image successively shows a long range of arteries and veins around the pancreas, it is useful for evaluating cancer invasion in the arteries and/or the development of a collateral pathway because of vein occlusion (Fig. 9).

- 1) Yanaga Y, Awai K, Nakayama Y, et al. Pancreas: patient body weight tailored contrast material injection protocol versus fixed dose protocol at dynamic CT. *Radiology*. 2007; 245: 475–82.
- 2) Yanaga Y, Awai K, Nakayama Y, et al. Recent perception of contrast enhancement in abdominal MDCT: Contrast injection time protocol. *Multislice CT 2006 BOOK*. Eizojoho medical. 2006; 38: 106–11 (in Japanese).

Table 2 Dynamic CT protocol for the pancreas

	Imaging range	Imaging starting time after contrast media injection	Slice thickness	Additional slice thickness	Reconstructed image
Simple	Liver-kidney		2.5 mm		
Early arterial phase	Liver-kidney	25 sec	2.5 mm	1.25 mm	3D (VR) MIP
Late arterial phase (Pancreatic parenchyma phase)	Liver-kidney	40 sec	2.5 mm	1.25 mm	MIP (3 mm, 1 mm space)
Portal phase	Liver-kidney	70 sec	2.5 mm	1.25 mm	MIP (3 mm, 1 mm space)
Equilibrium phase	Liver-pelvis	180 sec	2.5 mm	1.25 mm	MIP (3 mm, 1 mm space)

High-concentration iodine contrast medium (350 mg/mL) injection time: 30 seconds (fixed time protocol)

350 mg/mL at 1.8 mL/kg, that is, 108 mL for patient weighing 60 kg, 126 mL for 70 kg

Injection rate: dose/30 seconds, that is, 3.6 mL/s for 60 kg; 4.2 mL/s for 70 kg

[Reprint from Atlas for Pancreatic Neoplasm to learn from comparison between imaging and pathology. Kitagawa H, Gabata T, Otsubo K, Gakken Medical Shujunsha (in Japanese)]



Fig. 7 Dynamic CT scan in 3D (VR) : arterial phase stereoscopic view

In the stereoscopic view of 3D imaging, vessel overlapping can be corrected to identify peripheral vessels precisely. The stereoscopic view is recommended for preoperative evaluation of arterial anatomy.

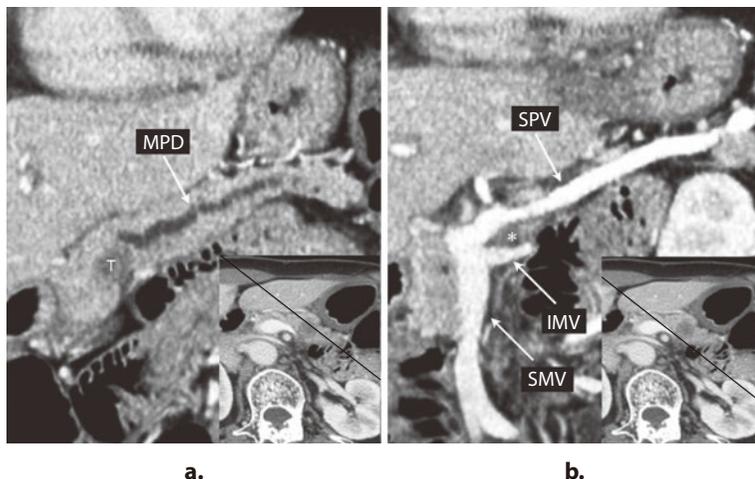


Fig. 8 Carcinoma in the body of the pancreas invading SPV and IMV
MIP sagittal views parallel to the body of the pancreas in the portal phase of dynamic CT (a, b). The tumor (T), which is obstructing MPD, extends inferoposteriorly, and is invading (*) IMV that joins SMV.

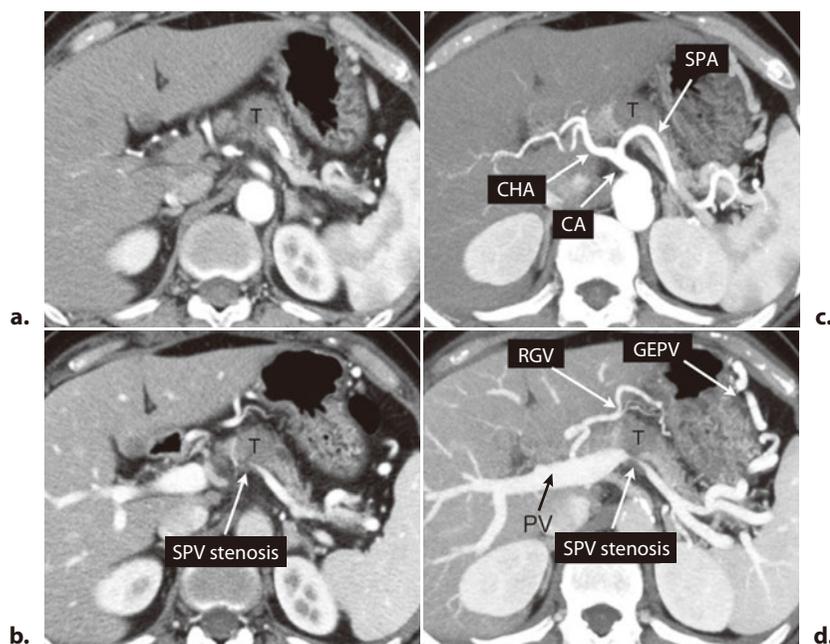


Fig. 9 CT scan showing a carcinoma in the body of the pancreas, SPA, SPV invasion, and collateral pathway formation (slab MIP images)

An ischemic tumor (T) is observed in the arterial phase (a) dynamic CT image (slice width, 2.5 mm). In the portal phase (b), SPV is stenosed by tumor invasion. A 17.5 mm thick slab MIP arterial phase image clearly shows the tumor invading SPA, which is branching out from CA; however, no invasion of CHA is observed. A 17.5 mm slab MIP portal phase image consisting of seven 2.5 mm slice layers (d) clearly shows the development of a collateral pathway around the stomach (RGV and GEPV) because of SPV stenosis.

[Figs. 8 and 9 are reprints from Atlas for Pancreatic Neoplasm to learn from comparison between imaging and pathology. Kitakawa H, Gabata T, Otsubo K, Gakken Medical Shujunsha (in Japanese)]

ii) Evaluation of peripancreatic invasion by dynamic CT

1) Serosal invasion (S), Retropancreatic tissue invasion (RP)

In case of neoplasms in the head of the pancreas, diagnosis of S or RP is simple when spicule-shaped projections are found toward the peripancreatic adipose tissues, beyond the anterior or posterior pancreatic parenchyma (Fig. 10). However, diagnosis is challenging when the neoplasm reaches the pancreatic surface but no distinct spicules are visible in CT images. In some cases, S or RP may be histologically confirmed even though no invasion is observed in CT images.

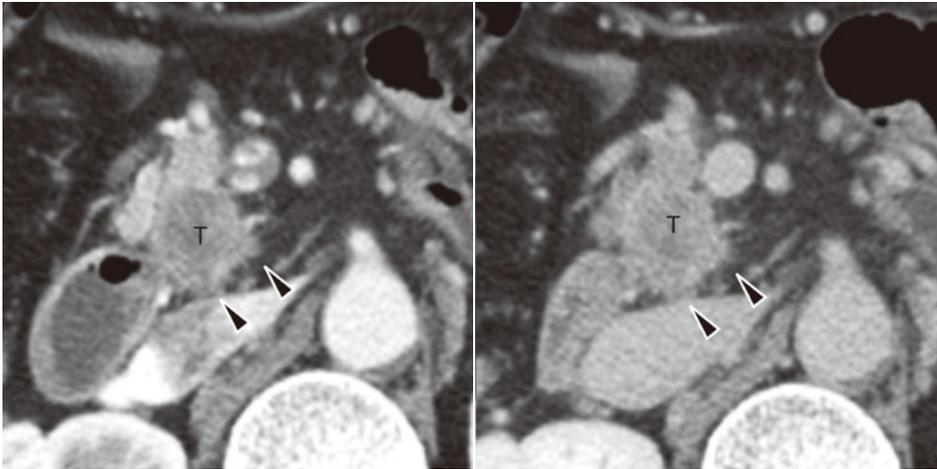


Fig. 10 Pancreas head carcinoma, invasion of the posterior pancreatic tissue (cRP1)

When a serrated posterior projection is observed from the ischemic tumor (T) in the arterial (a) and equilibrium (b) phases of dynamic CT, the case can be diagnosed as invasion of the retropancreatic tissue (RP1).

2) Extrapancreatic nerve plexus invasion (PL)

Neoplasms in the head of the pancreas tend to develop around CA or along the nerve plexus around SMA. If dynamic CT reveals a rod-shaped or trabecular soft-tissue mass pointing directly from the pancreatic lesion toward the proximal portion of the celiac or superior mesenteric arteries, invasion of the extrapancreatic nerve plexus can be suspected (Fig. 11). When the extrapancreatic nerve plexus enlarged by invasion surrounds CA or SMA, the artery appears greatly dilated (Fig. 12).

3) Vessel invasion: artery invasion (A), PV invasion

If neoplasms surround the artery or vein (PV) accompanied by irregular encasement or occlusion, invasion is likely to have occurred (Figs. 13 and 14). Diagnosis is challenging when no adipose tissue is found between the tumor and PV, these are adjacent to each other, or no vessel change is found despite continuous soft tissue enhancement from the tumor. Of these cases, some show invasion of the PV adventitia, and others show no invasion histologically (assident or post-therapy inflammation or fibrosis are confirmed). Therefore, accurate diagnosis of PV invasion is difficult. Generally, inva-

sion is considered positive when the contact range of the tumor and vessels is 180 degrees or greater (Fig. 15).

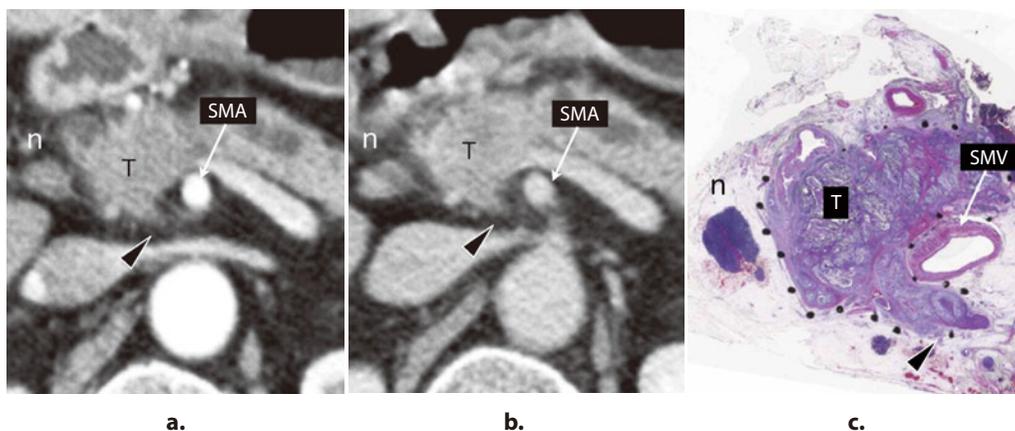


Fig. 11 Carcinoma in the head of the pancreas, invasion of the extrapancreatic nerve plexus [cPL1 (PlphII)]

On the arterial (a) and equilibrium (b) phase views of dynamic CT, the rod-shaped projections (arrow heads) from the tumor in the head of the pancreas toward the posterior SMA correspond to the invasion (arrow head) extending from the dorsal side of SMV to the extrapancreatic nerve plexus (part II) in the microscopic view of the resected specimen (c). CT images show lymph node enlargement greater than 10 mm in the shorter diameter on the lateral side of the head of pancreas (shown as “n” in the figures a and b). Lymph node metastasis was confirmed histologically (shown as “n” in the figure c).

[Reprint from Atlas for Pancreatic Neoplasm to learn from comparison between imaging and pathology. Kitagawa H, Gabata T, Otsubo K, Gakken Medical Shujunsha (in Japanese)]

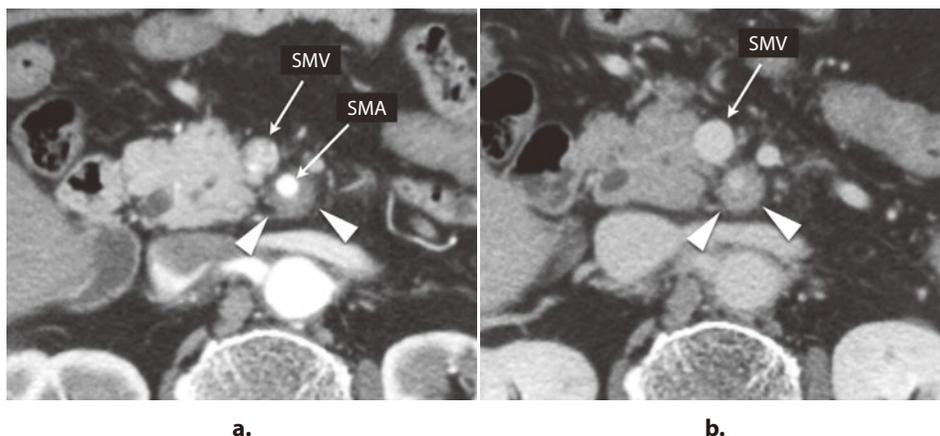


Fig. 12 Carcinoma in the head of the pancreas, invasion of the extrapancreatic nerve plexus [cPL1 (Plsma)]

The arterial phase view of dynamic CT (a) shows a soft tissue tumor (arrow heads) surrounding SMA. The equilibrium phase view (b) shows no difference in enhancement between SMA and surrounding soft tissue tumor. The artery appears greatly dilated.

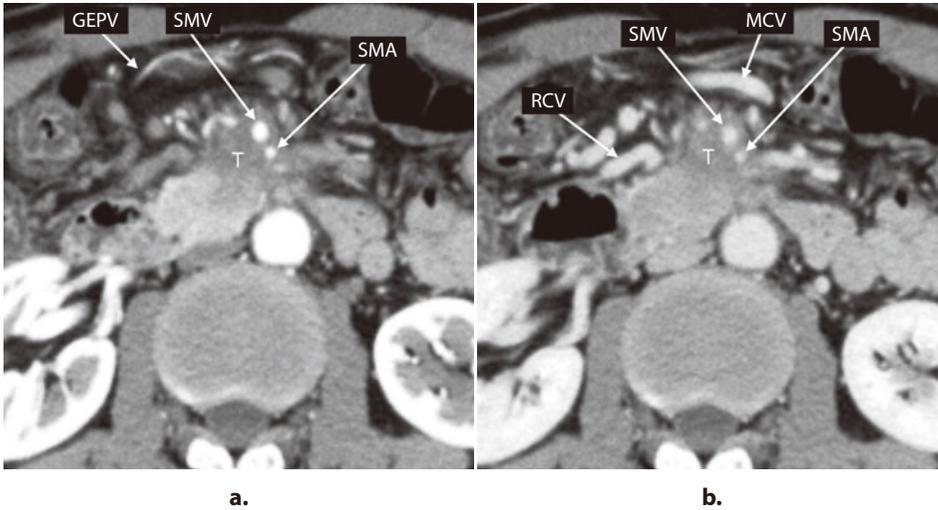


Fig. 13 Carcinoma in the head of the pancreas, invasion of SMA [cA1 (Asm)] and to SMV [cPV1 (PVsm)]

An ischemic tumor (T) is observed in the arterial phase view of dynamic CT (a). The tumor extends to SMA and SMV. Tumor invasion occludes GCT, causing venous congestion that results in the enlargement of GEPV, MCA, and RCV.

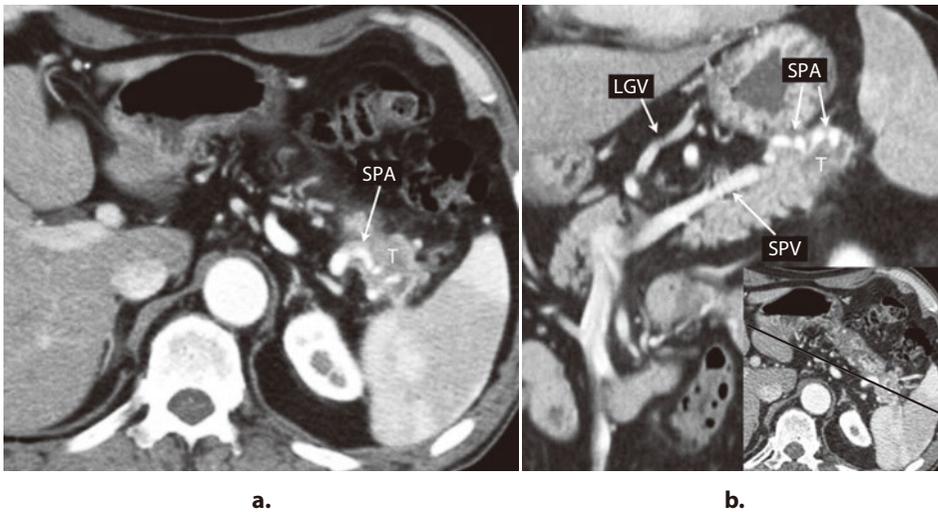


Fig. 14 Carcinoma in the tail of the pancreas, invasion of SA [cA1 (Asp)], invasion of SV [cPV1 (PVsp)]

An ischemic tumor (T) is observed in the tail of the pancreas in the arterial phase view of dynamic CT (a). Invasion of the serosal (S) and retropancreatic (RP) tissue is suspected. SPA is surrounded by the tumor, indicating invasion. The reconstructed image (b), with a view parallel to the tail of the pancreas, clearly shows encasement of the splenic vein because of pancreatic cancer invasion. SPV is also occluded in the splenic hilum; therefore, LGV, which is used as a collateral pathway, is dilated along the lesser curvature.

[Figs. 13 and 14: reprint from Atlas for Pancreatic Neoplasm to learn from comparison between imaging and pathology. Kitagawa H, Gabata T, Otsubo K, Gakken Medical Shujunsha (in Japanese)]

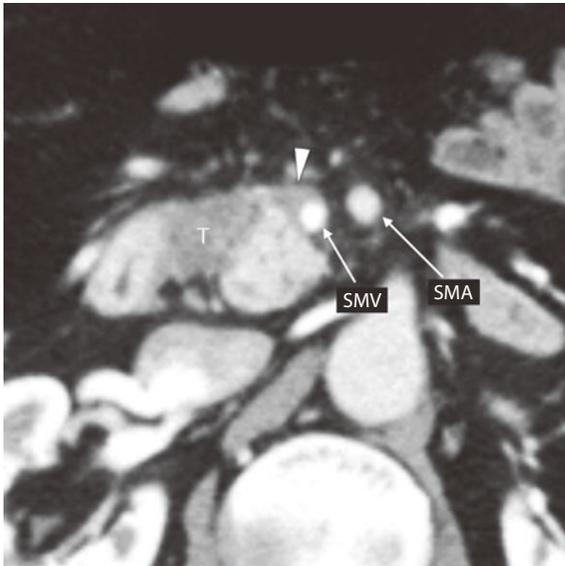


Fig. 15 Carcinoma in the head of the pancreas, suspected invasion of SMV [cPV1 (PVsm)]
An ischemic tumor (T) is observed in the arterial phase view of dynamic CT. Stenosis is not evident in SMV, but the contact range of over 180 degrees between the tumor and SMV suggests invasion of SMV (arrow head).

(3) CT imaging evaluating T category (comparison with the microscopic view)

This section provides an interpretation of the results regarding local extent of adenocarcinoma, comparing MDCT and microscopic findings.

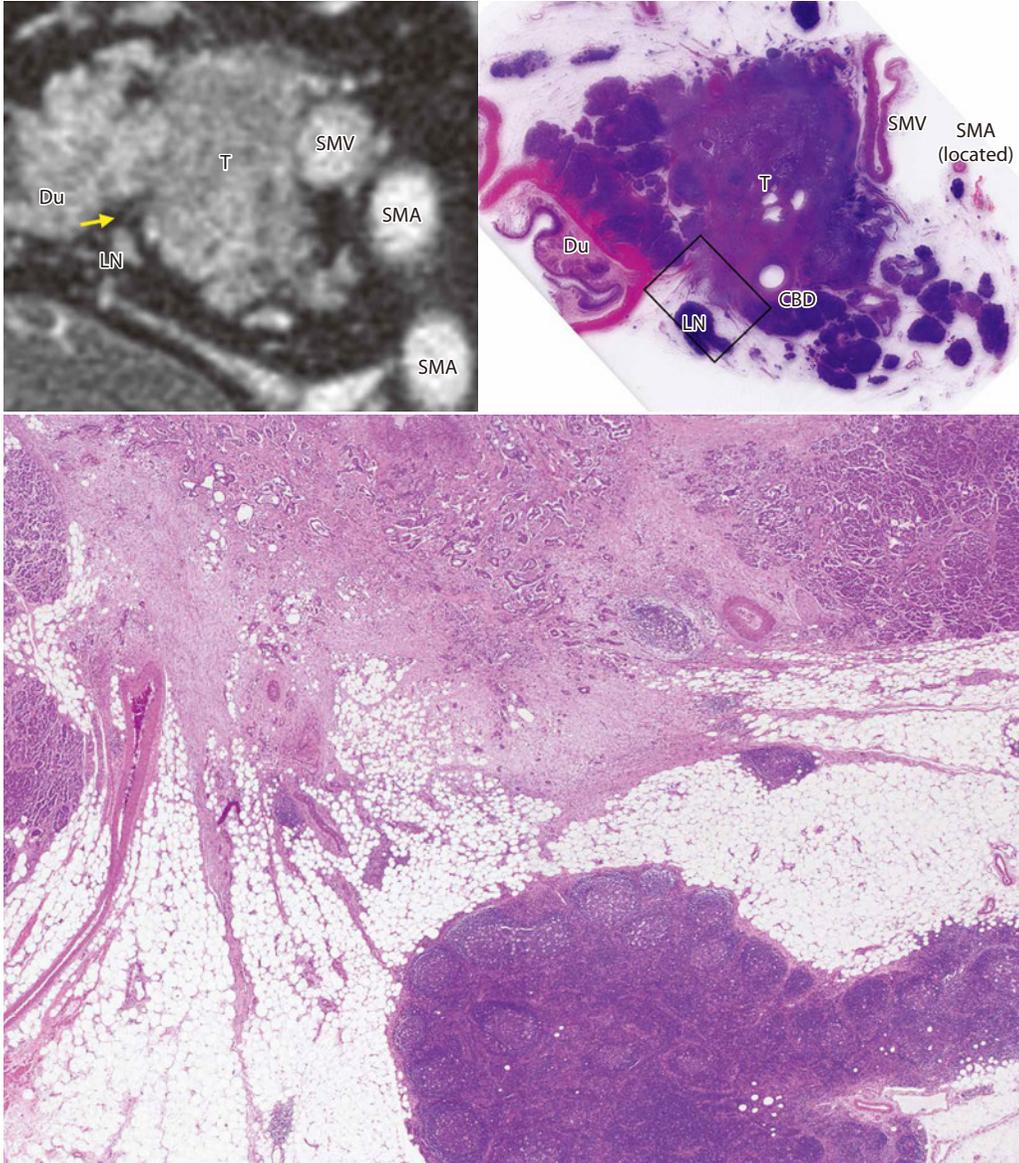


Fig. 16 CT imaging diagnosis: cRP1, cCH1, and cS1

A comparison between the imaging and microscopic findings on RP1: The MDCT images of a normal case show adipose-rich tissue with low CT numbers in the posterior portion of the pancreatic parenchyma, but when cancer invades the retropancreatic tissue, strand and/or reticular like shade (yellow arrow) is observed extending directly from the tumor (T). The microscopic view shows a desmoplastic lesion extending into the adipose tissue of the posterior side of the pancreas. (In this case, CBD was completely occluded by invasion; therefore, a tube was inserted at the time of fixation to specify the position of the bile duct.)

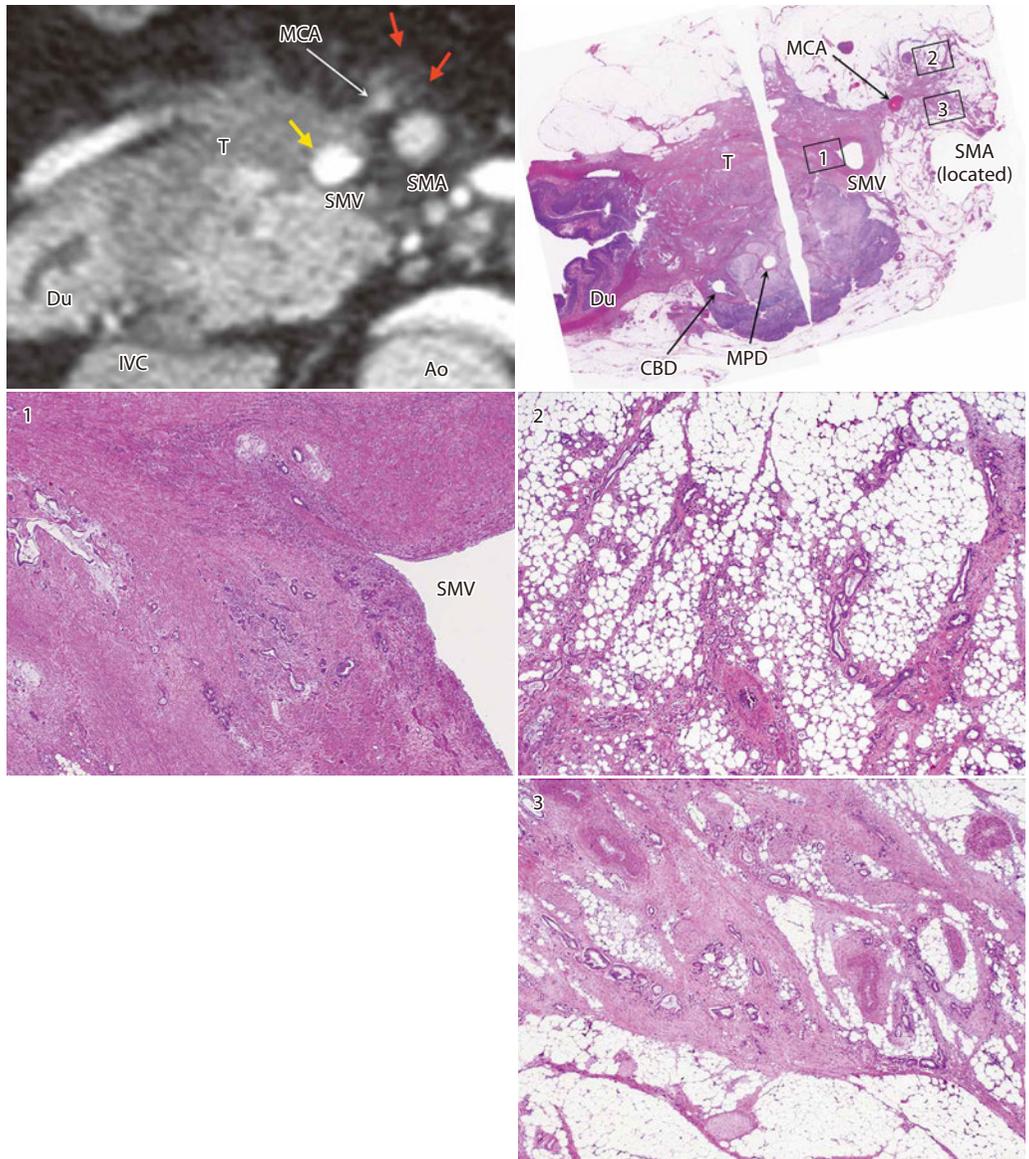


Fig. 17 CT imaging diagnosis: cS1, cDU1, cPL1 (PLsma), and cPV1 (PVsm)

A comparison of the imaging and microscopic findings on PV1 (PVsm)(1) : The MDCT image shows the tumor extending to surround SMV by approximately 75% of its circumference. The SMV lumen is narrower than SMA (yellow arrow). The microscopic views demonstrate the extending tumor destroyed SMV wall structure. The cancer cell invades the intima.

A comparison of the imaging and microscopic findings on S1 and PL1 (PLsma)(2, 3) : The MDCT image shows that the lesion extends to MCA and is succeeded by the strand and/or reticular like shade (red arrows) spreading to the nerve plexus at 12 o'clock (direction). The SMA nerve plexus was resected all around, but the cancer advances close to this SMA margin. The microscopic views show desmoplastic lesions extending beyond MCA and spreading widely into the surrounding adipose tissue. Strand like spreading of cancer is seen toward the SMA nerve plexus, as if the desmoplastic neoplasms are replacing the nerve plexus composed mainly of adipose cells. Poorly to moderately differentiated cancer cells are found in the desmoplastic tumor.

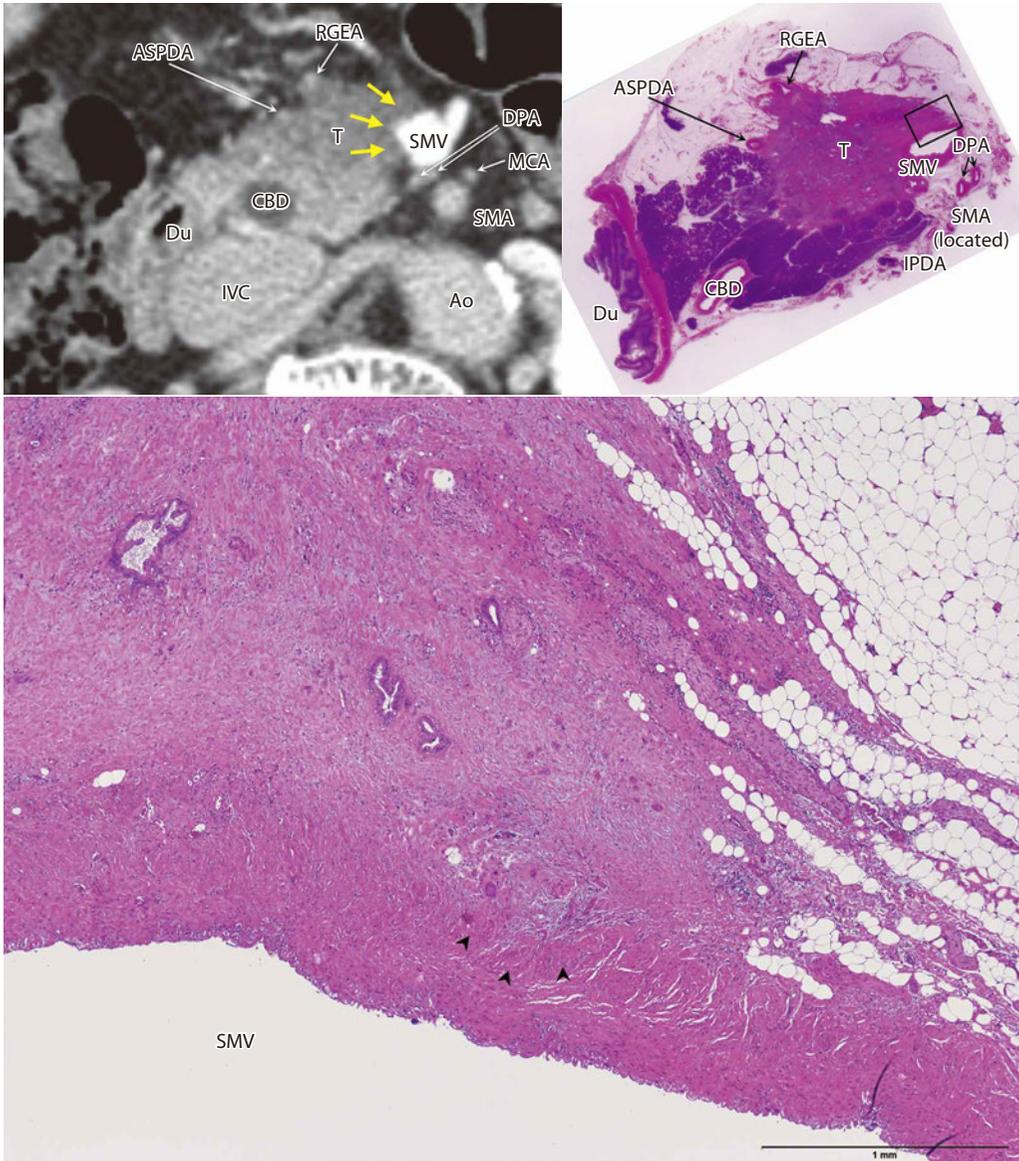


Fig. 18 CT imaging diagnosis: cS1 and cPV1 (PVsm)

A comparison of the imaging and microscopic findings on PV1 (PVsm) : The MDCT image shows the tumor (T) developing at 7 to 12 o'clock of the SMV adventitia. The layer of the low CT-number area seen in normal samples has disappeared, but deformation/stenosis is seen instead (yellow arrows). The microscopic views show the adventitia border of the vein has disappeared and the destruction of the wall structure is starting to take place. Cancer cells are infiltrating the media composed of thick smooth muscle fibers that run vertically (arrow heads).

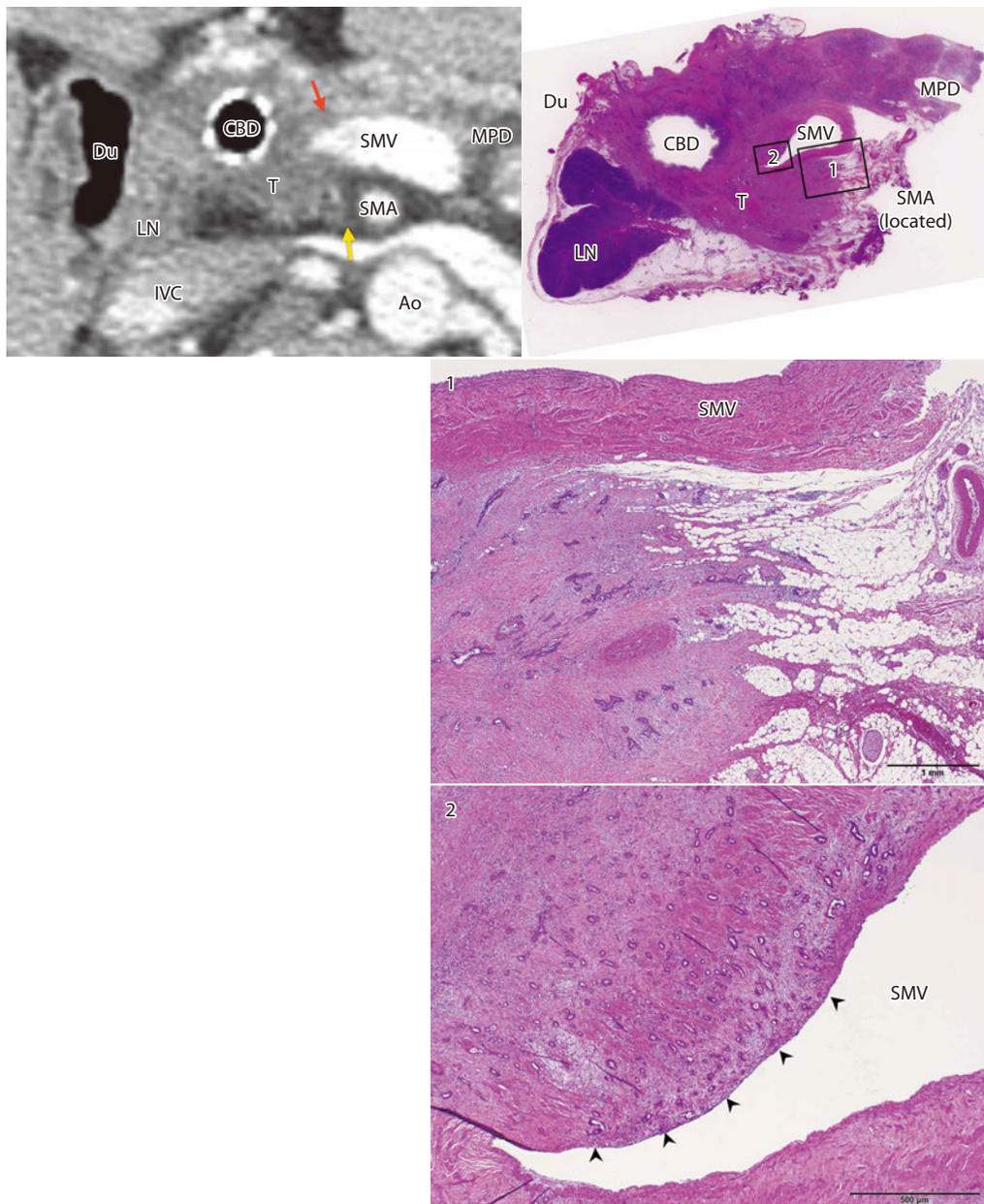


Fig. 19 CT imaging diagnosis: cPL1, cPV1 (PVsm), and cCH1

A comparison of the imaging and microscopic findings on PL1 (PLph II)(1) : The MDCT image shows the tumor extending from the SMV dorsal side towards SMA. The tumor's CT numbers look relatively lower than the pancreatic parenchyma's. Strand and reticular like shade is seen in the extending tip toward SMA (yellow arrow). The microscopic views show the desmoplastic cancer replacing the soft tissue behind SMV which should normally be abundant in adipose tissue.

A comparison of the imaging and microscopic findings on PV1 (PVsm)(2) : The MDCT image shows stenosis/deformation at 9 o'clock in SMV (red arrow). The microscopic views show the advancing tumor destroying the structure of the SMV wall. The endothelial structure is partially destroyed and replaced by cancer (arrow heads). (This case has a metallic stent installed because CBD was completely occluded).

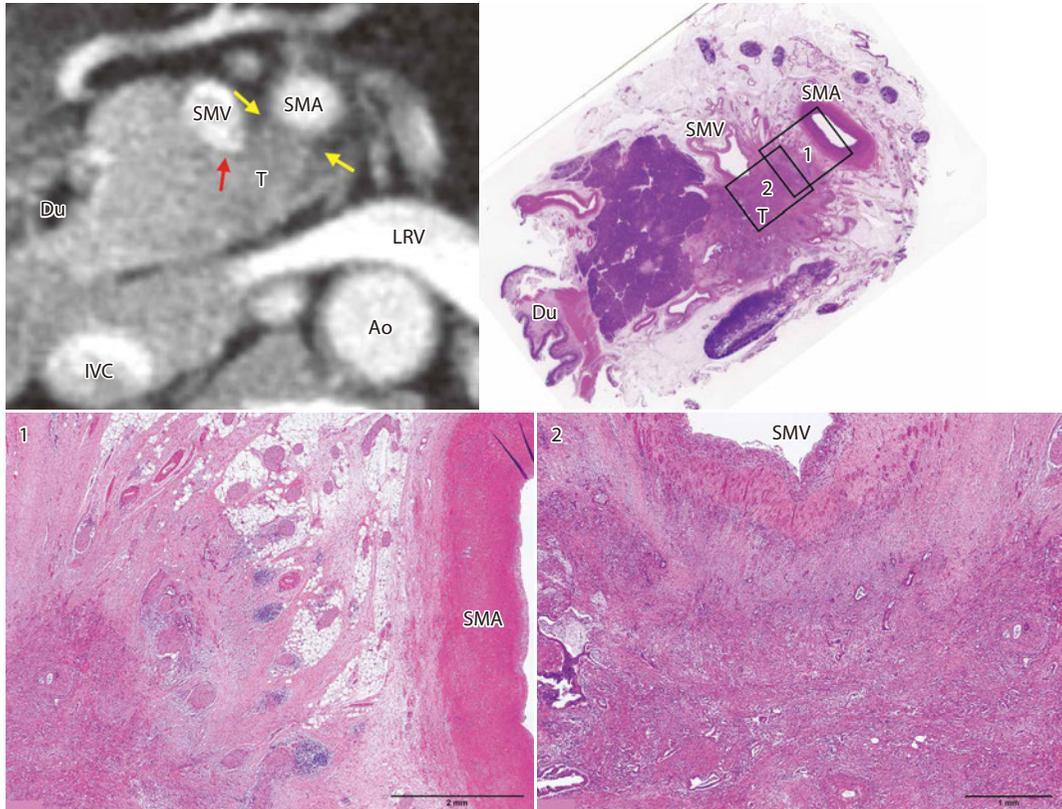


Fig. 20 CT imaging diagnosis: cPL1 (PLph II-PLsma), cPV1 (PVsm), and cA1 (Asm)

A comparison of the imaging and microscopic findings on PL1 (PLph II-PLsma)(1) : The MDCT image shows the extending cancer cells with higher CT numbers replacing the nerve plexus tissues in the head of the pancreas and the nerve plexus tissues around SMA. These nerve plexus tissues originally have abundant adipose cells, thus showing lower CT numbers. The microscopic views show cancer cells with a high level of fibrosis are invading the nerve plexus around SMA and reaching the SMA adventitia. Scattered cancer cells and perineural invasions are seen.

A comparison of the imaging and microscopic findings on A1 (Asm)(1) : The MDCT image shows cancer advancing at 6 o'clock to 9 o'clock of SMA, blurring the border (yellow arrows). The microscopic views show the desmoplastic cancer reaching SMA adventitia. Cancer cells themselves are not invading SMA.

A comparison of the imaging and microscopic findings on PV1 (PVsm)(2) : The MDCT image shows cancer advancing at 4 o'clock to 7 o'clock of SMV, blurring and deforming the border (red arrow). The microscopic views show desmoplastic cancer reaching the SMV adventitia, blurring the border and destroying the wall structure.

[Reprint from Atlas for Pancreatic Neoplasm to learn from comparison between imaging and pathology. Kitagawa H, Gabata T, Otsubo K, Gakken Medical Shujunsha (in Japanese)]

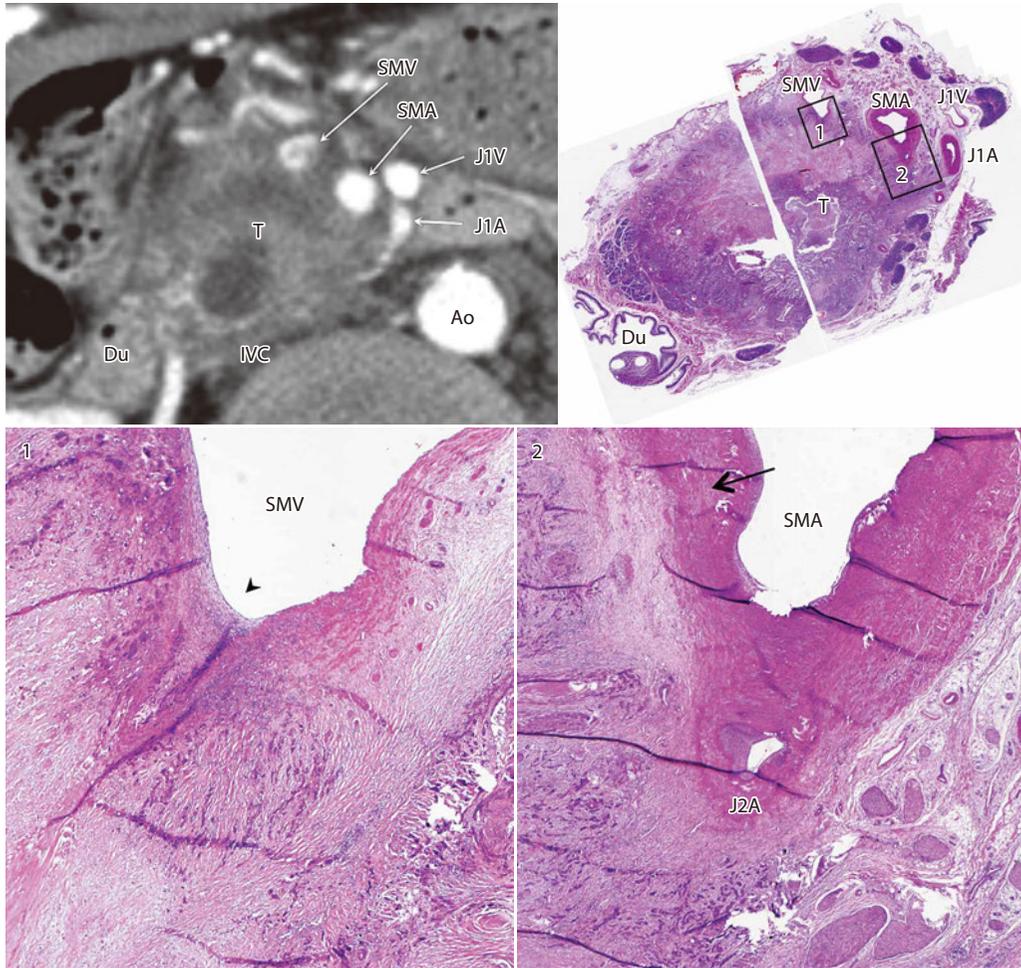


Fig. 21 CT imaging diagnosis: cS1, cRP1, PL1 (PLph II-PLsma), cPV1 (PVsm), and cA1 (Asm)

A comparison of the imaging and microscopic findings on PL1 (PLph II-PLsma), A1 (Asm), and PV1 (PVsm) : The MDCT image demonstrates the tumor (T) showing degeneration in the center and extending to contact more than half the circumference of both SMA and SMV. The microscopic views show cancer invasion destroying the SMV wall structure mainly at 7 o'clock. The vessel endothelium is thickening (arrow head in the view 1). The nerve plexus around SMA originally consists of tissues rich in adipose cells, but it is replaced by desmoplastic cancer tissues along with cancer invasion. The SMA wall structure is partially destroyed, blurring the adventitia (arrow in the view 2).

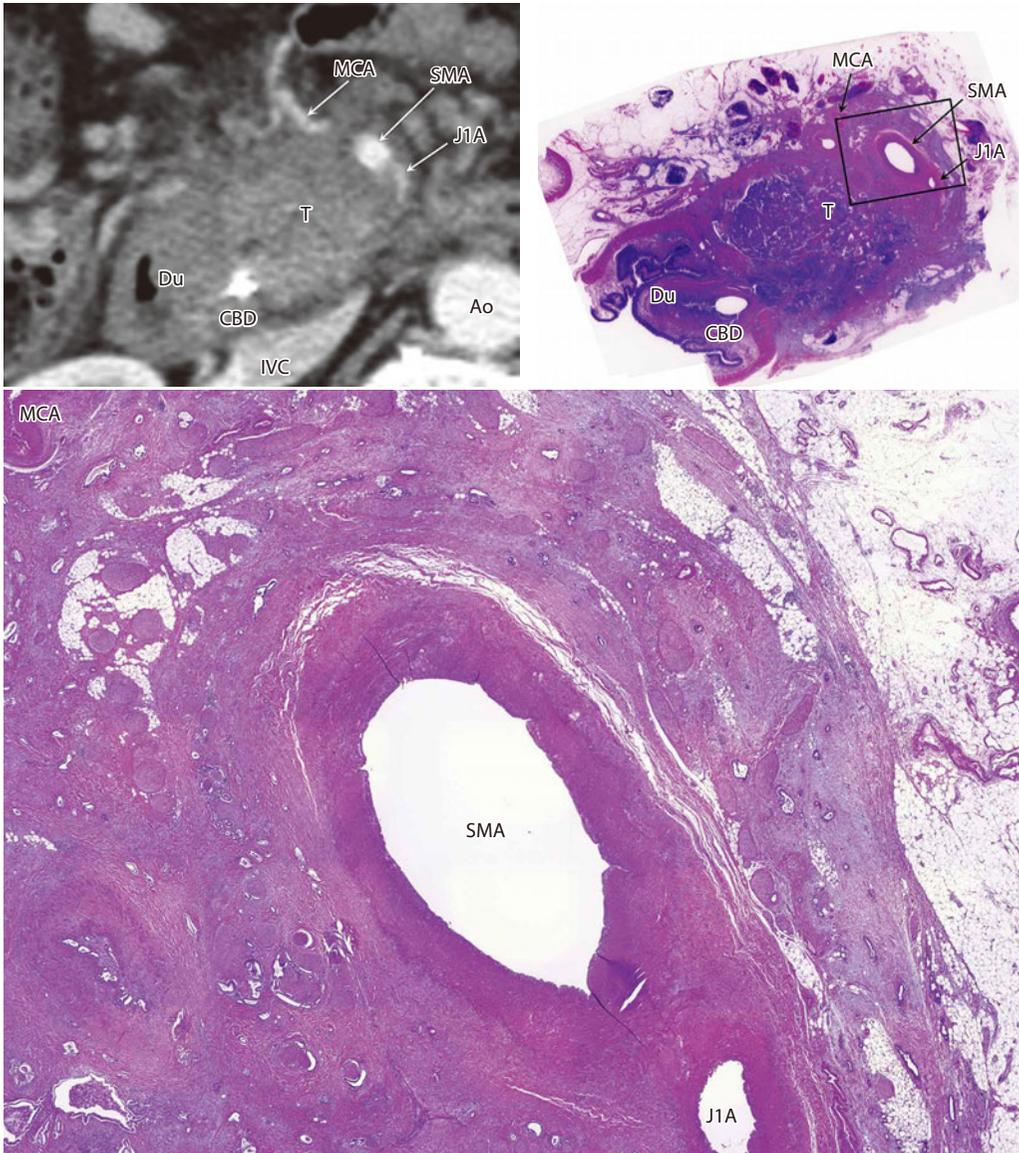


Fig. 22 CT imaging diagnosis: cS1, cCH1, PL1 (PLph II-PLsma), and cA1 (Asm)

A comparison of the imaging and microscopic findings on PL1 (PLph II-PLsma) and A1 (Asm) : The MDCT image shows the tumor replacing the nerve plexus that was originally rich in adipose tissue. The neoplasms entirely surround SMA. The microscopic views show the desmoplastic cancer tissue replacing the nerve plexus around SMA in which tubular gland forming cancer cells are dispersed, demonstrating perineural invasion. The SMA adventitia is blurred at 7 o'clock to 10 o'clock, and the tunica media is widely in contact with the cancer. (In this case, CBD was completely occluded by invasion; therefore, a biliary drainage tube was installed. SMV was also almost occluded; therefore, a tube was inserted at the time of fixation to specify the position of the bile duct.)

[Reprint from Atlas for Pancreatic Neoplasm to learn from comparison between imaging and pathology. Kitagawa H, Gabata T, Otsubo K, Gakken Medical Shujunsha (in Japanese)]

2. Lymph node metastases

1) Identification of the lymph nodes

(1) Station numbers, names, and boundaries of lymph nodes related to the pancreas

These are defined in Table 3 and Figs. 23 to 26.

Table 3 Station numbers and names of lymph nodes related to the pancreas

Number	Name
1	Right cardial lymph nodes
2	Left cardial lymph nodes
3	Lymph nodes along the lesser curvature of the stomach
4	Lymph nodes along the greater curvature of the stomach
5	Suprapyloric lymph nodes
6	Infrapyloric lymph nodes
7	Lymph nodes along LGA
8a	Lymph nodes in the anterosuperior group along CHA
8p	Lymph nodes in the posterior group along CHA
9	Lymph nodes around CA
10	Lymph nodes at the splenic hilum
11p	Lymph nodes along the proximal SPA
11d	Lymph nodes along the distal SPA
12a	Lymph nodes along the hepatic artery
12p	Lymph nodes along PV
12b	Lymph nodes along the bile duct
13a	Lymph nodes on the posterior aspect of the superior portion of the head of the pancreas
13b	Lymph nodes on the posterior aspect of the inferior portion of the head of the pancreas
14p	Lymph nodes along the proximal SMA
14d	Lymph nodes along the distal SMA
15	Lymph nodes along MCA
16a1	Lymph nodes around the aortic hiatus of the diaphragm
16a2	Lymph nodes around the abdominal aorta (from the superior margin of the celiac trunk to the inferior margin of LRV)
16b1	Lymph nodes around the abdominal aorta (from the inferior margin of LRV to the superior margin of IMA)
16b2	Lymph nodes around the abdominal aorta (from the superior margin of IMA to the aortic bifurcation)
17a	Lymph nodes on the anterior surface of the superior portion of the head of the pancreas
17b	Lymph nodes on the anterior surface of the inferior portion of the head of the pancreas
18	Lymph nodes along the inferior margin of the pancreas

Note 1: Lymph node station No. 14 was further subclassified into 14a, 14b, 14c, and 14d in the first English edition of this Classification, but since the second English edition, it has been subdivided into proximal (14p) and distal (14d) lymph nodes. The boundary between 14p and 14d is defined as the midpoint of the distance between the root of SMA and the origin of the middle colic artery. SMA lymph nodes that are distal to the base of the middle colic artery are not considered as regional nodes, and therefore, any metastasis in these lymph nodes is classified as distant metastasis.

Note 2: The 14v lymph nodes (lymph nodes along SMV) as per the first English edition are included in station number 17b in this fourth edition. Similarly, the 12c lymph nodes (lymph nodes along the bile duct) mentioned in the first English edition are included in station number 12b.

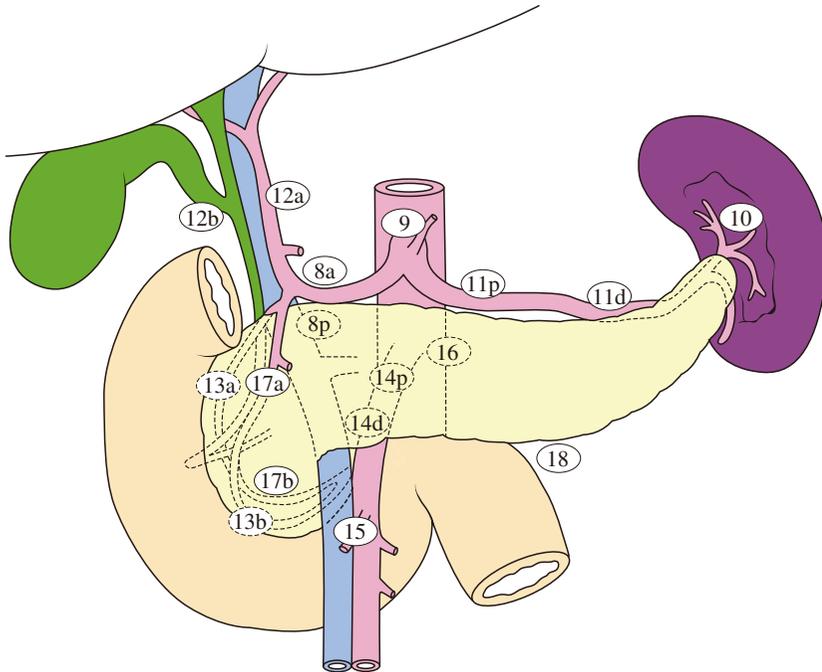


Fig. 23 Station numbers of lymph nodes related to the pancreas

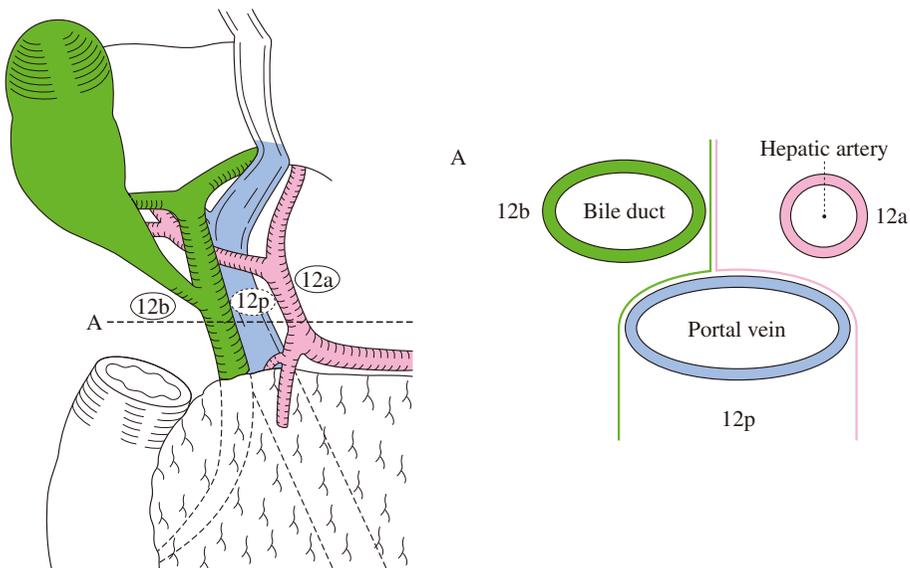


Fig. 24 Location and boundaries of lymph node stations within the hepatoduodenal ligament
The diagram on the right is the transversal scheme at line A in the diagram on the left.

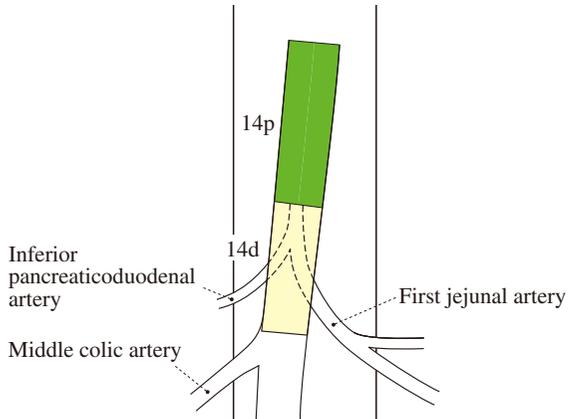


Fig. 25 Location and boundaries of lymph node stations along SMA

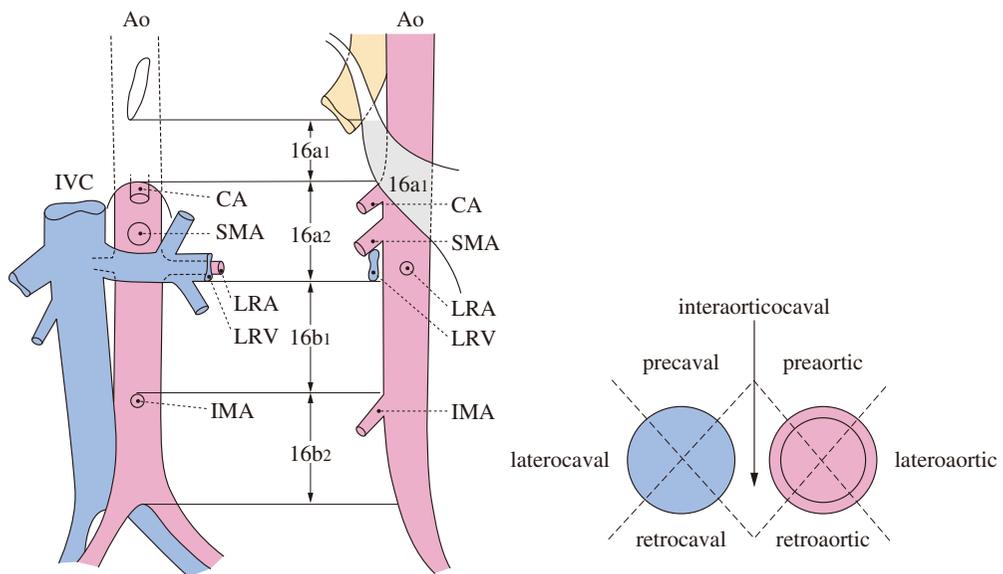


Fig. 26 Location and boundaries of lymph node stations around the abdominal aorta

(2) Lymph node numbers related to the pancreas and diagnostic CT criteria for lymph node metastasis

The numbers of lymph nodes related to the pancreas are shown in Figs 27 a–d. Numbering one large lymph node metastasis that combines multiple lymph node metastases may be challenging. In pancreatic neoplasms, lymph node metastasis often involves local peritumoral nodes as well as nodes around SMA, CA, the hepatoduodenal ligament, and aorta. The hepatoduodenal ligament often shows flat lymph nodes on CT images, even in normal cases. Reactive lymph node enlargement is frequently observed in the region around the hepatoduodenal ligament and aorta in patients with diffuse liver diseases, including cirrhosis. Differentiation of metastatic lymph node enlargement from normal or reactive cases is challenging.

Generally, an enlargement of more than 10 mm in the shorter diameter is diagnosed as lymph node enlargement (Fig. 28). However, enlargement does not necessarily mean metastasis, and a lymph node ≤ 5 mm may be metastatic histologically.

Normal or reactive lymph node enlargement usually displays homogeneous enhancement in contrast-enhanced CT scans. Therefore, an enlarged node that includes a low absorption area, thus suggesting necrosis, may be metastatic (Fig. 29). Additionally, lymph node enlargement involving the fusion of multiple nodes, or occlusion of PV or the aorta, may involve metastasis.

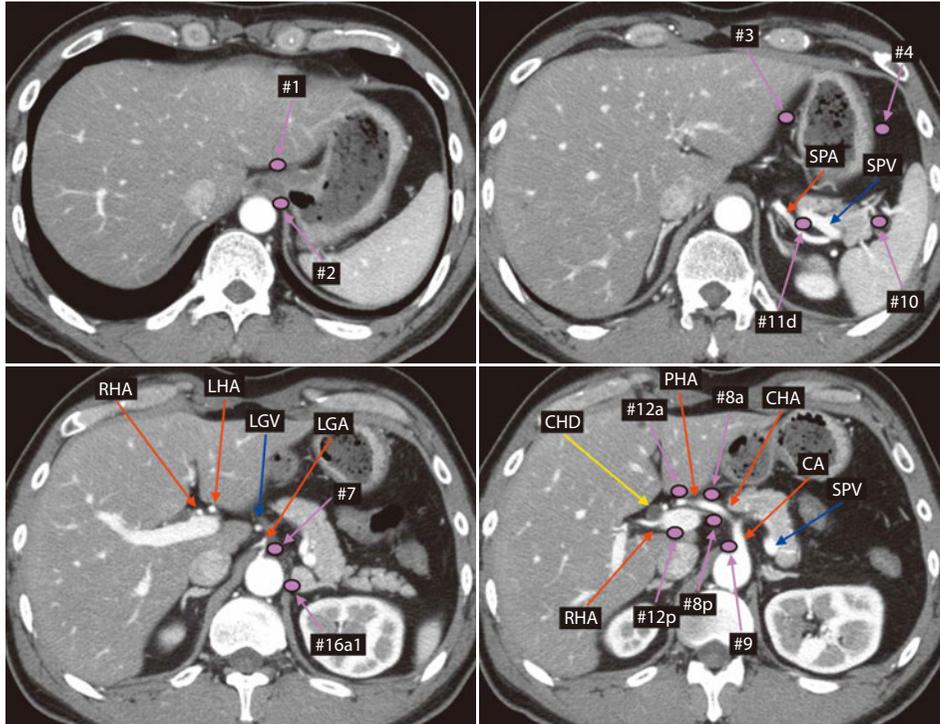


Fig. 27a Lymph nodes related to the pancreas on CT images—transverse view (1)
Lymph node numbers are indicated by the prefix #.

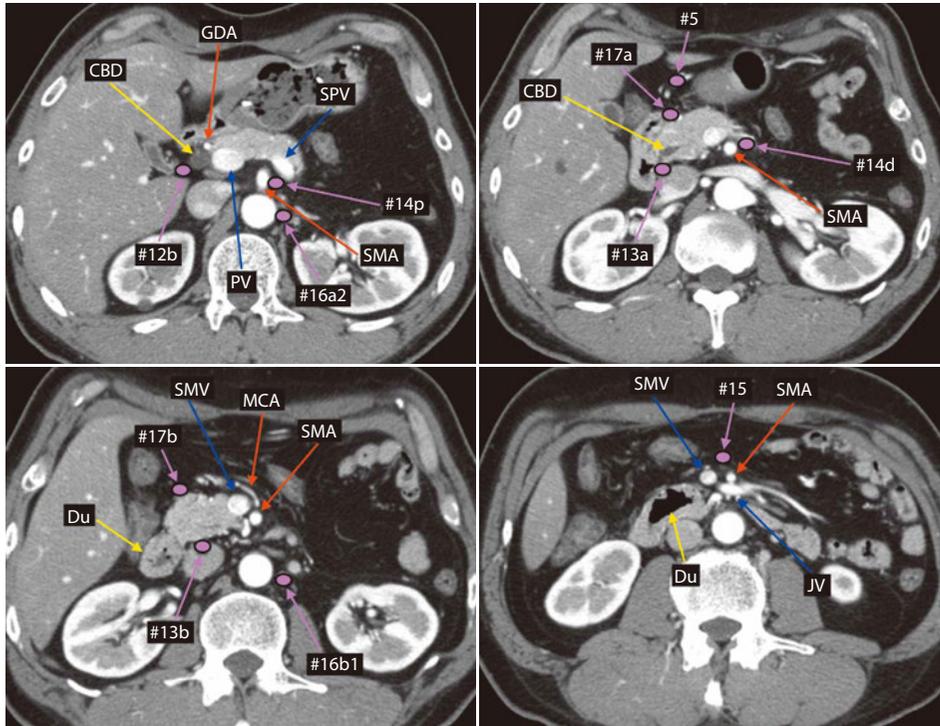


Fig. 27b Lymph nodes related to the pancreas on CT images—transverse view (2)

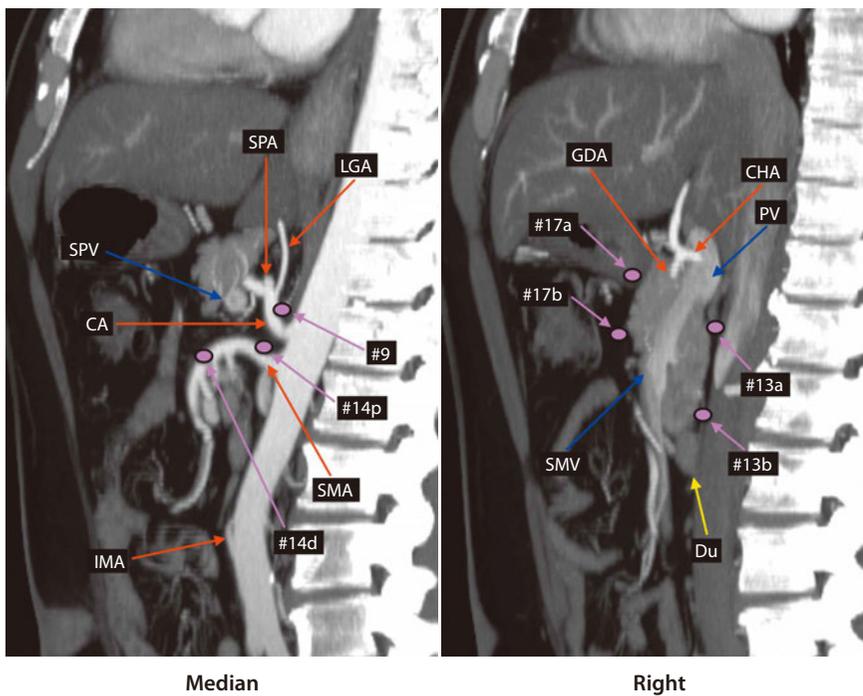


Fig. 27c Lymph nodes related to the pancreas on CT images—sagittal view (sagittal MIP)

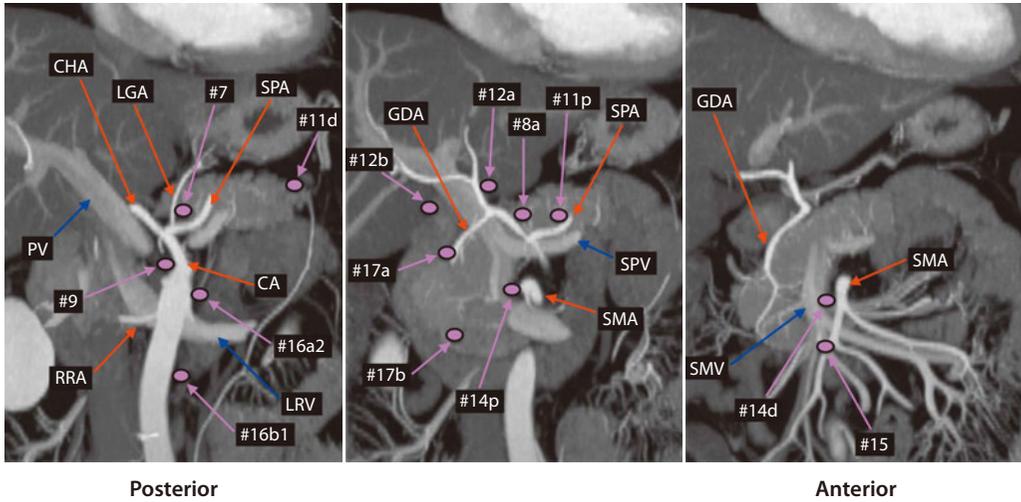


Fig. 27d Lymph nodes related to the pancreas on CT images—coronal view (coronal MIP)

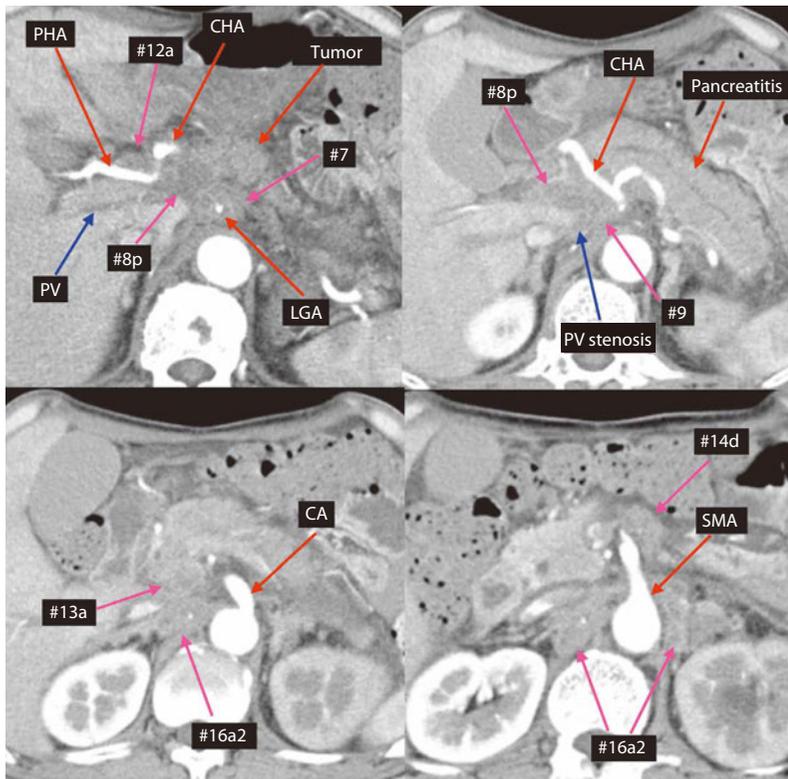


Fig. 28 Carcinoma in the head of the pancreas with multiple lymph node metastases
Fused lymph node enlargement is observed in the area around CA and the hepatoduodenal ligament. Lymph node enhancement is insufficient in the arterial phase view of dynamic CT. PV and CHA are compressed and stenosed by the enlarged lymph node. Lymph nodes are also enlarged in the distal SMA and around the aorta.

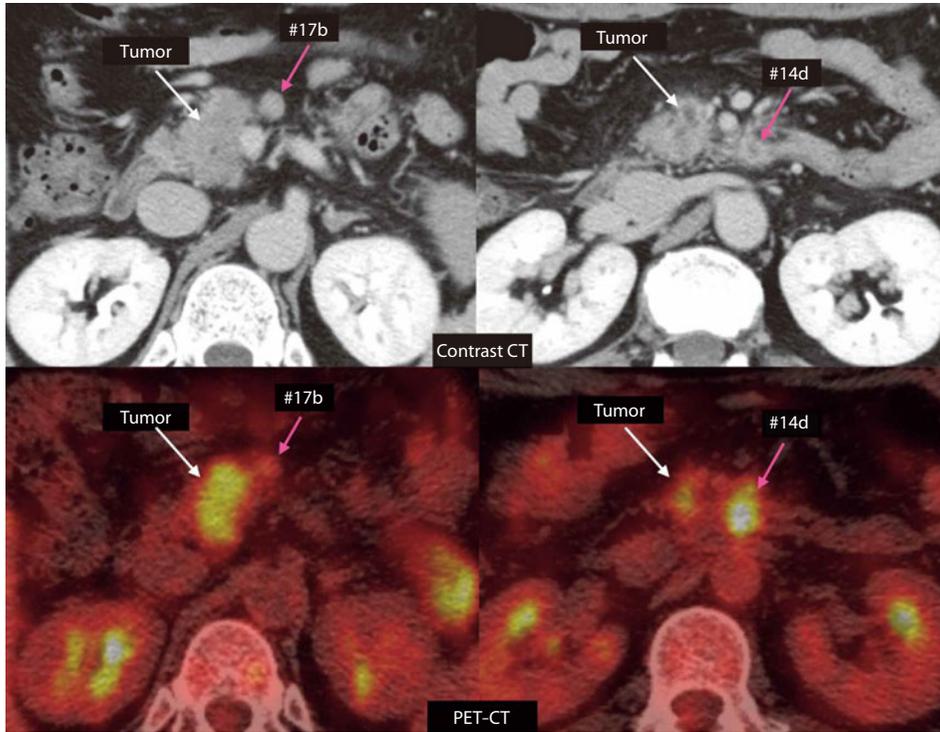


Fig. 29 Carcinoma in the head of the pancreas with lymph node metastases
Enlarged lymph nodes of ≥ 10 mm diameter are found in the lower anterior aspect of the head of the pancreas (#17b) and around SMA (#14d). #17b shows homogeneous enhancement and mild PET uptake. #14d lacks sufficient enhancement on the inside and shows significant PET uptake. The lymph node #17b showed no change in the follow-up and was considered to be a reactive enlargement. The lymph node #14d became further enlarged and was diagnosed as lymph node metastasis.

2) Regional lymph nodes

Lymph node numbers 5, 6, 7, 8a, 8p, 9, 10, 11p, 11d, 12a, 12b, 12p, 13a, 13b, 14p, 14d, 17a, 17b, and 18 are defined as pancreatic regional lymph nodes irrespective of the tumor location. Metastasis to any lymph node other than those mentioned above, including numbers 1, 2, 3, 4, 15, 16a1, 16a2, 16b1, and 16b2, should be classified as M1.

3) Recording lymph node metastases

In resected cases, the numbers of dissected and metastatic nodes should be recorded by the lymph node stated number.

(1) Degree of lymph node metastasis (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Regional lymph node metastasis

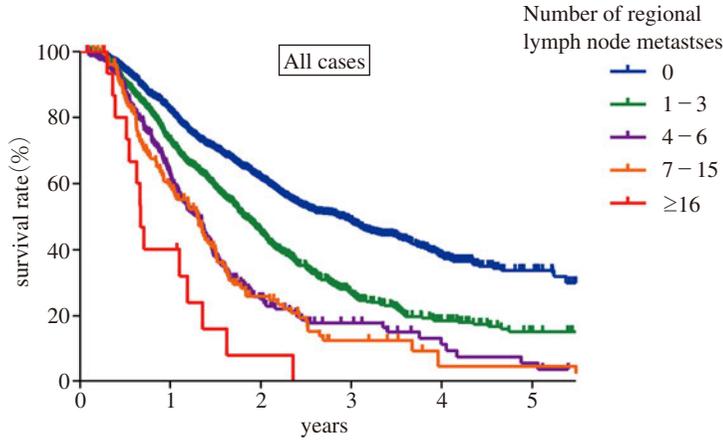
N1a: Metastasis in one to three regional lymph nodes

N1b: Metastasis in four or more regional lymph nodes

(2) Ratio of lymph node metastasis

The ratio of metastasis is calculated as the number of metastasis-positive nodes divided by the total number of dissected nodes for each of the relevant station numbers.

- Correlation between the number of regional lymph node metastases and survival curves in the resected cases with pancreatic ductal carcinoma (based on data compiled in Japan Pancreatic Cancer Registry of Japan Pancreatic Society (JPS))

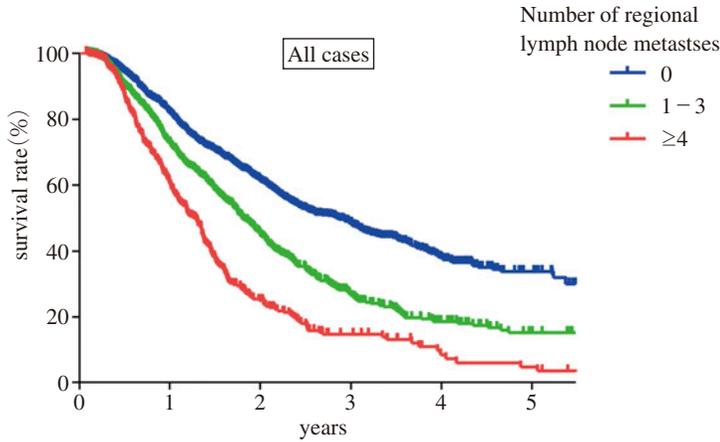


Number of regional lymph node metastases	MST (mo)	Survival rate				
		1-year	2-year	3-year	5-year	
0 (n=1,003)	34.7	81.7%	61.3%	48.4%	33.8%	} $p < 0.0001$
1-3 (n=893)	21.9	72.9%	45.1%	26.7%	15.2%	
4-6 (n=258)	15.9	62.7%	25.2%	17.9%	5.7%	} $p = 0.0001$
7-15 (n=133)	15.9	58.8%	26.0%	12.5%	4.7%	} $p < 0.6286$
≥16 (n=17)	8.2	40.0%	8.0%	0%	0%	} $p = 0.0146$

Fig. 30 Correlation between the number of regional lymph node* metastases and survival curves in the resected cases with pancreatic ductal carcinoma (All cases)

JPS Pancreatic Cancer Registry 2001–2007: 2,304 cases

*Regional lymph node: Defined on the basis of the lymph node groups in the 3rd English edition of the Classification and the UICC TNM classification of malignant tumors 7th edition.



Number of regional lymph node metastases	MST (mo)	Survival rate			
		1-year	2-year	3-year	5-year
0 (n=1,003)	34.7	81.7%	61.3%	48.4%	33.8%
1–3 (n=893)	21.9	72.8%	45.1%	26.8%	15.3%
≥4 (n=409)	15.7	60.7%	25.0%	14.8%	4.9%

}

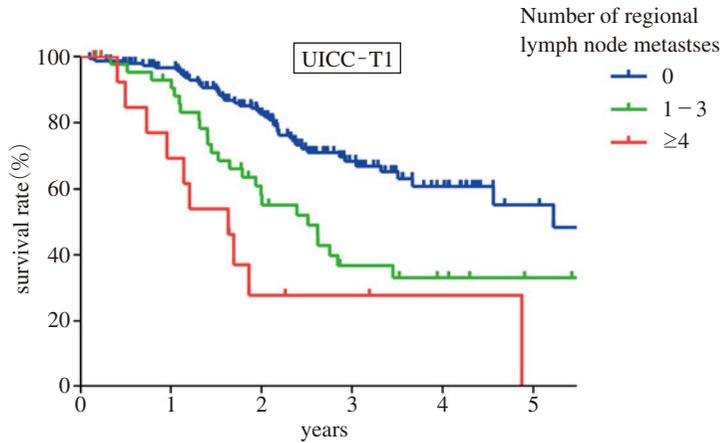
$p < 0.0001$

$p = 0.0001$

Fig. 31 Correlation of the regional lymph node* metastasis number and survival curves in the resected cases with pancreatic ductal carcinoma (All cases)

JPS Pancreatic Cancer Registry 2001–2007: Total of 2,304 cases including 211 T1, 458 T2, 1,388 T3, and 234 T4 cases in accordance with UICC TNM classification of malignant tumors 7th edition

*Regional lymph node: Defined on the basis of the lymph node groups in the 3rd English edition of the Classification and the UICC TNM classification of malignant tumors 7th edition.



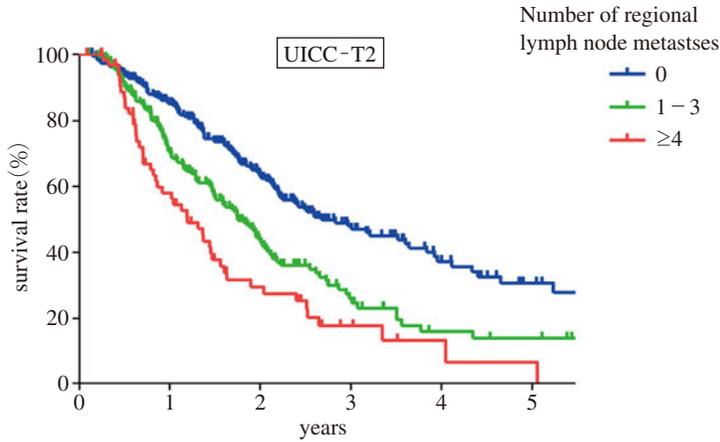
Number of regional lymph node metastases	MST (mo)	Survival rate			
		1-year	2-year	3-year	5-year
0 (n=151)	63.6	96.5%	82.6%	68.3%	55.2%
1-3 (n=45)	21.9	92.9%	57.9%	36.7%	33.0%
≥4 (n=15)	20.3	69.2%	27.7%	27.7%	0%

$p < 0.0008$
 $p = 0.0669$

Fig. 32 Correlation between the number of regional lymph node* metastases and survival curves in the resected cases with pancreatic ductal carcinoma (T1 cases in accordance with UICC TNM classification of malignant tumors 7th edition)

JPS Pancreatic Cancer Registry 2001–2007: 211 T1 cases in accordance with UICC TNM classification of malignant tumors 7th edition

*Regional lymph node: Defined on the basis of the lymph node groups in the 3rd English edition of the Classification and the UICC TNM classification of malignant tumors 7th edition.



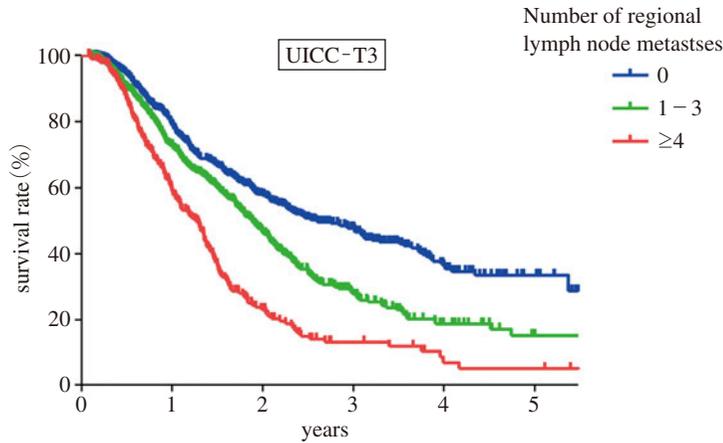
Number of regional lymph node metastases	MST (mo)	Survival rate			
		1-year	2-year	3-year	5-year
0 (n=226)	32.6	85.1%	63.1%	48.0%	30.6%
1-3 (n=167)	21.3	70.6%	43.5%	25.9%	14.0%
≥4 (n=65)	14.6	57.9%	29.5%	17.7%	6.6%

$p < 0.0001$
 $p = 0.0134$

Fig. 33 Correlation between the number of regional lymph node* metastases and survival curves in the resected cases with pancreatic ductal carcinoma (T2 cases in accordance with UICC TNM classification of malignant tumors 7th edition)

JPS Pancreatic Cancer Registry 2001–2007: 458 T2 cases in accordance with UICC TNM classification of malignant tumors 7th edition

*Regional lymph node: Defined on the basis of the lymph node groups in the 3rd English edition of the Classification and the UICC TNM classification of malignant tumors 7th edition.



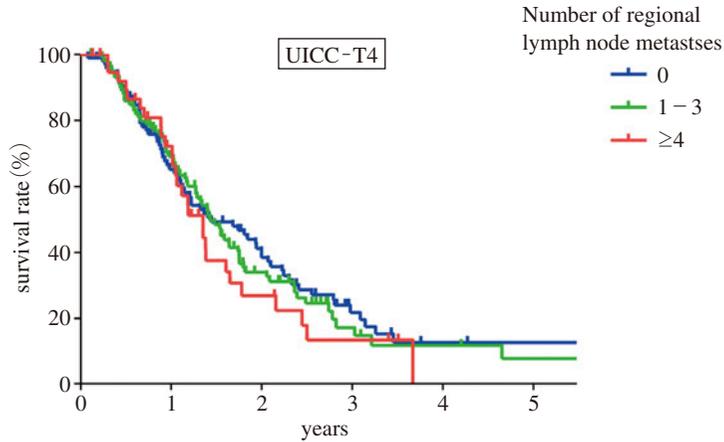
Number of regional lymph node metastases	MST (mo)	Survival rate			
		1-year	2-year	3-year	5-year
0 (n=524)	31.5	78.9%	57.7%	47.7%	33.5%
1-3 (n=577)	22.9	72.7%	46.5%	27.9%	15.2%
≥4 (n=287)	15.4	59.2%	23.1%	19.2%	5.2%

$p < 0.0001$
 $p = 0.0001$

Fig. 34 Correlation between the number of regional lymph node* metastases and survival curves in the resected cases with pancreatic ductal carcinoma (T3 cases in accordance with UICC TNM classification of malignant tumors 7th edition)

JPS Pancreatic Cancer Registry 2001–2007: 1,388 T3 cases in accordance with UICC TNM classification of malignant tumors 7th edition

*Regional lymph node: Defined on the basis of the lymph node groups in the 3rd English edition of the Classification and the UICC TNM classification of malignant tumors 7th edition.



Number of regional lymph node metastases	MST (mo)	Survival rate			
		1-year	2-year	3-year	5-year
0 (n=94)	17.6	65.1%	39.9%	21.8%	12.7%
1-3 (n=101)	17.5	69.0%	34.0%	17.2%	7.9%
≥4 (n=39)	16.5	72.2%	26.9%	13.4%	0%

Fig. 35 Correlation between the number of regional lymph node* metastases and survival curves in the resected cases with pancreatic ductal carcinoma (T4 cases in accordance with UICC TNM classification of malignant tumors 7th edition)

JPS Pancreatic Cancer Registry 2001–2007: 234 T4 cases in accordance with UICC TNM classification of malignant tumors 7th edition

*Regional lymph node: Defined on the basis of the lymph node groups in the 3rd English edition of the Classification and the UICC TNM classification of malignant tumors 7th edition.

3. Distant metastases (M)

M0: No distant metastasis

M1: Distant metastasis

The M1 site should be recorded using the following codes:

PUL: pulmonary	MAR: bone marrow	OSS: osseous	PLE: pleura
HEP: hepatic	PER: peritoneum	BRA: brain	ADR: adrenals
LYM: lymph nodes	SKI: skin	OTH: others	

Note 1: Lymph node metastasis outside the regional nodes should be recorded as M1.

Note 2: The MX (metastasis cannot be accessed) category is deemed inappropriate because clinical evaluation of distant metastases is possible only through imaging. Use of the MX category may disallow staging.

Specifically, peritoneal and hepatic metastases classified as M1 should be recorded as follows:

1) Peritoneal metastasis (P, or M1 PER in the UICC TNM classification system)

P0: No peritoneal metastasis

P1: Peritoneal metastasis

2) Hepatic metastasis (H, or M1 HEP in the UICC TNM classification system)

H0: No hepatic metastasis

H1: Hepatic metastasis

Note: Peritoneal and hepatic metastases are important prognostic factors and therefore, should be recorded separately from other distant metastases. In case of M0 that evidently indicates H0P0, only one notation is sufficient.

Recording peritoneal washing cytology (CY)

CYX: Peritoneal washing cytology not performed

CY0: Peritoneal washing cytology negative for carcinoma cells

CY1: Peritoneal washing cytology positive for carcinoma cells

Note: The CY1 category is not considered as M1 in this Classification, but further discussion on this issue is expected to continue in the future. For cytological methods, please refer to Section 3, Method of performing peritoneal washing cytology, on page 67.

The H, P, and CY categories should be used in clinical studies or records where these factors are particularly important.

4. Staging (Table 4)

Our previous staging system was made based on data for resected cases of pancreatic cancer registry by JPS, focusing on stratification of prognosis according to each stage. In contrast, this 4th edition basically adopts staging system of UICC 7th edition, focusing on enabling clinicians to decide treatment option for each stage. Roughly, stages I and II are initially resectable pancreatic cancer. Stage III is borderline resectable or locally advanced pancreatic cancer for which neoadjuvant therapy may be recommended on the setting of clinical trial. Stage IV has distant metastasis for which systemic chemotherapy is recommended.

Table 4 Staging in the JPS TNM Classification 7th edition (2016)

Stage 0	Tis	N0	M0
Stage IA	T1 (T1a, T1b, T1c)	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1 (T1a, T1b, T1c), T2, T3	N1 (N1a, N1b)	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

According to the revised category N in the Classification of Pancreatic Carcinoma, 4th English Edition, N0 is defined as no regional lymph node metastasis and N1 as regional lymph node metastasis, with N1a and N1b representing 1–3 and 4 or more metastatic nodes, respectively.

[Reference]

Staging in the UICC TNM Classification 7th edition (2010)

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

TNM Clinical Classification of the UICC TNM Classification, 8th edition (2016)

T-Primary Tumour

TX: Primary tumour cannot be assessed

T0: No evidence of primary tumour

Tis: Carcinoma in situ*

T1: Tumour 2 cm or less in greatest dimension

T1a: Tumour 0.5 cm or less in greatest dimension

T1b: Tumour greater than 0.5 cm and no more than 1 cm in greatest dimension

T1c: Tumour greater than 1 cm but no more than 2 cm in greatest dimension

T2: Tumour more than 2 cm but no more than 4 cm in greatest dimension

T3: Tumour and more than 4 cm in greatest dimension

T4: Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery

*Note: Tis also includes the 'PanIN-III' classification.

N-Regional Lymph Nodes

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastases in 1 to 3 regional lymph node

N2: Metastases in 4 or more regional lymph node

M-Distant Metastasis

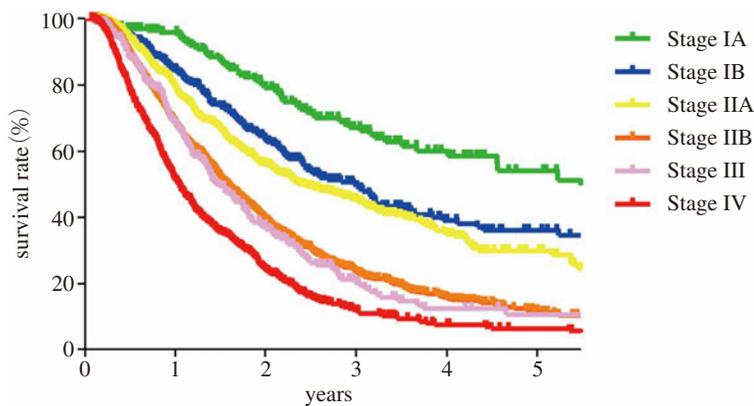
M0: No distant metastasis

M1: Distant metastasis

Staging in the UICC TNM Classification, 8th edition (2016)

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

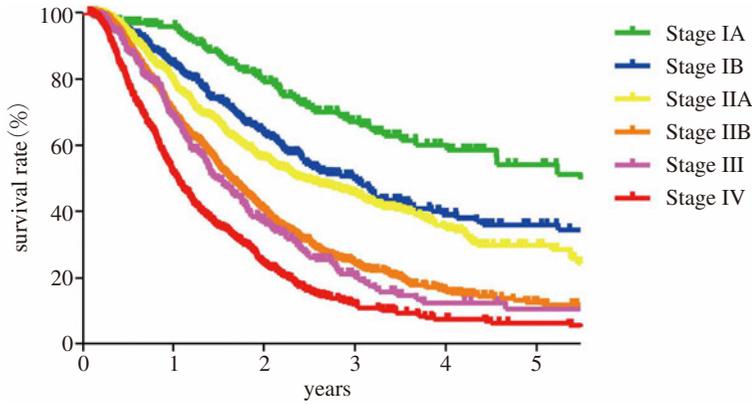
● Survival curves by stage of (resected/non-resected) cases in Pancreatic Cancer Registry of JPS



Stage	MST (mo)	Survival rate				
		1-year	2-year	3-year	5-year	
Stage IA (n=201)	69.4	95.9%	79.1%	67.1%	54.1%	} $p < 0.0001$
Stage IB (n=310)	36.1	84.7%	63.3%	50.0%	36.2%	
Stage IIA (n=615)	29.4	79.3%	56.0%	45.3%	29.9%	} $p = 0.0757$
Stage IIB (n=1,367)	19.2	68.6%	39.2%	23.4%	11.8%	
Stage III (n=257)	18.1	68.4%	36.9%	20.4%	10.7%	} $p < 0.0001$
Stage IV (n=565)	12.7	51.5%	24.2%	12.2%	6.5%	

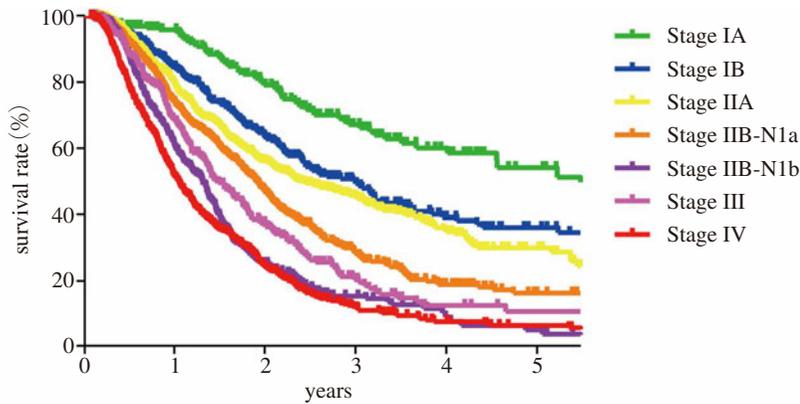
Fig. 36 Survival curves by stage of cases in Pancreatic Cancer Registry of JPS

(Total number of cases: 3,315; Stage IIB cases without records for the metastatic node number are included in the analysis; 2001–2007)



Stage	MST (mo)	Survival rate				
		1-year	2-year	3-year	5-year	
Stage IA (n=201)	69.4	95.9%	79.1%	67.1%	54.1%	} $p < 0.0001$
Stage IB (n=310)	36.1	84.7%	63.3%	50.0%	36.2%	
Stage IIA (n=615)	29.4	79.3%	56.0%	45.3%	29.9%	} $p < 0.0001$
Stage IIB (n=1,118)	19.7	69.8%	40.2%	24.3%	12.7%	
Stage III (n=257)	18.1	68.4%	36.9%	20.4%	10.7%	} $p < 0.0001$
Stage IV (n=565)	12.7	51.5%	24.2%	12.2%	6.5%	

Fig. 37 Survival curves by stage of cases in Pancreatic Cancer Registry of JPS (Total number of cases: 3,066; 249 Stage IIB cases without records for the metastatic node number are excluded from analysis; 2001–2007)



Stage	MST (mo)	Survival rate				
		1-year	2-year	3-year	5-year	
Stage IA (n=201)	69.4	95.9%	79.1%	67.1%	54.1%	$p < 0.0001$ $p = 0.0757$ $p < 0.0001$ $p < 0.0001$ $p = 0.0090$ $p < 0.0001$
Stage IB (n=310)	36.1	84.7%	63.3%	50.0%	36.2%	
Stage IIA (n=615)	29.4	79.3%	56.0%	45.3%	29.9%	
Stage IIB-N1a (n=761)	23.1	74.0%	46.7%	28.3%	16.3%	
Stage IIB-N1b (n=357)	16.0	60.9%	25.3%	15.4%	5.2%	
Stage III (n=257)	18.1	68.4%	36.9%	20.4%	10.7%	
Stage IV (n=565)	12.7	51.5%	24.2%	12.2%	6.5%	

Fig. 38 Survival curves by stage of cases in Pancreatic Cancer Registry of JPS

(Total number of cases: 3,066; 249 Stage IIB cases without records for the metastatic node number are excluded from analysis; 2001–2007)

5. Resectability classification

Most pancreatic cancer cases are not resectable because of distant metastasis or local advancement, even though various advanced diagnostic imaging modalities are now available. The factors predicting non-resectability related to local advancement are invasion of SMV, PV, SMA, CA, and CHA. To date, resectability has neither been classified in Japan nor been determined in institutions based on their own criteria or the NCCN guidelines in the US. The NCCN guidelines have based resectability categories on multi-phase contrast-enhanced MDCT findings since 2006, and been used for clinical trials and defining treatment modality. However, frequent revisions and more complicated criteria of the NCCN guidelines make their use challenging for physicians other than pancreatic surgery specialists. In contrast, our resectability classification proposes objective and effective criteria based on pancreatic dynamic CT images after multiple discussions with pancreatic surgery specialists, inter-nists, diagnostic imaging specialists, and pathologists.

Our Classification proposes resectable (R), borderline resectable (BR), and unresectable (UR) categories according to the probability of achieving an R0 resection with standard resection. R indicates lesions for which an R0 resection is possible with standard resection, and BR indicates lesions for

which R1 resection with residual cancer is highly probable with standard resection. In addition, UR cancers due to local advancement have a high possibility of R2 resection with macroscopic residual cancer, owing to arterial involvement. Please note that this resectability classification does not consider the primary tumor site or arterial anomalies.

1) Resectability

Resectable: R

No tumor contact with SMV or PV or less than 180 contact or invasion without occlusion. Clear fat planes around SMA, CA, and CHA, showing no contact or invasion.

Borderline resectable: BR

Subclassified according to SMV/PV invasion alone or arterial invasion.

BR-PV (SMV/PV invasion alone)

No findings of contact and invasion of SMA, CA, and CHA. Tumor contact or invasion of the SMV/PV of 180 or more degrees or occlusion of the SMV/PV, not exceeding the inferior border of the duodenum.^[1]

BR-A (Arterial invasion)

Tumor contact or invasion of SMA and/or CA of less than 180 degrees without showing stenosis or deformity. Tumor contact or invasion of CHA without showing tumor contact or invasion of PHA and/or CA.^[2]

Note 1: Reconstruction is challenging when images show SMV/PV having contact with/invasion of the tumor or an occlusion, or display tumor invasion beyond the lower margin of the duodenum.

Note 2: Cases of contact or invasion are classified as BR-A for both the portal venous and arterial systems.

Unresectable: UR

Subclassified according to the status of distant metastasis.

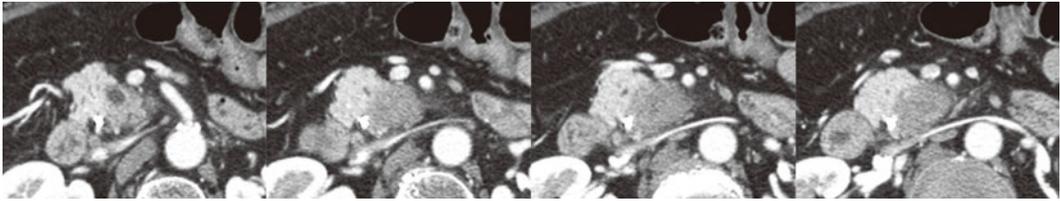
UR-LA (Locally advanced)

Tumor contact or invasion of SMV/PV of 180 or more degree or occlusion of SMV/PV, exceeding the inferior border of the duodenum. Tumor contact or invasion of SMA and/or CA of 180 or more degree. Tumor contact or invasion of CHA showing tumor contact or invasion of the PHA and/or CA. Tumor contact or invasion of the aorta.

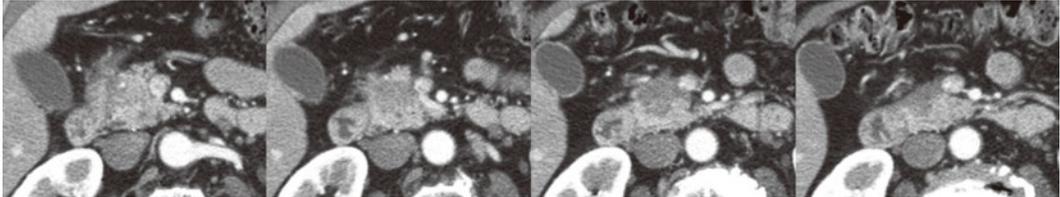
UR-M (Tumor with distant metastasis)

Distant metastasis including non-regional lymph node metastasis.

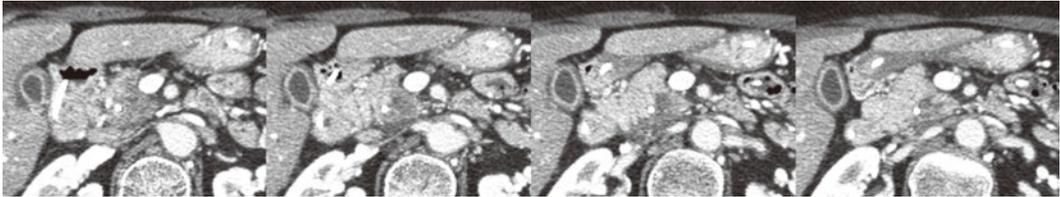
2) Examples of CT images for resectability classification



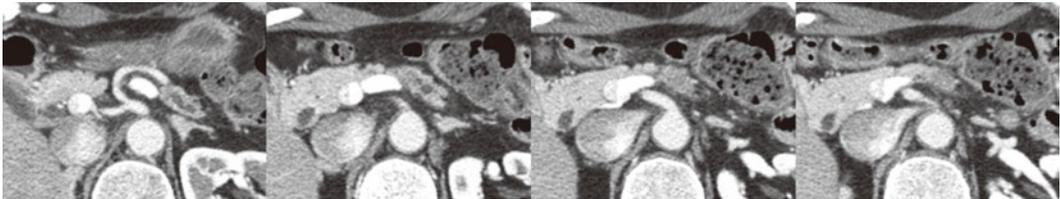
R: cPL1 (PLph II-PLsma), cAsm0, cPVsm1 (<math><180^\circ</math>)(carcinoma in the head of the pancreas)



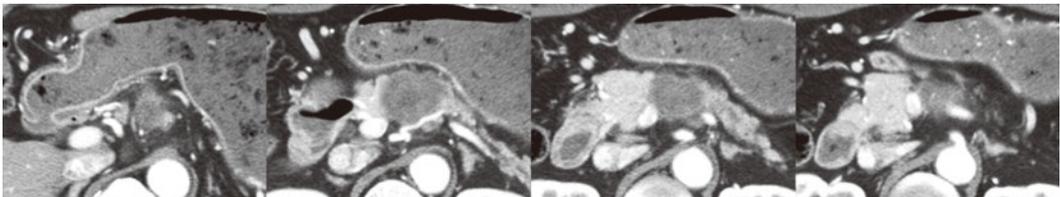
R: cPV sm1, (<math><180^\circ</math>)(carcinoma in the head of the pancreas)



R: cPL1 (PLph II-PLsma), cAsm0, cPVsm1 (<math><180^\circ</math>)(carcinoma in the head of the pancreas)

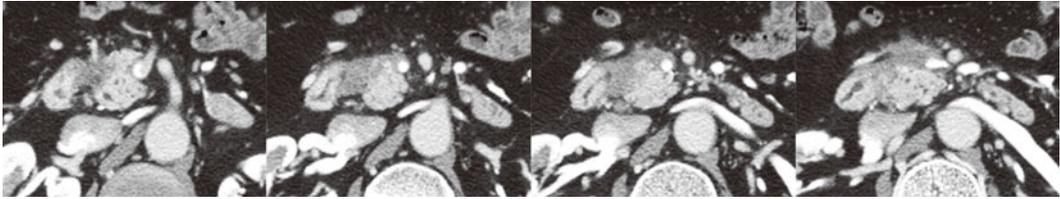


R: cPL1 (PLsma), cAsm0 (carcinoma in the body of the pancreas)

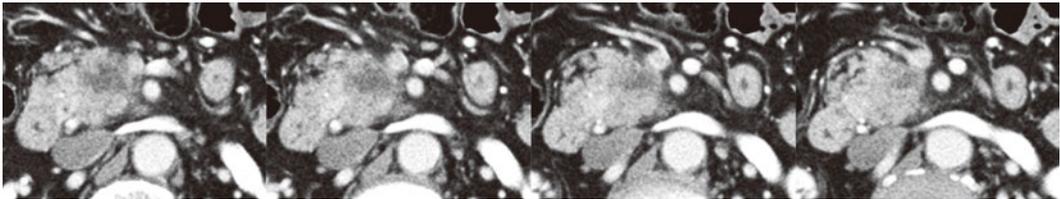


R: cAsp1, cPVsp1, cPVp/sm1 (<math><180^\circ</math>), cA0 (carcinoma in the body of the pancreas)

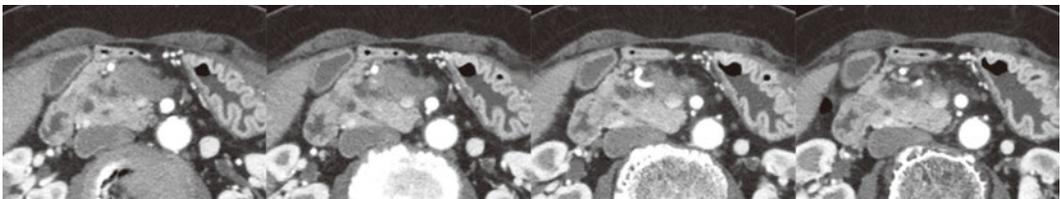
Fig. 39 CT images of resectable (R) lesions



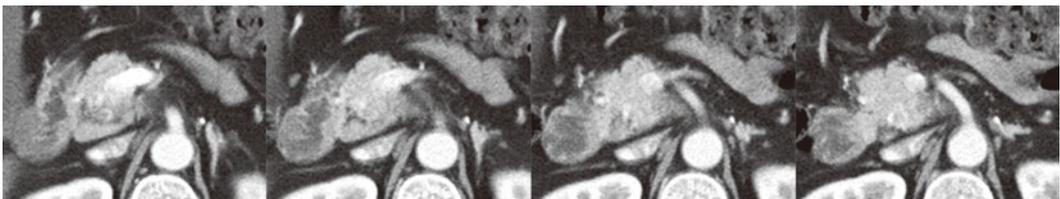
BR-PV: cPVsm1 ($\geq 180^\circ$), cA0 (carcinoma in the head of the pancreas)



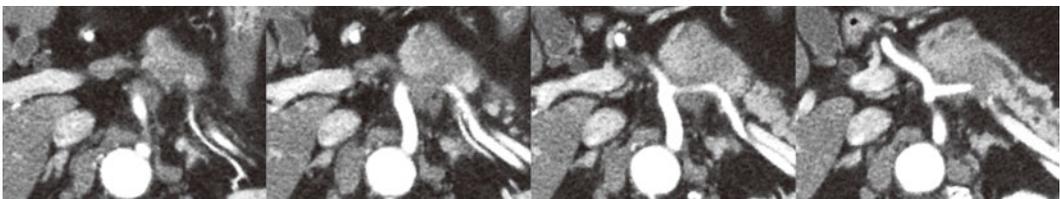
BR-A: cAsm1 ($< 180^\circ$) without stenosis or deformity. (carcinoma in the head of the pancreas)



BR-A: cAsm1 ($< 180^\circ$) without stenosis or deformity. (carcinoma in the head of the pancreas)

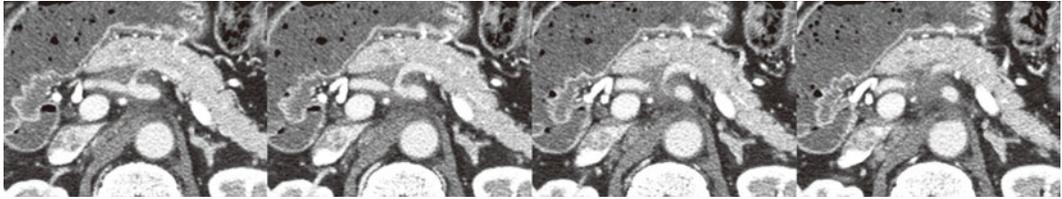


BR-A: cAsm1 ($< 180^\circ$) without stenosis or deformity. (carcinoma in the head of the pancreas)



BR-A: cAce1 ($< 180^\circ$) without stenosis or deformity, Ach1, Asp1 (carcinoma in the tail of the pancreas)

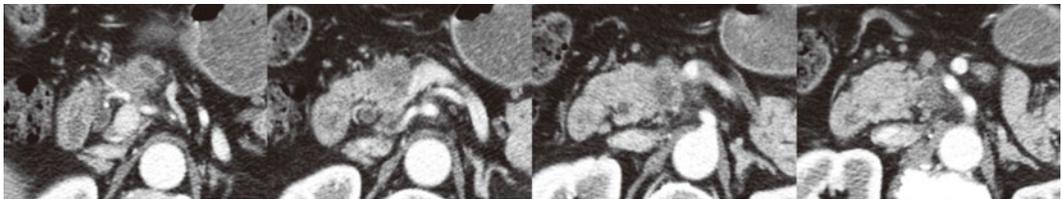
Fig. 40 CT images of borderline resectable (BR)



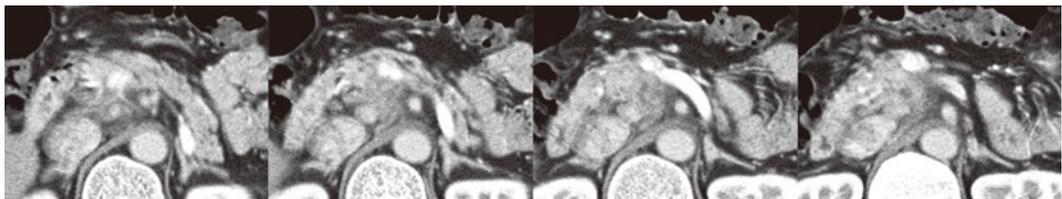
UR-LA: cAce1 ($\geq 180^\circ$). (carcinoma in the head of the pancreas)



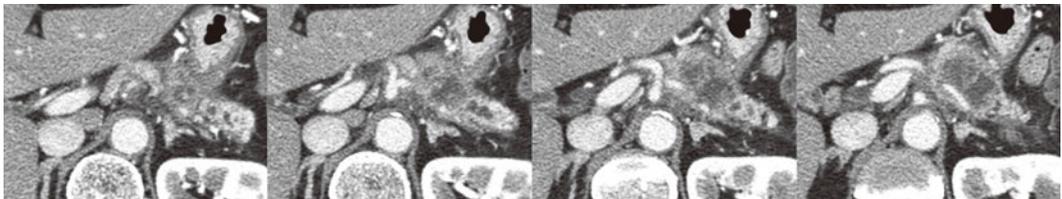
UR-LA: cAsm1 ($\geq 180^\circ$) (carcinoma in the head of the pancreas)



UR-LA: cAch1 ($\geq 180^\circ$) to cAce1 ($< 180^\circ$), cAsm1 ($< 180^\circ$) (carcinoma in the head of the pancreas)



UR-LA: cAce1 ($\geq 180^\circ$). (carcinoma in the body of the pancreas)



UR-LA: cAce1 ($\geq 180^\circ$). (carcinoma in the tail of the pancreas)

Fig. 41 CT image for UR-LA

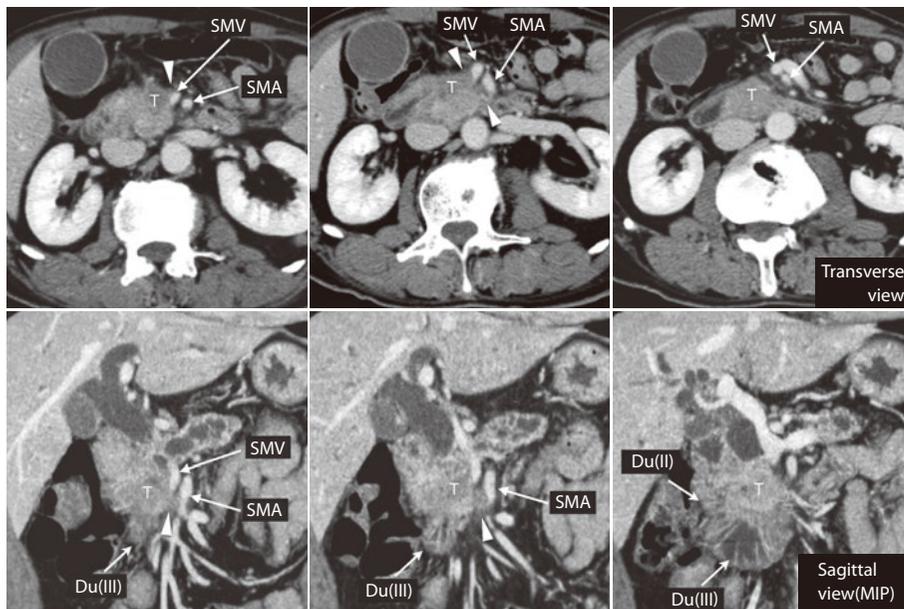


Fig. 42 BR-A: cPVsm1 (up to the level of the 3rd portion of the duodenum), cAsm1 ($<180^\circ$), DU1 (3rd portion of the duodenum). (carcinoma in the head of the pancreas)

The tumor advances forward medially and shows invasion of SMV and SMA (arrow heads). The invasion involves the horizontal portion of the duodenum [Du (III)] but not lower than the duodenum. Du (II) : The second portion of the duodenum

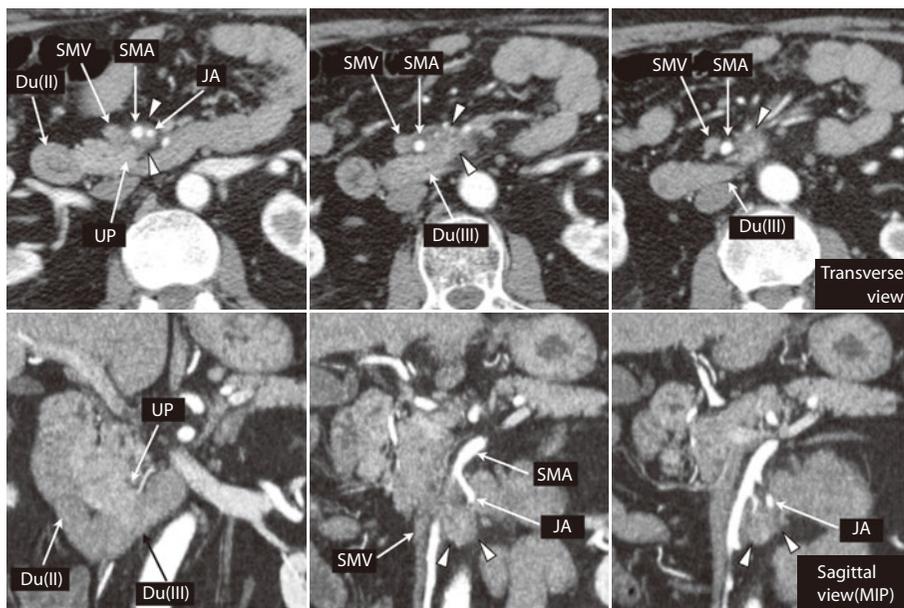


Fig. 43 UR-LA: cPVsm1 (exceeding lower border of the duodenum), cAsm1, cDU1 (3rd portion). (carcinoma in the head of the pancreas)

Neoplasm in the head of the pancreas invades along and around SMA and the jejunal artery (JA) down to the level lower than the horizontal portion of the duodenum [Du (III)]. UP: uncinete process, Du (II) : second portion of the duodenum

IV. Surgical Treatment

1. Type of operative procedure

1) Surgery with or without resection

Pancreatic resections

Palliative operations (bypass operations, including cholangiojejunostomy and gastrojejunostomy)

Other operations (exploratory laparotomy, staging laparoscopy, etc.)

2) Method of operative approach

Open surgery

Hand-assisted laparoscopic surgery (HALS)

Laparoscopic surgery (including robotic surgery)

Other

2. Description of pancreatic resection

1) Type of resection

Pancreatic head resection (PHR)

Pancreatoduodenectomy (PD)

Pylorus-preserving pancreatoduodenectomy (PPPD)

Subtotal stomach-preserving pancreatoduodenectomy (SSPPD)

Duodenum-preserving pancreatic head resection (DPPHR)

Pancreatic head resection with segmental duodenectomy (PHRSD)

Other pancreatic head resection

Distal pancreatectomy (DP)

Distal pancreatectomy (tail) [DP (tail)]

Distal pancreatectomy (body-tail) [DP (body-tail)]

Distal pancreatectomy (subtotal) [DP (subtotal)] *

Spleen-preserving distal pancreatectomy (SPDP)

Distal pancreatectomy with en-bloc celiac axis resection (DP-CAR)

Total pancreatectomy (TP)

Total pancreatectomy (TP)

Pylorus-preserving total pancreatectomy (PPTP)

Spleen-preserving total pancreatectomy (SPTP)

Pylorus-preserving, spleen-preserving total pancreatectomy (PPSPTP)

Duodenum-preserving total pancreatectomy (DPTP)

Total pancreatectomy with segmental duodenectomy (TPSD)

Middle pancreatectomy (MP)

Middle-segment preserving pancreatectomy (MSPP)

Partial pancreatectomy (PP)

Enucleation (EN)

* "Subtotal resection" refers to resection of more than two portions of the pancreas.

Sample notation: PD (subtotal), DP (subtotal)

2) Combined resection

When the duodenum, stomach, colon, spleen, portal system, or artery is resected in combination with pancreatic resection, the name of each resected organ should be recorded.

3) Reconstructions

(1) Reconstructions after PD, PPPD, or SSPPD

Reconstructions after PD, PPPD, or SSPPD are classified according to the order in which the pancreas, bile duct, and stomach are anastomosed to the jejunum, starting from the proximal end of the jejunum, as follows:

Type I: Bile duct, pancreas, stomach (PD-I, PPPD-I, SSPPD-1)

Type II: Pancreas, bile duct, stomach (PD-II, PPPD-II, SSPPD-II)

Type III: a. Stomach, pancreas, bile duct } (PD-III, PPPD-III, SSPPD-III)
b. Stomach, bile duct, pancreas }

Type IV: Other anastomoses (PD-IV, PPPD-IV, SSPPD-IV)

(2) Type of pancreatoenteric anastomosis

A) Pancreatojejunostomy

B) Pancreatogastrostomy

C) Pancreatoduodenostomy

D) End-to-end anastomosis of pancreas

They are further subclassified as:

1. Duct-to-mucosa anastomoses

Note: Duct-to-mucosa anastomoses include the procedure to anastomose the pancreatic duct along with the pancreatic parenchyma and the mucosa with the seromuscular layer.

2. Invagination or dunking methods

3. Other methods of anastomosis

Sample notation:

SSPPD-II-A-1

PPPD-IV-B-2

DPPHR-C-1

MP-A-2

MP-D

3. Classification of lymph node dissections (D)

D0: No dissection, or incomplete dissection of Group 1 lymph nodes

D1: Dissection of Group 1 lymph nodes alone

D2: Dissection of Group 1 and 2 lymph nodes

D3: Dissection of Group 1, 2, and 3 lymph nodes

Lymph node groups for TP, PD, and DP are summarized in Table 5.

Table 5 Lymph node groups

	Total pancreatectomy	Pancreatoduodenectomy	Distal pancreatectomy
Group 1	8a, 8p, 10, 11p, 11d, 13a, 13b, 17a, 17b, 18	8a, 8p, 13a, 13b, 17a, 17b	10, 11p, 11d, 18
Group 2	5, 6, 7, 9, 12a, 12b, 12p, 14p, 14d	5, 6, 12a, 12b, 12p, 14p, 14d	7, 8a, 8p, 9, 14p, 14d
Group 3	1, 2, 3, 4, 15, 16a2, 16b1	1, 2, 3, 4, 7, 9, 10, 11p, 11d, 15, 16a2, 16b1, 18	5, 6, 12a, 12b, 12p, 13a, 13b, 15, 17a, 17b, 16a2, 16b1

4. Assessment of residual tumor (R)

After pancreatic resection that includes the primary cancer, the gross or histological evidence of residual tumor (R) is classified as follows.

RX: Presence of residual tumor cannot be assessed

R0: No residual tumor

R1: Microscopic residual tumor

R2: Macroscopic residual tumor

For R0, it is desirable to record the shortest distance (mm) from the cut-end margin to the invasion site.

For localized residual tumors, the presence/absence of invasion at the cut-end and dissected margins should be recorded as below:

1) Pancreatic cut-end margin (PCM)

PCM0: No cancer infiltration

PCM1: Cancer infiltration present*

PCMX: Cancer infiltration cannot be assessed.

*Only PCM1 with carcinoma in situ should be recorded as PCM1e (epithelium), while PCM1 with invasive carcinoma or with both cancer in situ and invasive carcinoma should be recorded as PCM1i (invasive).

2) Bile duct cut-end margin (BCM)

BCM0: No cancer infiltration

BCM1: Cancer infiltration present*

BCMx: Cancer infiltration cannot be assessed.

*BCM1 with carcinoma in situ only is recorded as BCM1e (epithelium), while BCM1 with invasive carcinoma or with both cancer in situ and invasive carcinoma is recorded as BCM1i (invasive).

3) Dissected peripancreatic tissue margin (DPM)

DPM0: No cancer infiltration

DPM1: Cancer infiltration present

DCMX: Cancer infiltration cannot be assessed.

In the NCCN guidelines from 2017, DPM is further subcategorized into the SMA margin, posterior margin, PV groove margin, and anterior surface categories. Moreover, recording the distance to the cut-end margin is recommended.

V. Results of Treatment

1. Number of patients with pancreatic cancer

- 1) Total number of inhospital patients
- 2) Total number of surgical patients
- 3) Total number of non-surgical patients
- 4) Total number of pancreatic resection
- 5) Total number of operative deaths*
- 6) Total number of hospital deaths

*Operative death is defined as death within 30 days postoperatively without regard to whether the patient has been discharged.

2. Prognostic survey

- 1) Survived: Date survival confirmed
- 2) Died: Date of death
- 3) Lost to follow-up: The most recent date for survival information should be confirmed

3. Cause of death

- 1) Operation-related death: Death due to surgical complications or diseases accompanying surgical complications
- 2) Other treatment-related death: Death due to chemotherapy, radiotherapy, or other treatments
- 3) Death due to primary disease
- 4) Death due to other causes: State the diagnosis
- 5) Death due to accident (including suicide)
- 6) Cause of death unknown

4. Mode of recurrence

- 1) Recurrence in the residual pancreas
- 2) Recurrence in the pancreatic bed (pancreatic resection site)
- 3) Recurrence in the peritoneum
- 4) Recurrence in the liver
- 5) Hematogenous recurrence in organs other than the liver
- 6) Lymphogenous recurrence (other than in the pancreatic bed)
- 7) Mode of recurrence unknown

5. Survival rate

The method of calculating survival rates (e. g., the Kaplan–Meier method) and the method of testing for significant differences (e. g., the generalized Wilcoxon test) should be recorded. The type of data set (e. g., surgical cases, resection cases, or cases receiving chemotherapy) and the loss to follow-up rate should also be clearly recorded.

VI. Handling of Resected Specimens

1. Handling of resected pancreatic specimens

(1) The specimen should be examined grossly from both the dorsal and abdominal sides to confirm the status of invasion to the pancreatic capsule and desquamated surface*[†].

* If the pancreatic capsule or desquamated surface is involved by the tumor, the location, size, and appearance of the lesions should be recorded and the most invasive site should be microscopically examined.

[†] Methods including inking are recommended for histological residual tumor assessment¹⁾.

1) Verbeke CS. Resection margins and R1 rates in pancreatic cancer—are we there yet? *Histopathology*, 2008; 52: 787–96.

(2) The duodenum should be opened along its perpendicular axis on the external side or posterior wall to examine the papilla of Vater, accessory papilla, and duodenal mucosa (Fig. 44)*.

* The duodenum may be opened after closing both ends of the duodenum and fixing with formalin.

(3) CBD or MPD may be examined by opening the specimen before fixation or during stepwise sectioning after fixation. In the former case, generally either CBD or MPD is opened*. CBD should be opened posteriorly (Fig. 45) and MPD should be opened anteriorly. In the latter case, to fix the sample without opening CBD or MPD, it is recommended to inject formalin into CBD and MPD to ensure good fixation of the epithelium[†].

* If both CBD and MPDs are opened, the specimen shape will be too deformed to maintain the orientation.

[†] The epithelium of the bile and pancreatic ducts needs fixation as early as possible because it is easily autolyzed. This type of treatment is effective not only for microscopic assessment of pathohistologically challenging lesions but also for various immunohistochemical or genetic examinations.

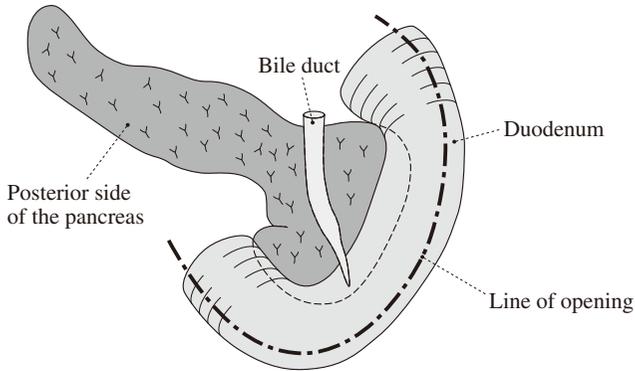


Fig. 44 Opening the duodenum

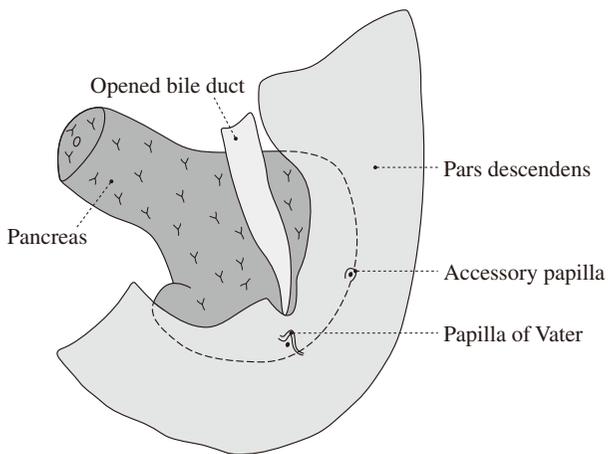


Fig. 45 Opening the intrapancreatic bile duct (posterior view of the pancreas)

2. Sectioning

1) Pancreatoduodenectomy specimens

The Kerckring's fold line that passes through the aperture of the papilla of Vater is used as the reference line. The specimen should be serially sectioned parallel to the reference line at approximately 5-mm intervals at the oral-side end and the anal-side end. In the section including the accessory papilla, the sectioning line should pass through its center (Figs. 46a-(1) and 46b) *.

* The sectioning lines from the duodenum in the head of the pancreas may not be necessarily parallel. Radial sectioning shown in the lowest figure in Fig. 46a- (1) is an alternative method that facilitates simultaneous viewing of CBD and MPDs.

2) Distal pancreatectomy specimens

The specimen should be serially sectioned perpendicular to the long axis of the pancreas at approximately 5-mm intervals (Fig. 46a-(2), Fig. 46b).

3) Total pancreatectomy specimens

The specimen should be sectioned by combining the procedures described in 1) and 2).

Note 1: Photographs of the resected specimen and cut surfaces should be taken with a scale included in the field of view.

Note 2: An axial section facilitates comparison with preoperative CT images.

3. Method of performing peritoneal washing cytology

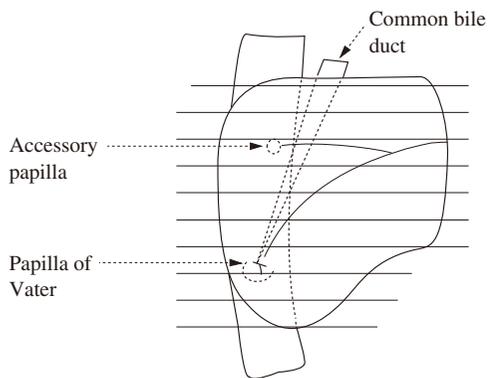
Immediately after the laparotomy, if ascites fluid is present, it is collected and examined, and if none is present, the peritoneal cavity is gently washed with 100 mL of physiological saline, and the fluid is collected from Douglas' pouch and examined.

The ascites fluid or washing fluid is centrifuged.

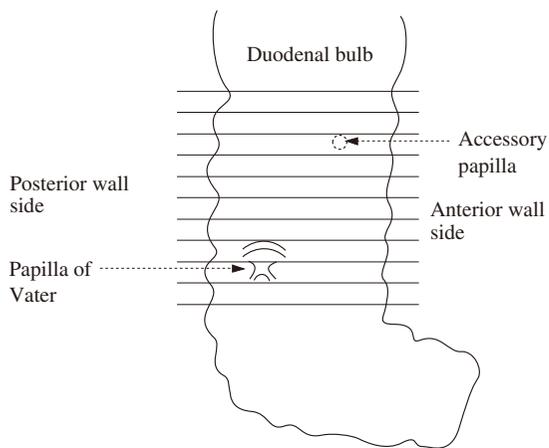
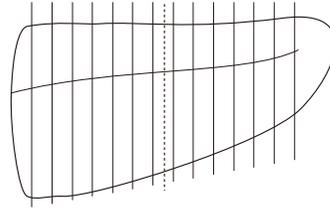
The sediment is placed on a glass slide, and a smear is prepared by the two-slide method.

Staining is generally performed with Papanicolaou or Giemsa stain, but when necessary, immunostaining is additionally performed.

(1) Pancreatoduodenectomy specimens



(2) Distal pancreatectomy specimens



< Alternative method >

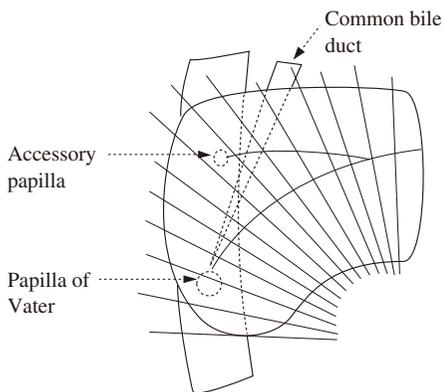
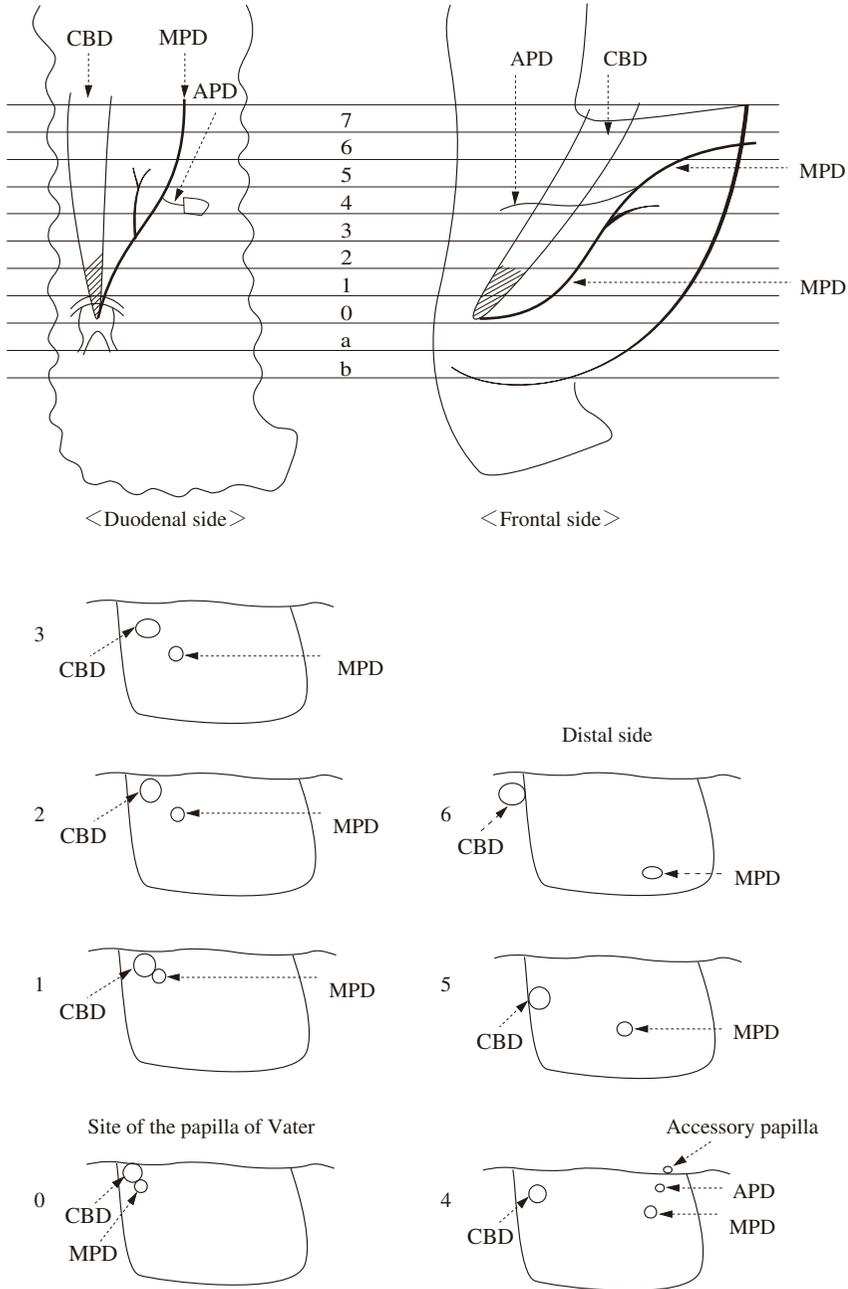


Fig. 46a Schematic diagrams showing how to section specimens of the head of the pancreas, duodenum, and the tail of the pancreas.



APD Duct of Santorini (accessory pancreatic duct)

Fig. 46b Schematic diagrams of the head of the pancreas and duodenum specimen showing the relationship between CBD and the pancreatic ducts on the duodenal and frontal aspects and the surfaces of the serial sections of the specimen.

VII. Histological Findings of Pancreatic Neoplasms

1. International Classification of Diseases for Oncology (ICD-O) code

[1] Epithelial neoplasms

A. Exocrine neoplasms

1. Serous neoplasms (SNs)

- a) Serous cystadenoma (SCA) 8441/0
- b) Serous cystadenocarcinoma (SCC) 8441/3

2. Mucinous cystic neoplasms (MCNs)

- a) Mucinous cystadenoma (MCA) 8470/0
- b) Mucinous cystadenocarcinoma (MCC), non-invasive 8470/2
- c) Mucinous cystadenocarcinoma (MCC), invasive 8470/3

3. Intraductal neoplasms

a) Intraductal papillary mucinous neoplasms (IPMNs)

- (1) Intraductal papillary mucinous adenoma (IPMA) 8453/0
- (2) Intraductal papillary mucinous carcinoma (IPMC), non-invasive 8453/2
- (3) Intraductal papillary mucinous carcinoma (IPMC), invasive 8453/3

b) Intraductal tubulopapillary neoplasms (ITPNs)

- (1) Intraductal tubulopapillary carcinoma (ITPC), non-invasive 8503/2
- (2) Intraductal tubulopapillary carcinoma (ITPC), invasive 8503/3

c) Pancreatic intraepithelial neoplasia (PanIN)

- (1) Low-grade PanIN
- (2) High-grade PanIN 8148/2

4. Invasive ductal carcinomas (IDCs)

a) Adenocarcinoma

- (1) Well differentiated type (wel) 8500/31
- (2) Moderately differentiated type (mod) 8500/32
- (3) Poorly differentiated type (por) 8500/33

b) Adenosquamous carcinoma (asc) 8560/3

c) Mucinous carcinoma (muc) 8480/3

d) Anaplastic carcinoma 8020/3

- (1) Anaplastic carcinoma, pleomorphic type

- (2) Anaplastic carcinoma, spindle cell type

- (3) Anaplastic carcinoma with osteoclast-like giant cells 8035/3

5. Acinar cell neoplasms (ACNs)

a) Acinar cell cystadenoma (ACA)	8551/0
b) Acinar cell carcinoma (ACC)	8550/3
B. Neuroendocrine neoplasms (NENs)	
1. Neuroendocrine tumors (NETs: NET G1, NET G2)	8240/3 (G1), 8249/3 (G2), 8150/3 (non-functioning G1/G2)
2. Neuroendocrine carcinoma (NEC)	8246/3
C. Combined neoplasms	
D. Epithelial neoplasms of uncertain differentiation	
1. Solid-pseudopapillary neoplasm (SPN)	8452/3
2. Pancreatoblastoma	8971/3
E. Unclassifiable	
F. Miscellaneous	

[2] Non-epithelial neoplasms

Defined according to the relevant classification norm
(Hemangioma, lymphangioma, leiomyosarcoma, malignant lymphoma, paraganglioma, others)

2. Cancer-stroma relationship

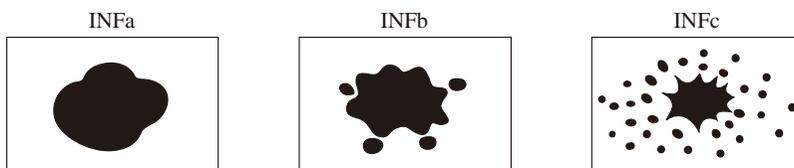
Tumors should be classified into the following types according to the proportion of stroma they contain:

- Medullary type (med): Tumors containing scant stroma.
- Intermediate type (int): Tumors containing a proportion of stroma intermediate between the scirrhous type and the medullary type.
- Scirrhous type (sci): Tumors containing abundant stroma.

3. Growth patterns of neoplasms infiltrating surrounding tissue (INF)

The most dominant growth patterns at the neoplasm margin are as follows:

- INFa: An expanding pattern of growth characterized by a distinct border with the surrounding tissue.
- INFb: A pattern intermediate between INFa and INFc.
- INFc: A diffusely infiltrating pattern of growth characterized by an indistinct border with the surrounding tissue.



4. Lymphatic invasion (ly)

ly0: No evidence of invasion

ly1: Slight invasion

ly2: Moderate invasion

ly3: Marked invasion

Note: Uncertain lymphatic invasion is classified as ly0.

5. Venous invasion (v)

v0: No evidence of invasion

v1: Slight invasion

v2: Moderate invasion

v3: Marked invasion

Note: Uncertain venous invasion is classified as v0.

6. Nerve invasion (ne)

ne0: No evidence of invasion

ne1: Slight invasion

ne2: Moderate invasion

ne3: Marked invasion

Note: The presence of extrapancreatic plexus (PL) nerve invasion is separately defined.

7. Intraductal spread in MPD (mpd)

Intraductal spread in MPD, beyond the area of the invasive tumor

mpd0: No evidence of spread

mpd1: Spread observed*

mpdx: Spread cannot be assessed

*Note: The distance that the tumor has spread within MPD should be recorded (Fig. 47). For pancreatoduodenectomy and distal pancreatectomy specimens, the distance from the cut end should also be recorded. The spread of intraductal tumors should be recorded as shown in Fig. 2 on p.13. Intraductal spread of invasive carcinomas that have developed from intraductal tumors should be recorded as shown in Fig. 47.

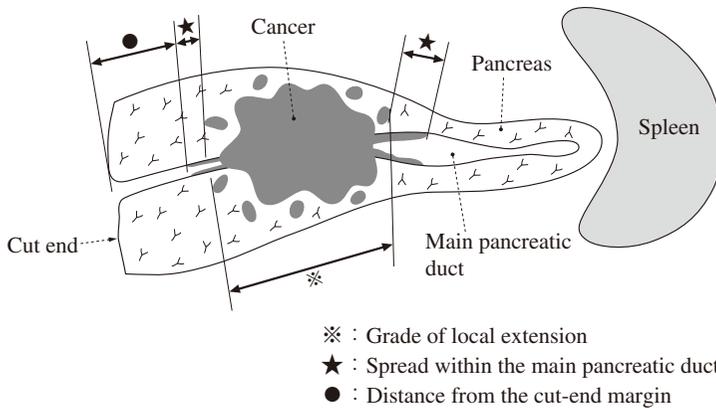


Fig. 47 Measurement of intraductal spread in MPD
The distances indicated by the stars (★) and sphere (●) should be measured.

8. Explanation of the histological classification

[1] Epithelial neoplasms

A. Exocrine neoplasms

1. Serous neoplasms (SNs)

a) Serous cystadenoma (SCA, Figs. 48–50)

SCA tends to occur in Pt of middle-aged women. The neoplasms have a spherical, rugged shape, and a thin capsule. They usually consist of small cysts up to 1 mm in diameter. However, some contain cysts that are larger than 10 mm in diameter or mainly large cysts (macro-cystic serous cystadenoma). The cysts contain a watery clear liquid. The cut surface of the neoplasm reveals stellate fibrosis or calcification. The small cysts are lined by a single layer of cuboidal or flattened epithelial cells containing clear cytoplasm, small round nuclei, and abundant intracytoplasmic glycogen. Mitoses are rare. Some cells grow in an adenoid or acinar form, giving a solid appearance (solid serous adenoma).

b) Serous cystadenocarcinoma (SCC)

SCC, a rare neoplasm, is the malignant counterpart of SCA. It is difficult to differentiate between these neoplasms and SCA histologically in the absence of metastatic growth, e. g., hepatic metastasis.

2. Mucinous cystic neoplasms (MCNs, Figs. 51–57)

a) Mucinous cystadenoma (MCA)

(Synonym: MCN with low- or intermediate-grade dysplasia¹⁾)

b) Mucinous cystadenocarcinoma (MCC), non-invasive

(Synonym: MCN with high-grade dysplasia¹⁾)

c) Mucinous cystadenocarcinoma (MCC), invasive

(Synonym: MCN with an associated invasive carcinoma¹⁾)

MCNs tend to occur in Pt of middle-aged or older women. The huge spherical monolocular or multilocular neoplasms have mucus and/or mucosanguineous fluid in the cysts. Their inner surface is either smooth, granular, or shows hemorrhagic erosions. Solid protrusions into the cyst cavities and nodular lesions in the septa suggest malignancy. Usually, imaging does not reveal communication with MPD. However, communication may be revealed by pancreatography of the resected specimens. Flat or papillary lesions grow on the inner surface of the cyst and are covered with mucinous high columnar epithelium showing varied degrees of atypia. A case of epithelial atypia grade inferior to that of carcinoma in situ is classified as MCA, while that with an equivalent atypia grade is classified as MCC, non-invasive; moreover, a case of neoplasms invading into or out of the cyst wall is classified as MCC, invasive. Sometimes, only scarce epithelium can be observed due to desquamation. This is characterized by ovarian-type stroma comprising dense spindle cells with abundant small vessels. In older patients or in those with a high degree of degeneration or inflammatory response, ovarian-type stroma may not be distinct. The histological type and invasion diameter of invasive carcinomas are also recorded.

3. Intraductal neoplasms (Figs. 58–77)

a) Intraductal papillary mucinous neoplasms (IPMNs)

(1) Intraductal papillary mucinous adenoma

(Synonym: IPMN with low- or intermediate-grade dysplasia¹⁾)

(2) Intraductal papillary mucinous carcinoma, non-invasive

(Synonym: IPMN with high-grade dysplasia¹⁾)

(3) Intraductal papillary mucinous carcinoma, invasive

(Synonym: IPMN with an associated invasive carcinoma¹⁾)

IPMNs are intraductal epithelial neoplasms characterized by macroscopic duct ectasia with mucus retention. Based on their principal location in MPD, its branches, or both, the neoplasms are classified as main duct type, branch duct type, or mixed type. They demonstrate neoplastic epithelial growth, exhibiting varied papillary structures and atypia on the dilated intraductal surface. They are classified into the aforementioned three categories based on the grade of atypia and the presence or absence of invasion. A case of epithelial atypia grade inferior to that of carcinoma in situ is classified as IPMA, while one of an equivalent grade of epithelial atypia is classified as IPMC, non-invasive. A case of neoplasms growing into or out of the pancreatic ductal wall is classified as IPMC, invasive. The histological type and invasion diameter of invasive carcinomas are also recorded. Tumor epithelium is classified into four histological types as follows: gastric type, which resembles gastric foveolar or pyloric

gland epithelium; intestinal type, which resembles intestinal goblet or villous tumor cells; pancreatobiliary type, which has a complex and irregular papillary structure; and oncocytic type, which shows leaf-shaped growth of oxyphilic cells with intraepithelial lumina.

b) Intraductal tubulopapillary neoplasms (ITPNs)

(1) Intraductal tubulopapillary carcinoma (ITPC), non-invasive

(2) Intraductal tubulopapillary carcinoma (ITPC), invasive

ITPNs grow as if they fit in a mold in the dilated pancreatic duct without macroscopic mucus. Histologically, cuboidal epithelium grows in a mass with a ductal or papillary form. Growth is often accompanied by necrosis, and sometimes, by hemorrhage. Tumor cells are always highly atypical, and the grade of atypia is considered to be equivalent to that of carcinoma in situ. A case of no invasion is classified/diagnosed as ITPN, non-invasive, while one with invasion into or out of the pancreatic duct wall is classified as ITPN, invasive. Some lesions comprise mostly tubular structures. These correspond to the intraductal tubular neoplasms described in the 3rd English edition of the Classification. Cases of low-grade atypical ITPNs equivalent to adenoma have not been reported. The current World Health Organization (WHO) Classification of Tumours of the Digestive System (2010)¹ also does not describe low-grade cases. Therefore, this classification does not have a category called “adenoma lesions.” Notably, intraductal tubular adenomas in the 3rd English edition are now considered to be pyloric gland type IPMNs, and not ITPNs equivalent to adenoma¹. In addition, ITPNs need to be differentiated from intraductal variant of acinar cell carcinomas. Hence, it is desirable to confirm their negative expression for trypsin. The differential findings from IPMN include no macroscopic mucus, poor intracellular mucus, and a negative expression for MUC5AC on immunohistochemical analysis.

c) Pancreatic intraepithelial neoplasia (PanIN)

(1) Low-grade PanIN (Figs. 78 and 79)

(Synonym: PanIN-1 or-2¹)

(2) High-grade PanIN (Figs. 80 and 81)

(Synonym: PanIN-3¹), carcinoma in situ (CIS) (Classification 3rd English Edition)

PanIN is an intraepithelial proliferative lesion limited within the pancreatic duct, which is in principle associated with microscopical duct ectasia (up to 5 mm). Using diagnostic imaging techniques such as magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS), the lesion may appear as a pancreatic ductal stenosis or a dilated part upstream from the stenosis. Histologically, it comprises columnar to cuboidal epithelium showing flat to low-papillary growth with various grades of atypia. A lesion with an atypia level lower than that of CIS is classified as

low-grade PanIN, and one with a level equivalent to that of CIS is classified as high-grade PanIN. IPMNs, in principle, show macroscopic duct ectasia and epithelial papillary growth with mucus production. Therefore, they can be differentiated from the microscopic intraductal proliferative lesion of PanIN by the degree and form of duct ectasia, and the grade and morphology of epithelial growth.

4. Invasive ductal carcinomas (IDCs) (Synonym: pancreatic ductal adenocarcinoma, PDAC¹⁾)

IDCs are malignant neoplasms with stromal invasion characterized by the formation of ducts resembling pancreatic ducts and/or differentiation to duct epithelium. Although they encompass a variety of histological findings, IDCs are classified into the categories shown below based on the predominant component. In WHO Classification, IDC is classified as the highest grade of histological type.

a) Adenocarcinoma

Adenocarcinoma is the most frequently seen histological type with various levels of duct formation. It is usually accompanied by distinctive desmoplasia and is rich in stromal fibrous tissue. According to the degree of duct formation (histologic differentiation), the adenocarcinoma is classified as follows:

(1) Well differentiated type (wel, Figs. 82 and 83)

The well differentiated type shows distinctive tubular/glandular formation, and is mainly composed of simple round glands or glands with small intraglandular papillary projections. The neoplastic cells are columnar or cuboidal in shape and have abundant cytoplasm. The nuclei are uniform in size and are usually arranged basally.

(2) Moderately differentiated type (mod, Figs. 84 and 85)

The moderately differentiated type is composed of smaller and more irregular glands than the well differentiated type. Cellular atypia is more marked, and the size and shape of the nuclei are more variable.

(3) Poorly differentiated type (por, Figs. 86 and 87)

Poorly differentiated adenocarcinoma has lower tendency to form tubular structures and grows in trabeculae or cobblestone-like nests. Mucin is identified more frequently than in anaplastic and undifferentiated carcinomas.

b) Adenosquamous carcinoma (asc, Figs. 88 and 89)

Adenosquamous carcinoma consists of a mixture of adenocarcinoma and squamous cell carcinoma components, where the squamous cell component should account for at least 30% of the neoplasm. Mucoepidermoid carcinoma is included in this category. A case is practically classified in this category when only squamous cell carcinoma components can be found in the routine examination.

c) Mucinous carcinoma (muc, Figs. 90–93) (Synonym: colloid carcinoma¹⁾)

Mucinous carcinoma is characterized by prominent mucus production forming distinct mucus lake (50% or more of the entire lesion), and marked fibrosis around each mucus lake. Carcinoma with various grades of differentiation can be found in and at the margin of the mucus lake. Signet-ring cell carcinoma is practically included in this category, because signet-ring cells are usually seen floating in the mucus lakes. If signet-ring cells are observed only in a part of the tumor, a remark should be added to the dominant histological type.

d) Anaplastic carcinoma (Figs. 94–97) (Synonym: undifferentiated carcinoma¹⁾)

Anaplastic carcinoma has unclear differentiation. Since ductal carcinoma components are found in most lesions, it is probably a subtype of ductal carcinoma. Depending on tumor cell morphology, anaplastic carcinoma is classified as pleomorphic type, spindle cell type, or anaplastic carcinoma with osteoclast-like giant cells; however, mixtures of these types are often found in the same neoplasm. Osteoclast-like giant cells show positive expression for CD68 and are negative for cytokeratin.

- (1) Anaplastic carcinoma, pleomorphic type
- (2) Anaplastic carcinoma, spindle cell type
- (3) Anaplastic carcinoma with osteoclast-like giant cells

5. Acinar cell neoplasms (ACNs)

a) Acinar cell cystadenoma (ACA)

ACA is a rare cystic tumor of acinar cells with little atypia.

b) Acinar cell carcinoma (ACC, Figs. 98–100)

ACC is a malignant tumor comprising eosinophilic (occasionally granular) cells resembling acinar cells. The neoplasms usually show acinar structure, but may also display a glandular structure or cribriform pattern, or consist of solid components. They are generally medullary and contain little stroma. Immunohistochemically, they are positive for trypsin, BCL10, etc., but negative for mucin. Electron microscopy can be used to detect the presence of zymogen granules in the cell.

B. Neuroendocrine neoplasms (NENs, Figs. 101–106)

1. Neuroendocrine tumors (NETs: NET G1, NET G2)

2. Neuroendocrine carcinoma (NEC)

NENs are tumors that demonstrate differentiation into neuroendocrine cells. Tumors with symptoms of hormone excess are called symptomatic (functional) tumors and those without hormone excess are called non-symptomatic (non-functional) tumors. The functional tumor may produce

more than one hormone simultaneously. An NEC is generally a solid tumor with a relatively distinct border, but some may have an indistinct border or cyst formation due to degeneration. Histologically, typical cells grow in a trabecular, ribbon-like, or organoid structure. Rosette or pseudorosette formation may also be seen. Diagnosis requires positive immunohistochemical findings for neuroendocrine markers including chromogranin A and synaptophysin. Depending on the case, the presence of neuroendocrine granules must be demonstrated using an electron microscope.

According to the WHO Classification of Tumours of the Digestive System (2010)¹⁾, neuroendocrine neoplasms are classified into neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs), and mixed adenoneuroendocrine carcinoma (MANEC). In accordance with proliferation kinetics, they are further classified into the following grades:

NET G1: mitotic count <2 per 10 high-power fields (HPF) or Ki67 index $\leq 2\%$;

NET G2: 2–20 per 10 HPF or Ki67 index 3–20%;

NEC: mitotic count >20 per 10 HPF or Ki67 index >20%.

This grading requires a mitotic count in at least 50 HPFs (1 HPF=0.2 mm²). The Ki67 index is determined using a Ki67 antibody (Clone: MIB) and calculated as a percentage after 500–2000 cells are counted in areas with the strongest nuclear labeling. If the grades based on the mitotic count and Ki67 index are different, the higher grade should be recorded as the tumor grade.

NETs (G1 and G2) are highly differentiated tumors with organoid structures, while NECs are poorly differentiated tumors with an indistinct organoid structure and possibly, significant nuclear atypia, multifocal necrosis, or high proliferative potential. However, some NETs with organoid structures may also demonstrate a high proliferative potential (Ki67 index >20%, mitotic count >20 per HPF). These are sometimes called well differentiated NECs or NET G3.

Note 1: Functional neuroendocrine neoplasms are also named by adding the suffix “-oma” to the hormone responsible for the syndrome. The syndromes of patients with such neoplasms correlate well with the grade of malignancy. Insulinomas are mostly benign, while gastrinomas, glucagonomas, and somatostatinomas are frequently malignant. The name “carcinoid of the pancreas” tends to be reserved for serotonin neoplasms. Attachment of the suffix “-oma” to a hormone is restricted to neoplasms manifesting syndromes and should not be used simply because immunohistochemical staining is positive for a particular hormone.

Note 2: Some pancreatic neuroendocrine neoplasms may be multiple endocrine neoplasia type 1 (MEN1: Wermer's syndrome) lesions. In such a case, a careful search for multiple endocrine neoplasms in the pancreas is necessary.

C. Combined neoplasms

Combined neoplasms exhibit a mixture or coexistence of exocrine and neuroendocrine neoplasms. Examples include duct-neuroendocrine carcinoma (Synonym: mixed adenoneuroendocrine carcinoma or MANEC¹⁾), where ductal and neuroendocrine carcinomas coexist, and duct-neuroendocrine-acinar cell carcinoma where ductal, neuroendocrine, and acinar cell carcinomas coexist.

D. Epithelial neoplasms of uncertain differentiation

1. Solid-pseudopapillary neoplasm (SPN, Figs. 107–109)

SPNs are rare tumors that occur mostly in young females. They usually follow a benign course, but are considered to have low-grade malignant potential. Most neoplasms are spherical and have a thick fibrous capsule with mixed patterns of solid and hemorrhagic necrotic cystic areas. Hemorrhagic necrotic cystic areas are rarely absent. Histologically, the solid area is composed of eosinophilic cells that are small to medium in size and round to oval in shape. The stroma consists of capillary vessels and pseudopapillary structures that can be observed around vascular cores. Gland-like structures can also be seen. Eosinophilic globules (hyaline globules), aggregates of foamy histiocytes, and occasional cholesterol granulomas can be seen. It is important to demonstrate that tumor cells are β -catenin-positive (nucleus) and CD10-positive in immunohistochemistry. It is also useful to confirm that the tumor is negative for acinar cell markers (trypsin and BCL10) and the neuroendocrine cell marker (chromogranin A) to differentiate SPNs from acinar cell carcinomas and NENs. Electron microscopy reveals immature neoplastic cells containing numerous mitochondria.

2. Pancreatoblastoma (Figs. 110 and 111)

Pancreatoblastoma is a rare neoplasm that is most common in children under 10 years of age, especially boys, and is therefore also called “infantile carcinoma of the pancreas”. Macroscopically, the neoplasms are of the solid type and are composed of parts differentiating into pancreatic duct epithelial cells and acinar cells. The former have “squamous corpuscles” that look like spirals, while the latter have zymogen granules. These cell groups are organized into an organoid structure. Alpha-fetoprotein (AFP) production by the neoplasm is often observed.

E. Unclassifiable

Tumors whose histological type cannot be determined because of the effects of radiotherapy, chemotherapy, or artificial deformation, are recorded as unclassified.

F. Miscellaneous

[2] Non-epithelial neoplasms

These are defined according to the applicable classification norms.

(Hemangioma, lymphangioma, leiomyosarcoma, malignant lymphoma, paraganglioma, etc.)

- 1) WHO Classification of Tumours of the Digestive System, Fourth Edition (Bosman FT, Carneiro F, Hruban RH, Theise ND, eds, International Agency for Research on Cancer, Lyon, France, 2010)

■ Atlas of Pathology

Exocrine Neoplasms

Serous neoplasms



Fig. 48 Serous cystadenoma (Cut surface of the resected specimen)
The neoplasm consists of numerous small cysts measuring a few millimeters each and has a sponge-like consistency. It often mimics lymphangioma. The cysts contain clear serous fluid.

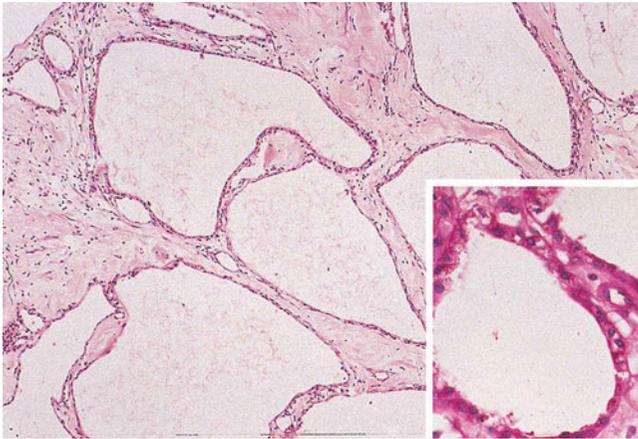


Fig. 49 Serous cystadenoma
The cysts are lined by columnar or flat epithelial cells that have clear cytoplasm. Inset: An abundant amount of glycogen is detected by Periodic acid-Schiff (PAS) staining.

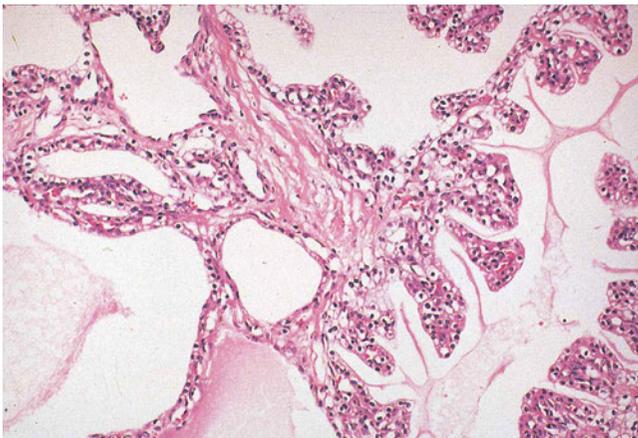


Fig. 50 Serous cystadenoma
Occasionally, neoplasms show papillary projections. The presence of a papillary structure does not imply malignancy.

Mucinous cystic neoplasms

Fig. 51 Mucinous cystadenoma (Cut surface of the resected specimen)
The cysts have thick walls and a large cavity is found in the upper central part. The cysts contain mucinous or mucosanguineous fluid. The inner surface of the cysts is smooth or finely granular.



Fig. 52 Mucinous cystadenoma
This figure shows papillary epithelial growth in part of the wall. Ovarian-type stroma is observed (inset).

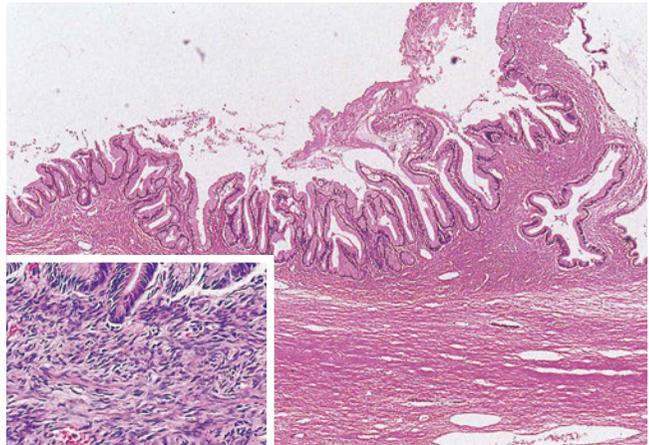
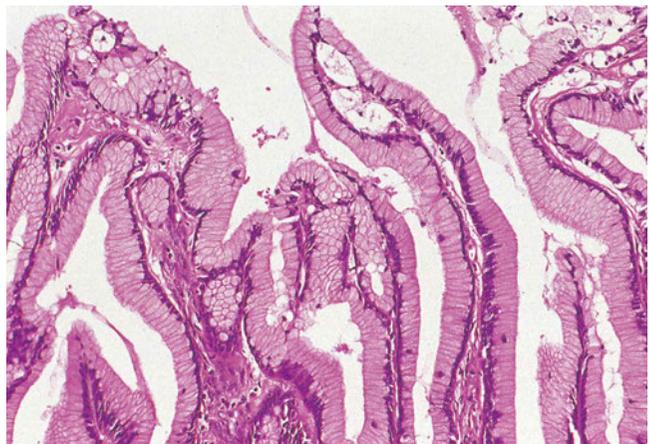


Fig. 53 Mucinous cystadenoma (High-power view of Fig. 52)
The papillary structure is lined by tall, columnar epithelium that shows evidence of mucus production. The nuclei are small, uniform, and basally located.



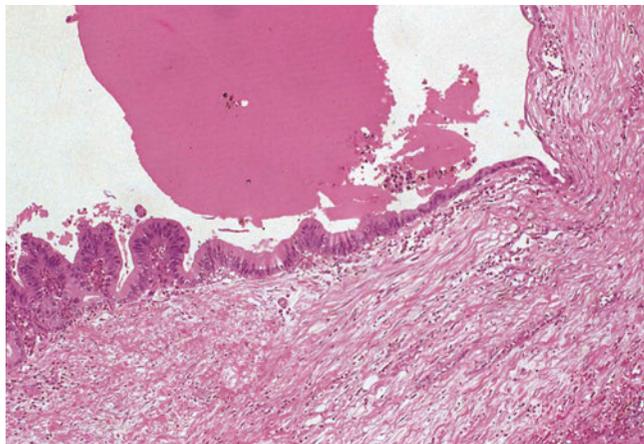


Fig. 54 Mucinous cystadenoma
Mucus in the cytoplasm of neoplastic epithelium is scant and nuclear enlargement is present (moderate atypia).



Fig. 55 Mucinous cystadenocarcinoma (Surgical specimen)
The inner surface of the cystic neoplasm contains an area of papillary projections (arrow). The pancreas is at the top left of the specimen, and the spleen is at the right (dark part).

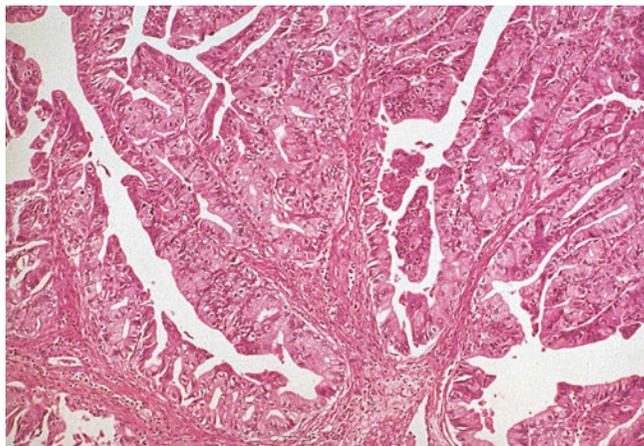


Fig. 56 Mucinous cystadenocarcinoma (Area indicated by the arrow in Fig. 55)
Irregular papillary growth is visible. Nuclei are small and basally located, and show slightly irregular shapes.

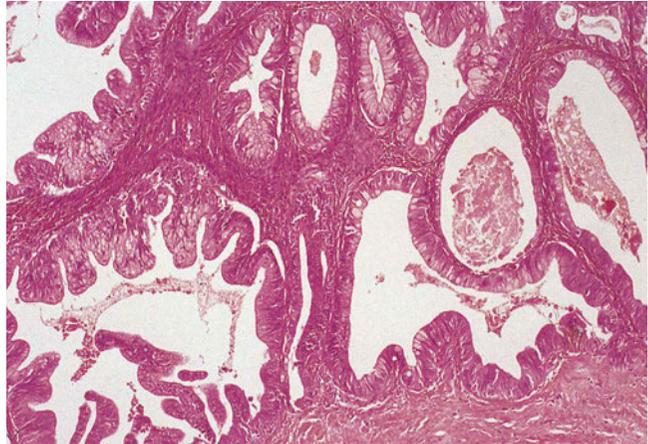


Fig. 57 Mucinous cystadenocarcinoma (Same neoplasm as in Figs. 55 and 56) This portion consists of tubular structures.

Intraductal neoplasms

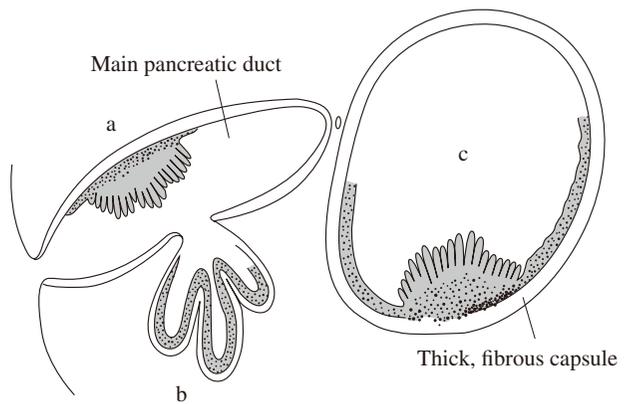


Fig. 58 Schematic diagram comparing an intraductal papillary mucinous neoplasm and a mucinous cystic neoplasm
 a. Intraductal papillary mucinous neoplasm, the main duct type. b. Intraductal papillary mucinous neoplasm, branch duct type. c. Mucinous cystic neoplasm.

Fig. 59 Endoscopic view of an intraductal papillary mucinous neoplasm (Surgical specimen)
 Mucus has been removed from the dilated MPD, and an electronic endoscope has been inserted into MPD from the caudal side. A flat-topped elevated lesion can be seen (arrow) in MPD (duct of Wirsung). The accessory pancreatic duct (duct of Santorini) can be seen at the top right.

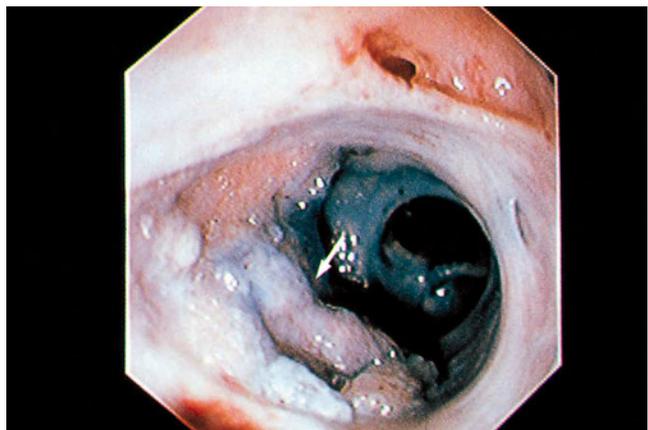




Fig. 60 Intraductal papillary mucinous neoplasm (Cut section of surgical specimen; same neoplasm as in Fig. 59)
The papillary neoplasm (arrow) is confined to MPD. The papillary structure is clear under a magnifying glass. Duct wall thickening is visible, and the surrounding pancreatic parenchyma is atrophic.

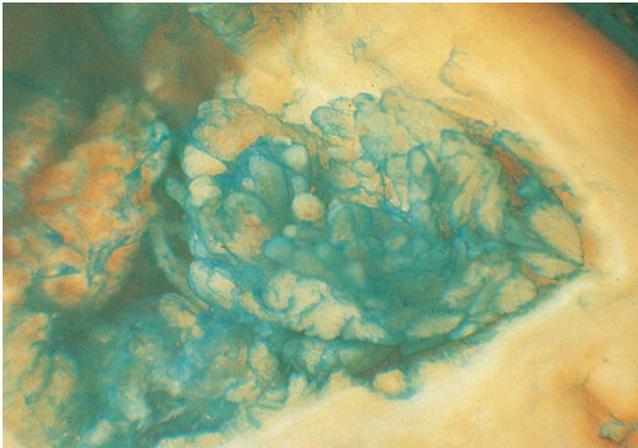


Fig. 61 Intraductal papillary mucinous neoplasm (Stereomicroscopic view)
The mucous cells were positive for alcian blue staining, which highlights the papillary structure of the neoplasm. This staining is efficient for intraductal observation.

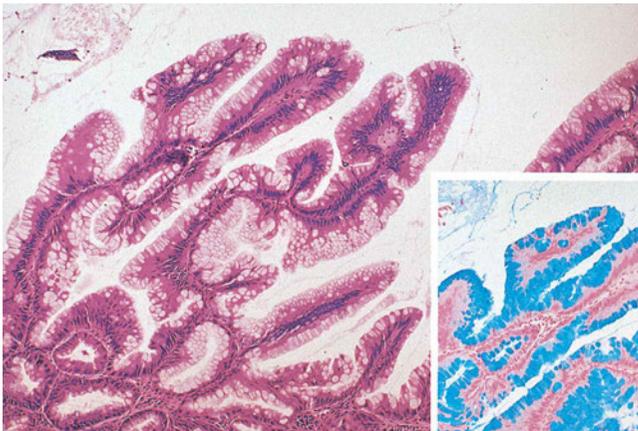


Fig. 62 Intraductal papillary mucinous adenoma: same specimen as in Fig. 61
The papillary structure is often composed of tall, columnar mucous cells. The mucus is acidic, and positive for alcian blue staining (inset). The nuclei are small, uniform, and basally located.

Fig. 63 Intraductal papillary mucinous carcinoma: same specimen as in Fig. 61
 Although the nuclei are small, they tend to show loss of polarity. Well differentiated. This specimen was diagnosed as well differentiated adenocarcinoma (non-invasive).

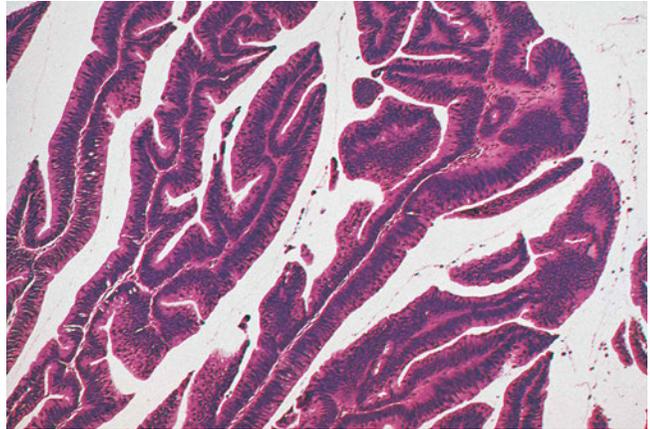


Fig. 64 Intraductal papillary mucinous neoplasm (main duct type)
 Two villous neoplasms (arrows) containing abundant mucus are present in a markedly dilated MPD (main duct type). The pancreatic parenchyma is atrophic. This neoplasm was diagnosed as intraductal papillary mucinous carcinoma, non-invasive.



Fig. 65 Intraductal papillary mucinous carcinoma: loupe view of the same specimen as in Fig. 64
 The tumor is a non-invasive papillary mucinous neoplasm confined to MPD.



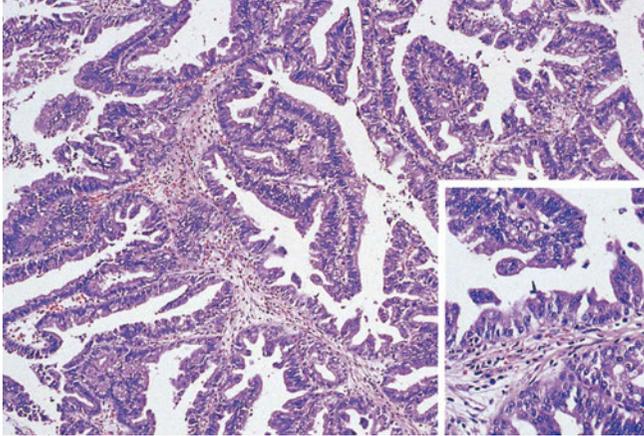


Fig. 66 Intraductal papillary mucinous carcinoma: high-power view of the lesion in Fig. 65

Papillary epithelial growth is seen along a fine stromal core. The growth pattern is irregular, and its serrated structure is conspicuous. Nuclear arrangement is irregular (inset). This neoplasm was diagnosed as intraductal papillary mucinous carcinoma, non-invasive.

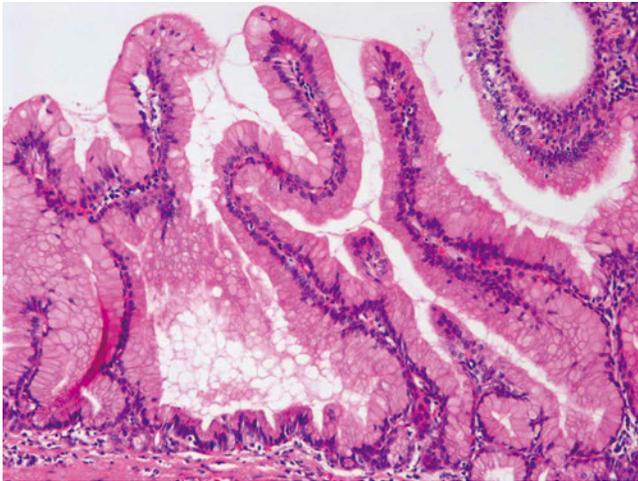


Fig. 67 Intraductal papillary mucinous adenoma, gastric type

Papillary tumor epithelium grows in a pattern resembling that of gastric foveolar epithelium. Low-grade atypia is seen.

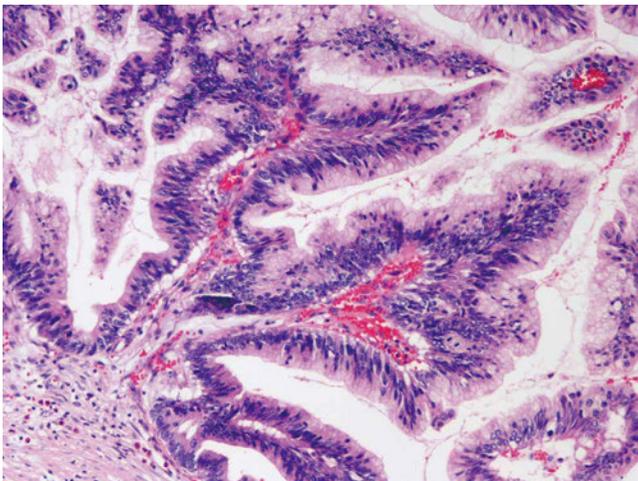


Fig. 68 Intraductal papillary mucinous carcinoma, non-invasive, intestinal type

Tumor epithelium grows in a pattern resembling that of an intestinal villous tumor. High-grade atypia is seen.

Fig. 69 Intraductal papillary mucinous carcinoma, non-invasive, oncocytic type
 Oncocytic cells grow in a papillary shape.
 High grade atypia is seen.

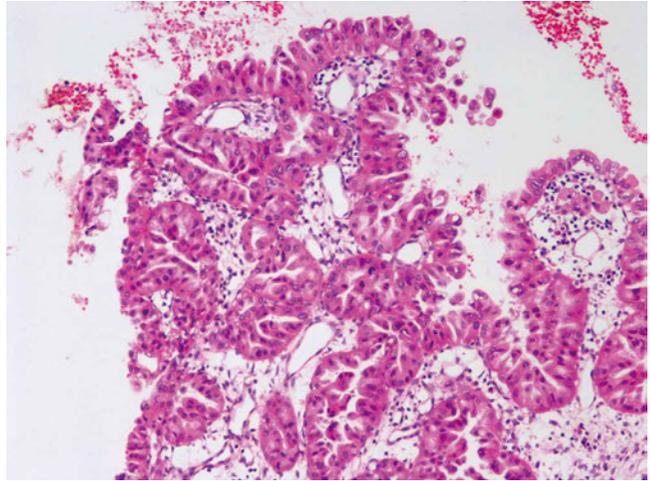


Fig. 70 Intraductal papillary mucinous carcinoma, non-invasive, pancreatobiliary type
 Tumor epithelial growth shows irregular and complex papillary structures, often in a “fern-leaf pattern”. High-grade atypia is seen.

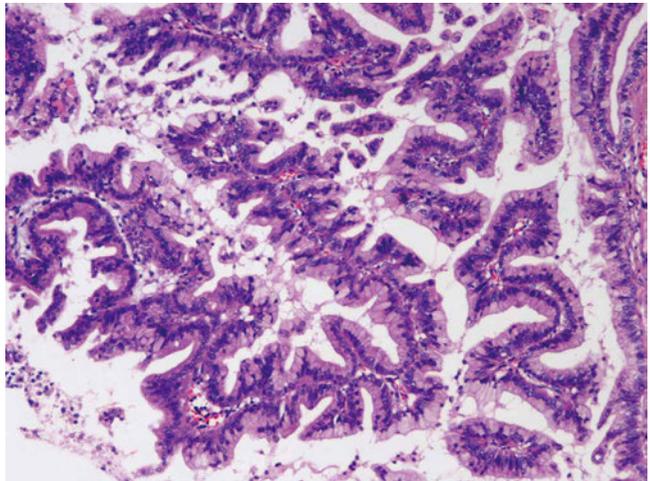


Fig. 71 Intraductal papillary mucinous adenoma, gastric type, pyloric gland variant
 Growth of the duct resembles that in the pyloric gland.
 Low-grade atypia is seen. The case corresponds to intraductal tubular adenoma in the previous classifications.

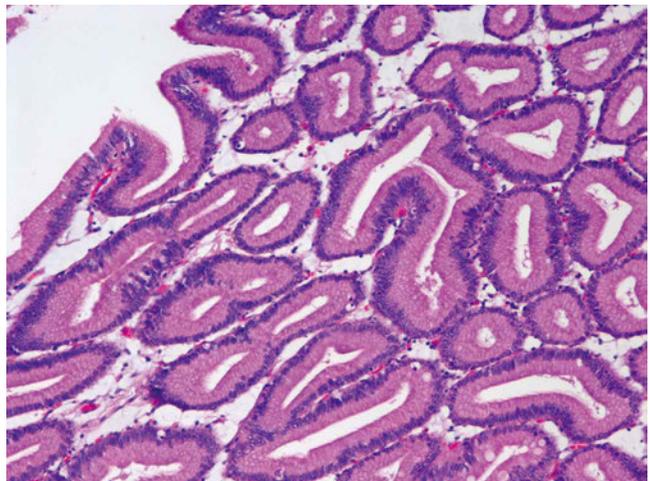




Fig. 72 Intraductal papillary mucinous carcinoma, invasive

Intraductal papillary mucinous carcinoma is seen in a dilated duct. The arrows point to the area of invasive carcinoma. An asterisk marks the papilla of Vater.

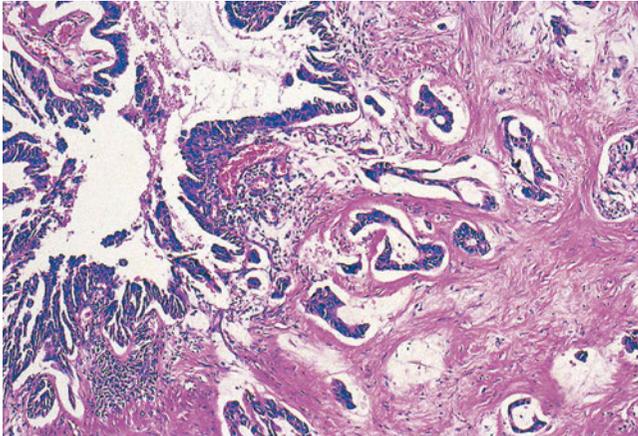


Fig. 73 Intraductal papillary mucinous carcinoma, invasive

The left side of the figure shows an intraductal papillary mucinous carcinoma that grows in the main duct. Tubular adenocarcinoma, which is visible on the right, invades the surrounding tissue.

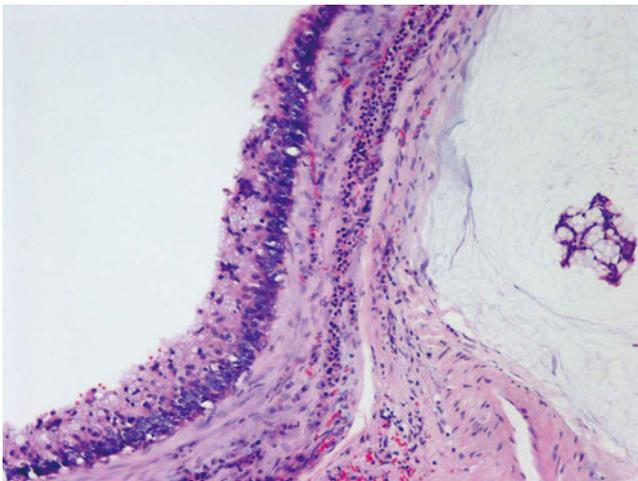


Fig. 74 Intraductal papillary mucinous carcinoma, invasive

Intestinal-type intraductal papillary mucinous carcinoma is accompanied by mucinous carcinoma.

Fig. 75 Intraductal tubulopapillary neoplasm

Growth of neoplasms, which fit in a mold in the dilated pancreatic duct, can be observed (arrows). No mucus is visible on macroscopic observation.



Fig. 76 Intraductal tubulopapillary carcinoma, non-invasive (Histological view of the sample shown in Fig. 75)

Tubulopapillary tumors have grown and filled the pancreatic duct.

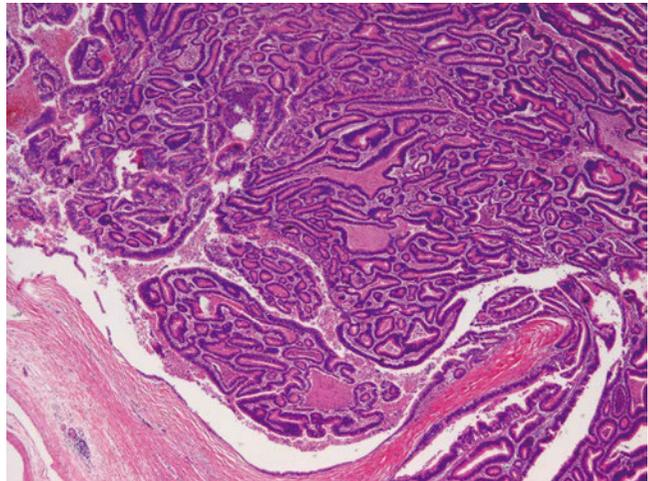
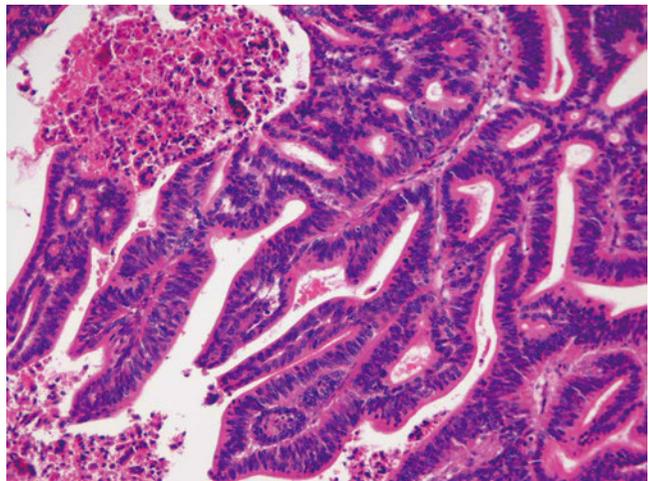


Fig. 77 Intraductal tubulopapillary carcinoma, non-invasive (High-power view of the sample shown in Fig. 76)

Tumor epithelium grows in a complex and irregular tubulopapillary structure with intraductal necrosis. The architectural irregularity, nuclear enlargement, nucleus-to-cytoplasm ratio, polarity disturbance, and nuclear stratification are all severe, corresponding to high-grade atypia. Cells have eosinophilic cytoplasm with little mucin.



Pancreatic intraepithelial neoplasia (PanIN)

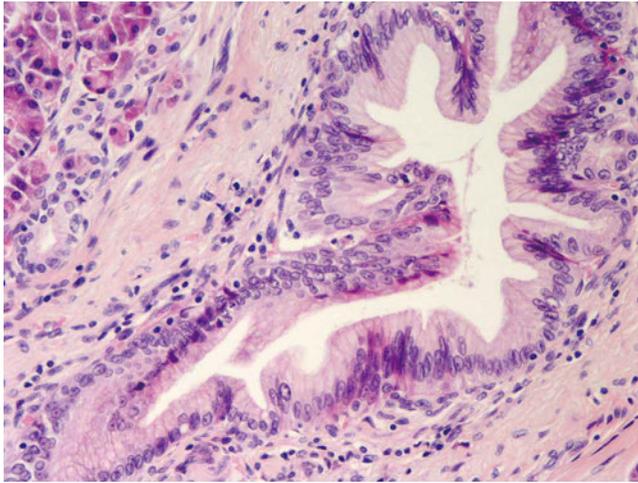


Fig. 78 Low-grade PanIN
The lesion comprises columnar epithelium that shows low papillary growth. Low- to intermediate-grade atypia is observed. The lesion corresponds to PanIN-2.

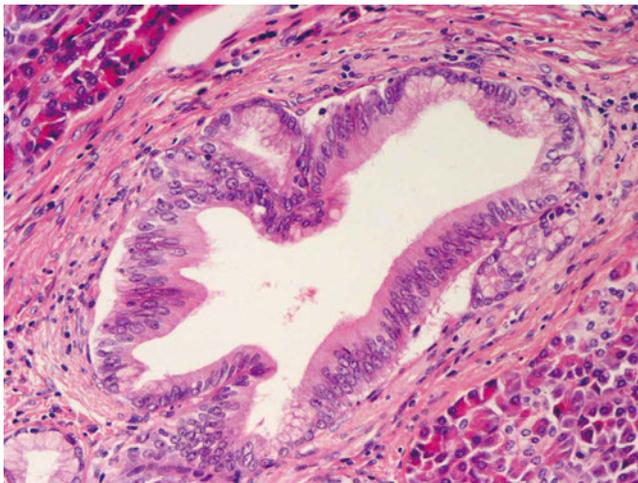


Fig. 79 Low-grade PanIN
The lesion comprises columnar epithelium that shows low papillary growth. Nuclei are slightly enlarged and are sometimes stratified, but lined in a relatively good order. The lesion corresponds to PanIN-2.

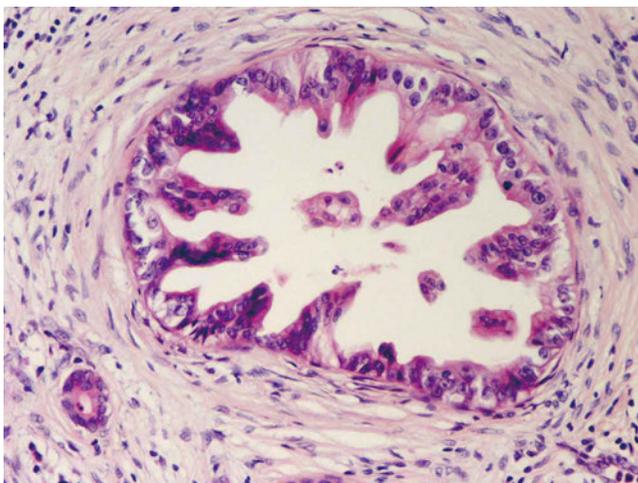
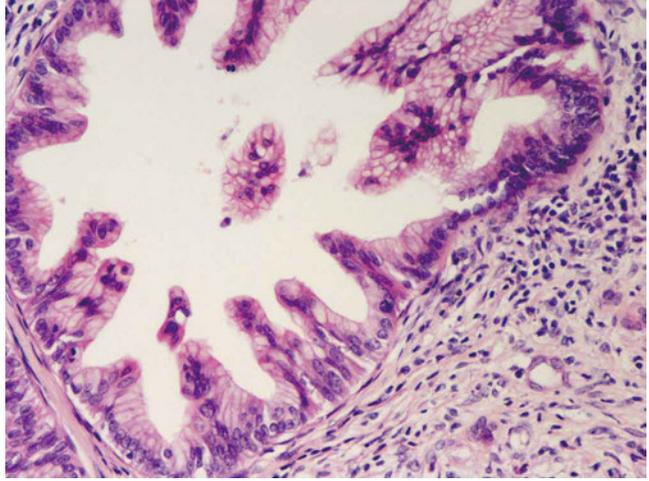


Fig. 80 High-grade PanIN
Columnar epithelium shows low papillary growth and a budding structure. Nuclear enlargement, size variation, alignment disorder, and polarity disturbance are high-grade. The lesion corresponds to PanIN-3, carcinoma *in situ*.

Fig. 81 High-grade PanIN

Columnar epithelium shows low papillary growth and a budding structure. Nuclear enlargement, size variation, alignment disorder, and polarity disturbance are high-grade. The lesion corresponds to PanIN-3, carcinoma *in situ*.



Invasive ductal carcinomas

Fig. 82 Adenocarcinoma, well differentiated type

Adenocarcinoma invades in papillotubular forms. The large glands with high-columnar atypical epithelium are consistent with well differentiated adenocarcinoma. The stroma is desmoplastic.

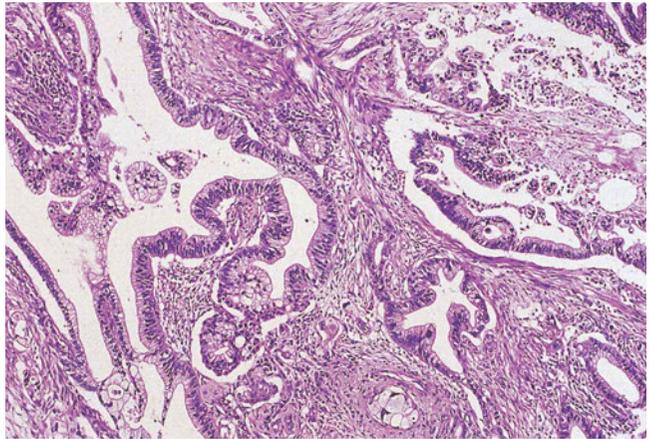
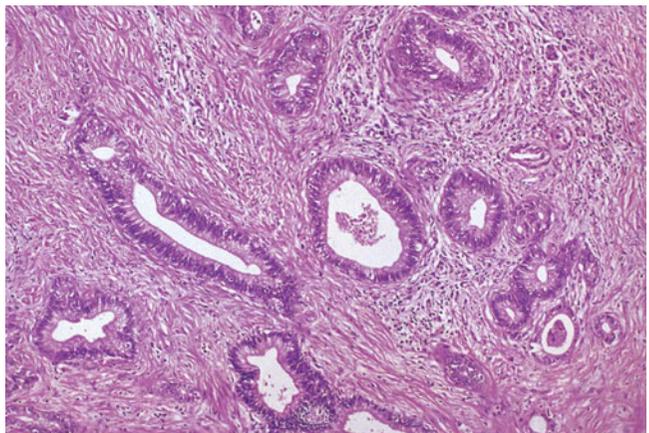


Fig. 83 Adenocarcinoma, well differentiated type

Typical example of well differentiated adenocarcinoma. The stroma is desmoplastic.



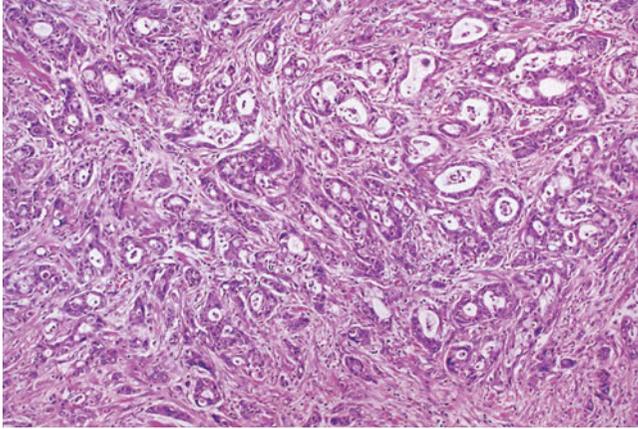


Fig. 84 Adenocarcinoma, moderately differentiated type

The neoplasm consists of small- to medium-sized irregular glands with cuboidal to flat atypical epithelium.

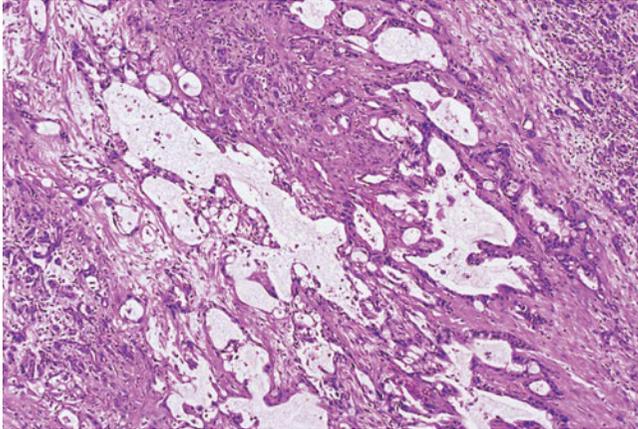


Fig. 85 Adenocarcinoma, moderately differentiated type

Some neoplastic glands are enlarged and extremely irregular in shape, but the neoplasm consists mainly of small glands. Therefore, the diagnosis is adenocarcinoma, moderately differentiated type.

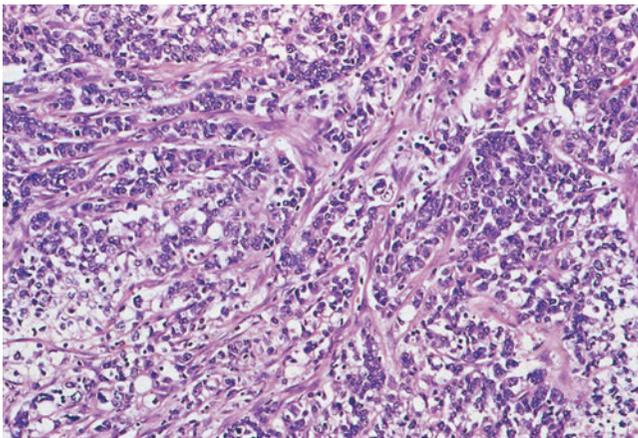


Fig. 86 Adenocarcinoma, poorly differentiated type

The neoplasm consists mainly of trabecular nests with few glands.

Fig. 87 Adenocarcinoma, poorly differentiated type

Small neoplastic nests with unclear glandular formation have invaded into desmoplastic stroma.

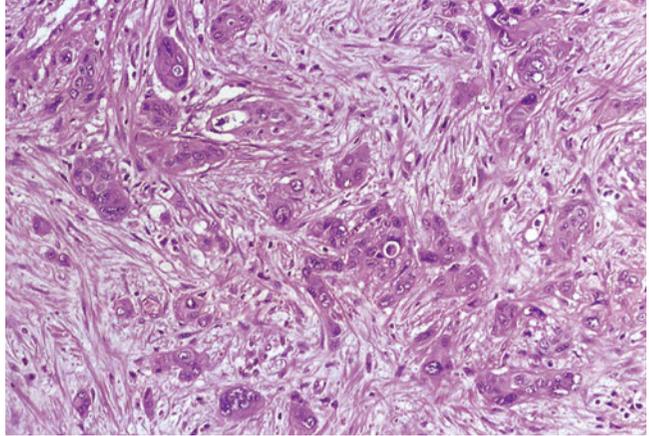


Fig. 88 Adenosquamous carcinoma

Both squamous and glandular neoplastic components are present. Some of the squamous epithelial cells are transformed into glandular, cancerous forms.

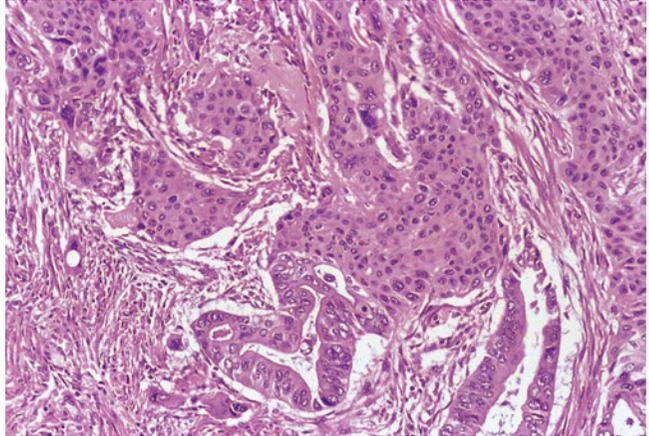


Fig. 89 Adenosquamous carcinoma

Small glands or signet-ring cells, rich in mucus, are present within the cancerous nest. This type of adenosquamous carcinoma is also referred to as mucoepidermoid carcinoma.

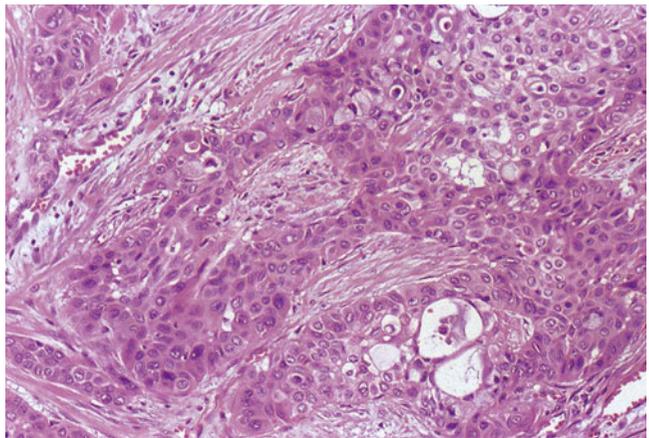




Fig. 90 Mucinous carcinoma (Cut surface of surgical specimen)
Mucinous carcinoma is usually localized and surrounded by fibrous tissue. Macroscopically, it is nodular.

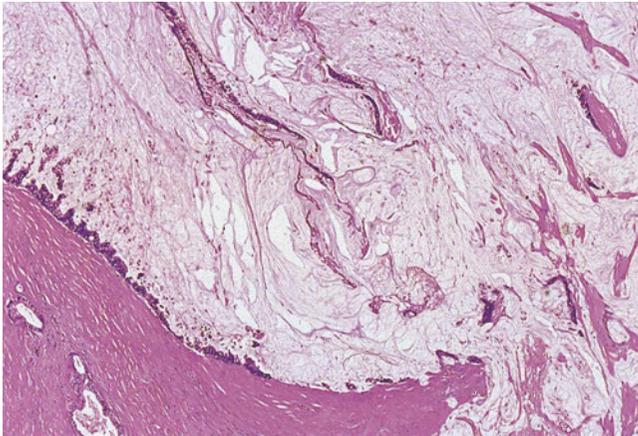


Fig. 91 Mucinous carcinoma
Well differentiated adenocarcinoma is observed in the periphery of the mucus lake.

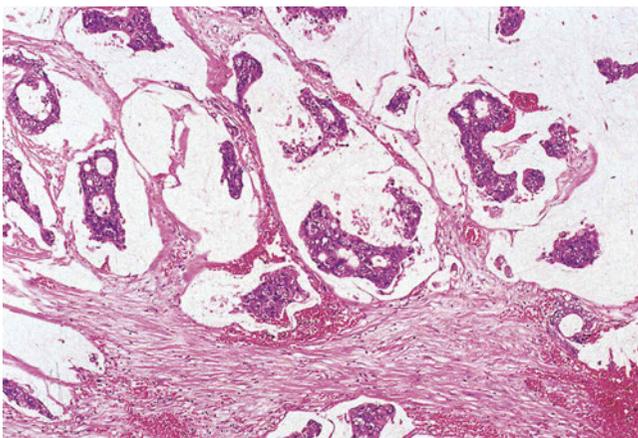


Fig. 92 Mucinous carcinoma
Clusters of adenocarcinoma cells are floating in the mucus lakes.

Fig. 93 Mucinous carcinoma
Signet-ring cells are floating in the mucus lakes. Most signet-ring cell carcinomas of the pancreas show this pattern.

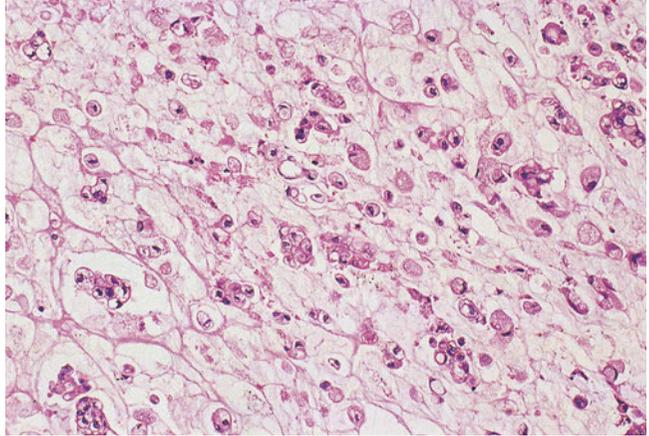
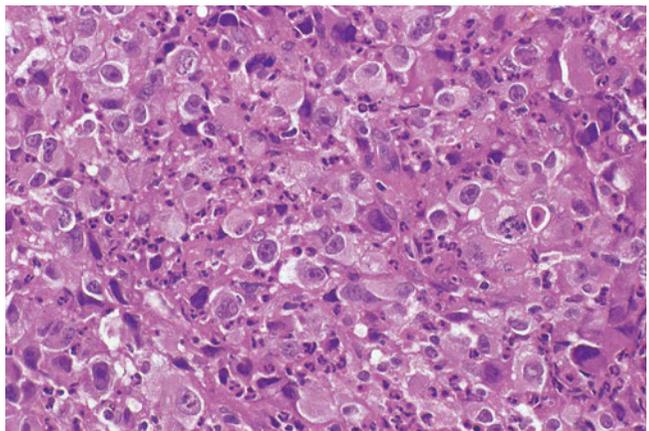


Fig. 94 Anaplastic carcinoma (Cut surface of surgical specimen)
The neoplasm is often hemorrhagic and necrotic, and surrounded by fibrous tissue. Cystic change may occur, but macroscopically, the neoplasm is classified as nodular type.



Fig. 95 Anaplastic carcinoma (Pleomorphic type)
The neoplastic cells (nuclei) are mostly large and extremely pleomorphic.



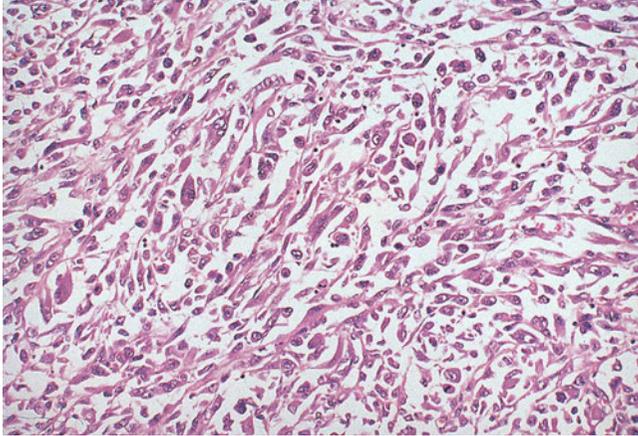


Fig. 96 Anaplastic carcinoma (Spindle cell type)

This is a rare type of anaplastic ductal carcinoma that consists of spindle-shaped neoplastic cells. This pattern may be seen mixed in adenocarcinoma or other sub-types of ductal carcinoma.

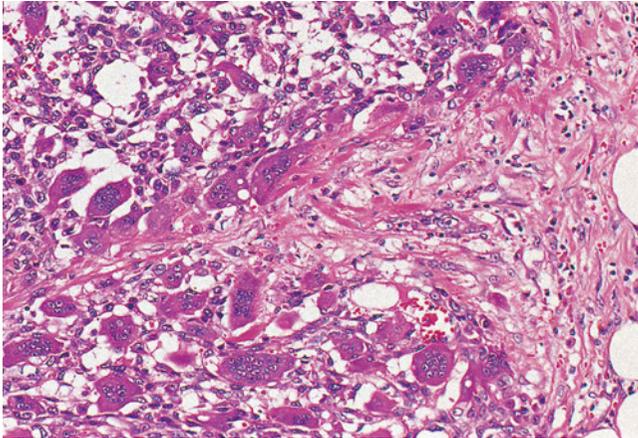


Fig. 97 Anaplastic carcinoma with osteoclast-like giant cells

The growth of undifferentiated cancer cells is accompanied by non-tumor multinuclear giant cells. Multinuclear giant cells have small round uniform nuclei in the center of the cell, and are called osteoclast-like multinuclear giant cells based on morphological similarity.

Acinar cell neoplasms



Fig. 98 Acinar cell carcinoma (Cut surface of resected specimen)

A nodular neoplasm with a relatively distinct border is seen.

Fig. 99 Acinar cell carcinoma (same neoplasm as in Fig. 98)

The acinar structure can be distinctly seen in the center and more solid cell areas can be seen in the lower and left parts.

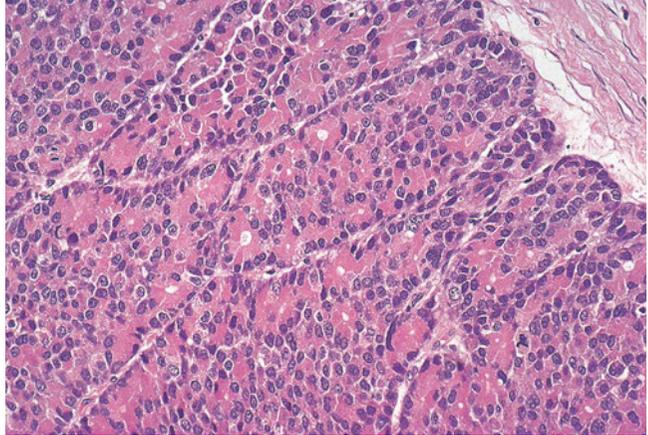
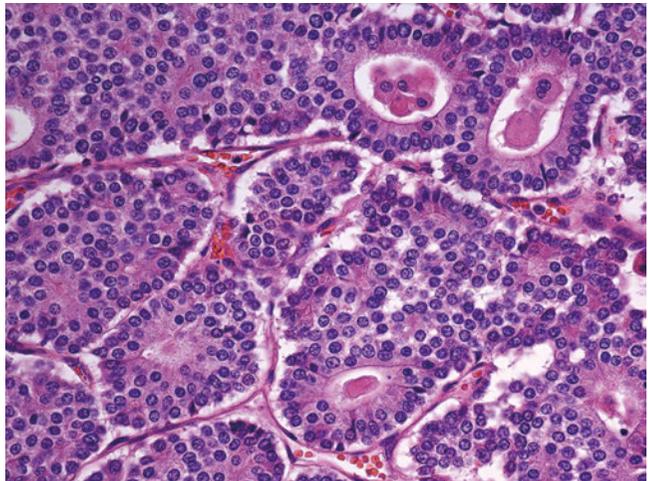


Fig. 100 Acinar cell carcinoma

Components showing tubular structure can be seen. The neoplastic cells showed trypsin-positive.



Neuroendocrine Neoplasms

Fig. 101 Neuroendocrine neoplasm (Cut surface of resected specimen)

This is a 10 mm nodular neuroendocrine neoplasm, also called an islet-cell tumor.





Fig. 102 Neuroendocrine tumor (Cut surface of resected specimen)
Solid neoplasms show some indistinctive borders.

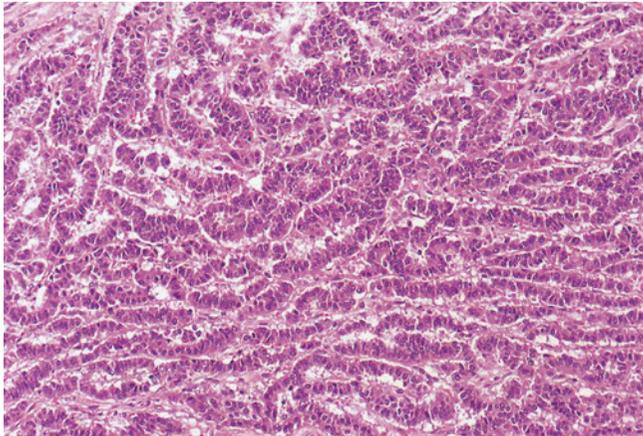


Fig. 103 Neuroendocrine tumor
The neoplastic cells are arranged in cords or trabeculae.

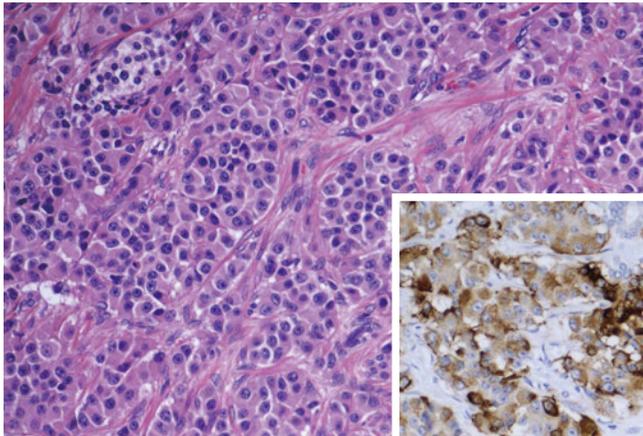


Fig. 104 Neuroendocrine tumor
The neoplastic cells are arranged in a thick trabecular or acinar structure. Cells are positive for chromogranin A (inset).

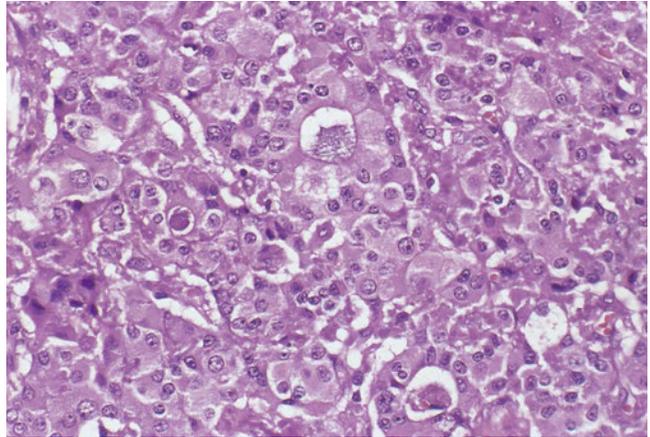


Fig. 105 Neuroendocrine neoplasm
Occasional gland-like formation is present.

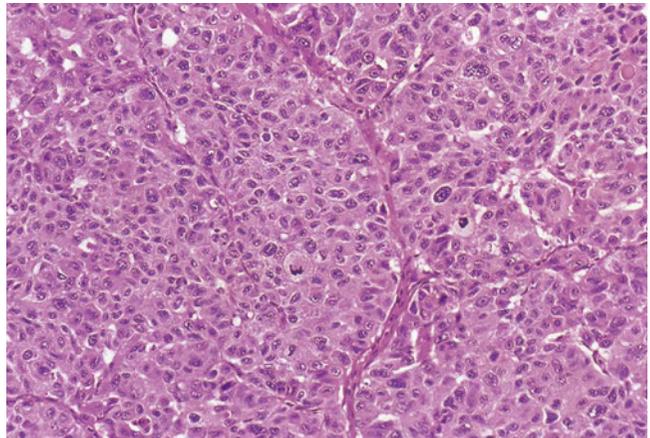


Fig. 106 Neuroendocrine neoplasm
The neoplastic cells have grown in solid nests. Increased mitoses indicate a higher grade neuroendocrine neoplasm.

Epithelial Neoplasms of Uncertain Differentiation



Fig. 107 Solid-pseudopapillary neoplasm (Cut surface of resected specimen)
A spherical neoplasm is surrounded by a fibrous capsule in the body of the pancreas. Solid and cystic areas coexist. Cysts are due to hemorrhagic necrosis. Macroscopically, the neoplasm is classified as nodule type.

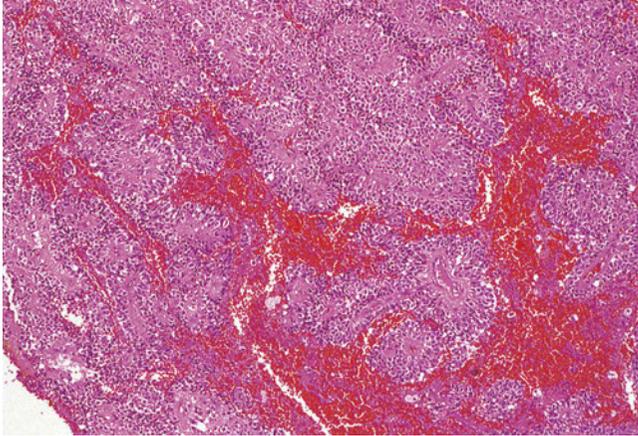


Fig. 108 Solid-pseudopapillary neoplasm
Border between the solid and hemorrhagic areas is seen. Neoplastic tissues are separated. Pseudopapillary structures can be seen around the blood vessels (middle to lower part).

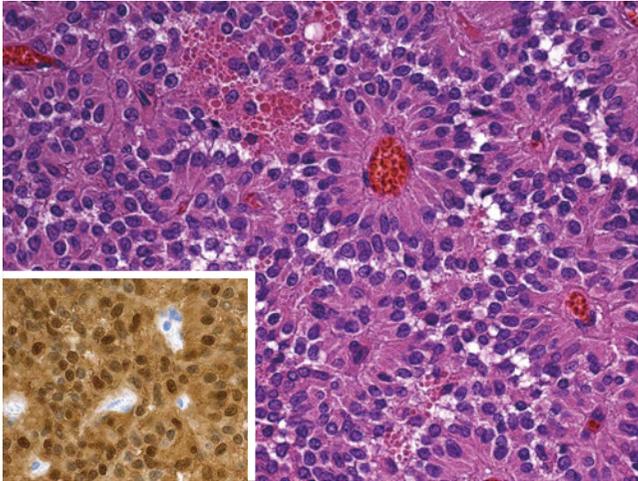


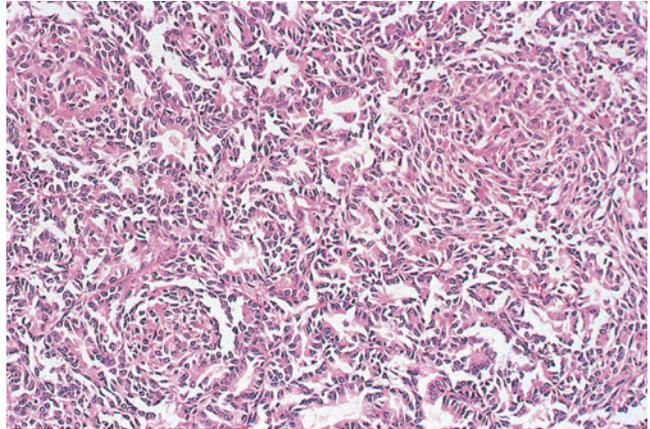
Fig. 109 Solid-pseudopapillary neoplasm
Pseudopapillary structures are evident around blood vessels. The neoplastic cells are eosinophilic and have round or oval nuclei. Both the cells and nuclei show a positive immunohistochemical reaction for β -catenin (inset).



Fig. 110 Pancreatoblastoma (Cut surface of surgical specimen)
This nodular neoplasm contains areas of hemorrhagic necrosis.

Fig. 111 Pancreatoblastoma

In addition to acinar or tubular structures, so-called squamoid corpuscles consisting of spindle cells are present (upper right and lower left areas).



VIII. Biopsy/Cytology of Pancreatic Neoplasms

1. Reporting of pancreatic biopsy/cytology

In 2010, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) biopsy was included in Japan's national healthcare insurance system. Since then, biopsies have been performed more often for pancreatic lesions. Therefore, the reporting format is recommended for pathological diagnosis as follows:

[Report form for pancreatic biopsy/cytology]

1. Inadequate sample
2. Adequate sample
 - 1) No neoplastic lesion
 - 2) Definite diagnosis of neoplasm is difficult.
 - 3) Neoplastic lesion present (histological diagnosis, differentiation degree, grade, etc. are stated)

Explanation

1. Inadequate sample

Reason for inadequacy should be mentioned (e.g., sample size, degeneration, artifact).

2. Adequate sample

- 1) Mention whether the tissue sample is sufficient or not. Notify if a particular non-neoplastic lesion (e.g. autoimmune pancreatitis) is suspected.
- 2) If a definite diagnosis is difficult, mention the reason. Reasons could be the sample size, degree of structural/cellular atypia, etc.
- 3) Mention the histological diagnosis along with supporting information regarding the degree of differentiation, grade based on tissue structure, and cellular characteristics including atypia in accordance with the histological classification. Diagnosis of carcinoma should be mentioned if the lesion can be histologically diagnosed as such, whether it is invasive or not. The "PanIN" is not to be used in biopsy diagnosis. Depending on the histological findings, mention about malignant/benign, epithelial/non-epithelial, exocrine/endocrine, etc.

■ Biopsy Histology

Fig. 112 A loupe image and a higher power view of a sample collected by EUS-FNA (25 G)

A neoplastic lesion is present: Ductal carcinomas.

A relatively large amount of tissue has been collected.

High-power view: A papillary structure, which is suspected to protrude into the cavity, can be observed. The cell nuclei are relatively small, and polarity disturbance is small. Differential diagnosis is required between carcinoma and adenocarcinoma with high-grade atypia. The sample shows some parts with high cellularity with irregular papillary structure. Well differentiated adenocarcinoma is suggested.

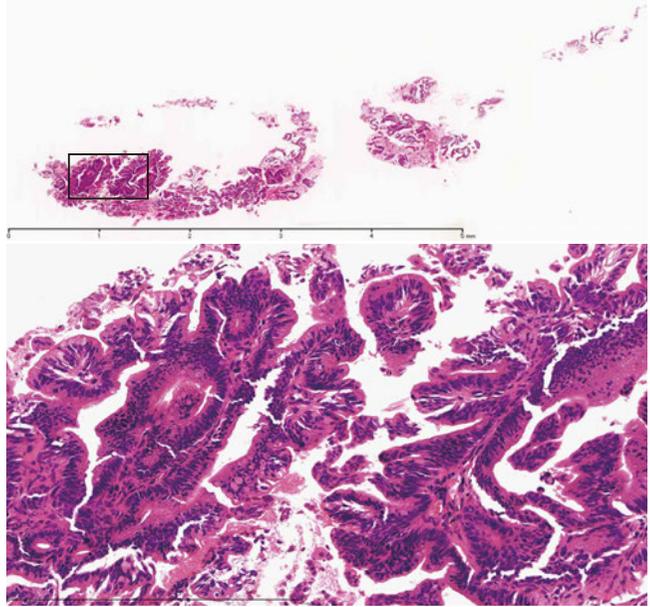
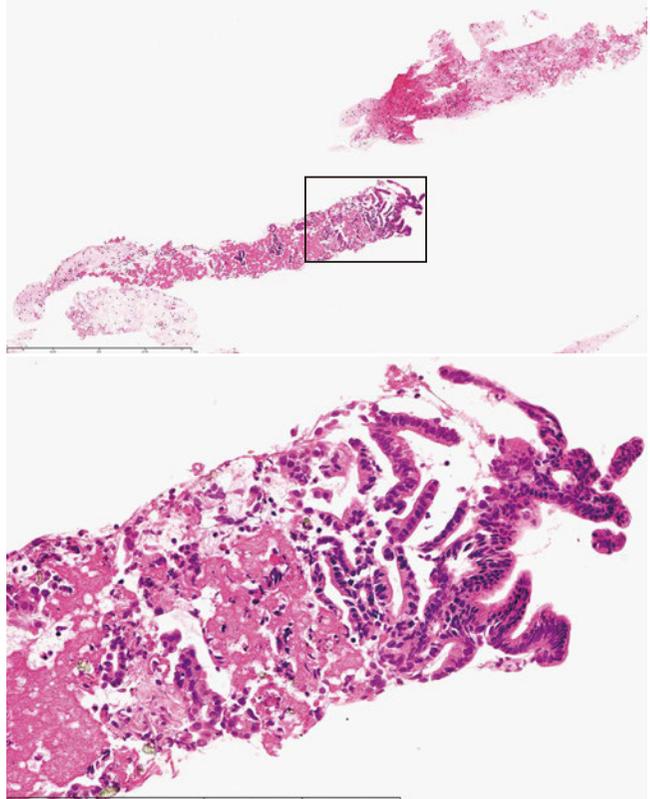


Fig. 113 A loupe image and a higher power view of a sample collected by EUS-FNA (25 G)

A neoplastic lesion is present: Ductal carcinomas.

The sample includes several tissue fragments.

High-power view: Irregular glands and low papillary lesions can be seen. Well differentiated adenocarcinoma is suggested.



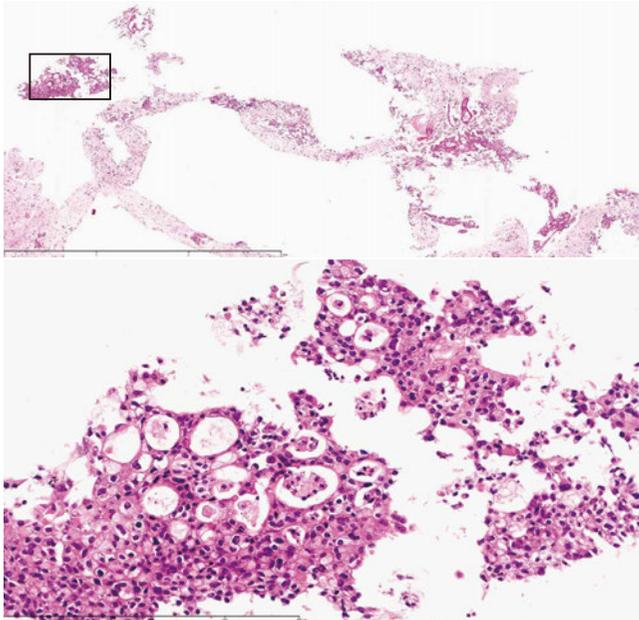


Fig. 114 A loupe image and a magnified image of a sample collected by EUS-FNA (25 G)
A neoplastic lesion is present: Ductal carcinomas.
High-power view: Cribriform structure is visible. The cell components vary in size. Moderately differentiated adenocarcinoma is suggested.

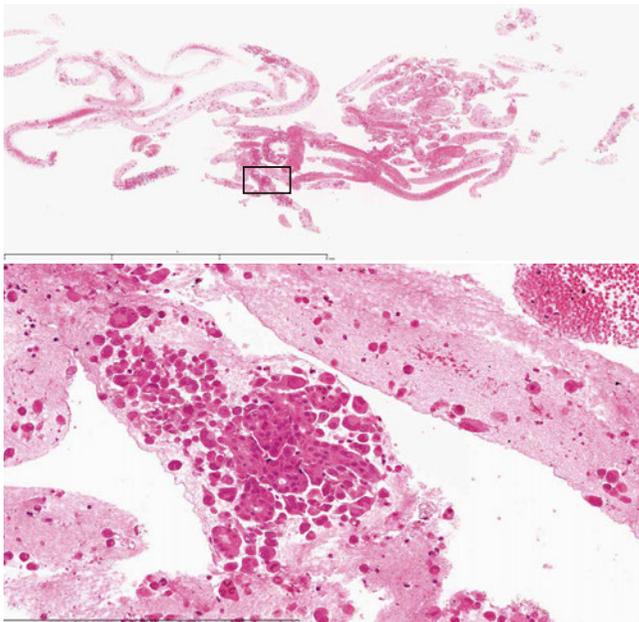


Fig. 115 A loupe image and a higher power view of a sample collected by EUS-FNA (25 G)
A neoplastic lesion is present: Ductal carcinomas.
The sample includes numerous isolated cells with weak adhesion.
High-power view: Scattered cells with weak adhesion and high-grade atypia, and cells showing formation of small ducts are seen. Poorly differentiated adenocarcinoma is suggested.

Fig. 116 A loupe image and a higher power view of a sample collected by EUS-FNA (25 G)

A neoplastic lesion is present: Ductal carcinomas.

A few epithelial masses have been collected. High-power view: Low papillary growth is found in part of the single-layer epithelium. Component cells are small and the grade of atypia is low, but based on the disturbed alignment and polarity, the diagnosis is carcinoma. The single-layered epithelium cells are relatively well-aligned. Carcinoma *in situ* is suspected.

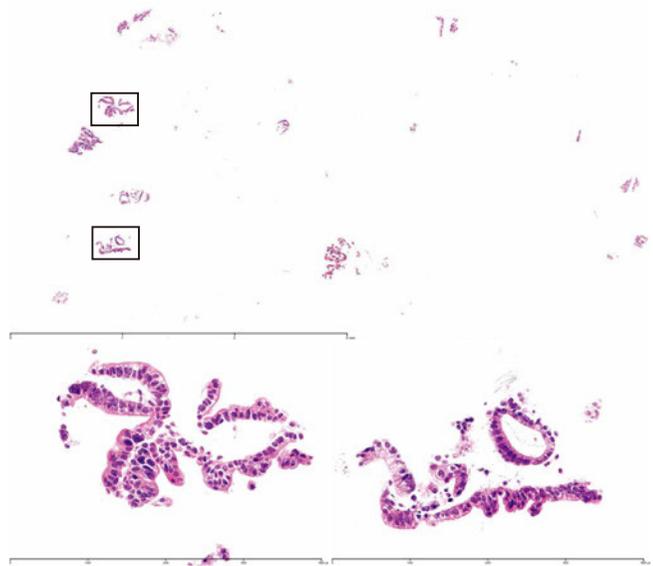
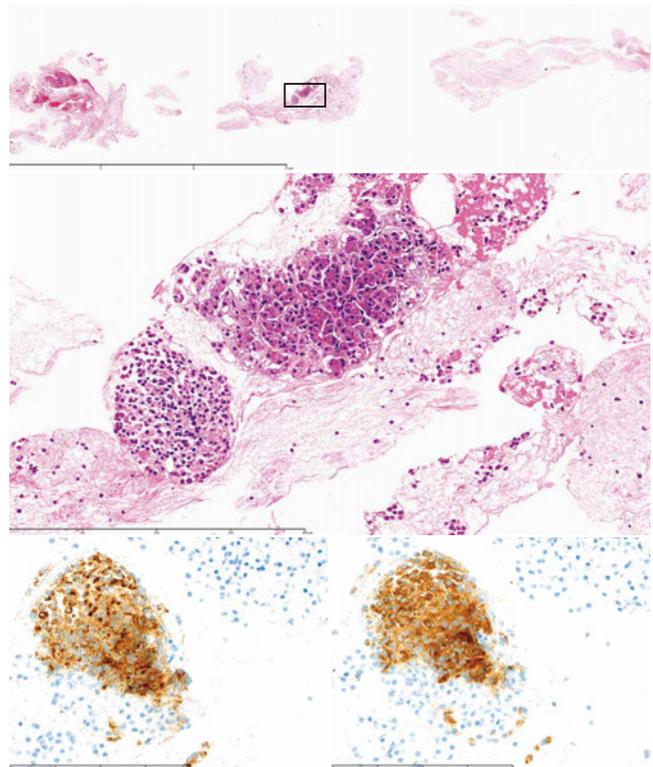


Fig. 117 A loupe image and a higher power view of a sample collected by EUS-FNA (25 G)

Neoplastic lesion is present: Neuroendocrine neoplasm.

Grade 1 (Ki67 index $\leq 2\%$)

High-power view: Non-neoplastic acinar cells and neuroendocrine neoplasms can be seen in sheet forms. A positive reaction for chromogranin A (lower left) and synaptophysin is observed (lower right).



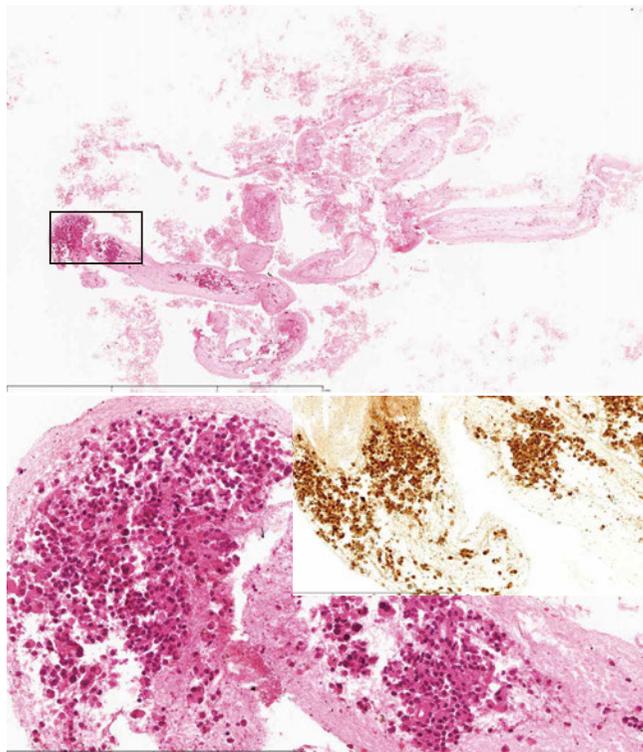


Fig. 118 A loupe image and a higher power view of a sample collected by EUS-FNA (25 G)

Neoplastic lesion is present: Solid-pseudo-papillary neoplasm.

High-power view: Neoplasm shows medullary growth, and although the cell arrangement is difficult to evaluate, it shows pseudo-papillary formation. The cytoplasm and nucleus show positive expression of β -catenin. Based on hematoxylin-eosin and β -catenin staining, it is diagnosed as solid-pseudopapillary neoplasm.

2. Pancreatic cytology report

This section describes the essential points regarding the cytology reporting format, and features cytological images along with the explanation of representative pancreatic neoplasms, including IPMN, IDC, ACC, NEN, and SPN.

Peritoneal washing cytology is outlined only briefly because it is not widely used.

Reporting in this format aims to support the clinicians in selecting the treatment method and to determine the necessity or urgency of retesting. Presumptive diagnosis requires clinical information and results from imaging. Appropriate clinical data are required. The cytological section of this Classification attempts to align the contents of the Papanicolaou Society of Cytopathology Guideline 2014 and the pancreatic section of the Atlas and Guideline for Cytopathological Diagnosis 2015 of the Japanese Society for Clinical Cytology.

1) Reporting format and diagnosis

The first step is to evaluate whether the sample is adequate or not. Check and state if the cell count is sufficient for a pancreatic fluid sample, if the sample is dry for an exfoliative sample, or if the tumor was definitely punctured for endoscopic ultrasound guided-fine needle aspiration cytology (EUS-FNAC). Determine if the sample shows a malignant or benign lesion with detailed cytological findings and presumptive diagnosis, if possible. When differentiation is difficult, it is recommended to mention which is more probable, benign or malignant lesion.

[Cytology reporting format in the pancreatic region]

1. Cytological classification

Inadequate sample

Adequate sample

Negative/benign

Atypical/indeterminate

Findings suggesting benign disease (favor benign)

Findings suggesting malignant disease (favor malignant)

Others

Suspicious for malignancy/at least low-grade malignancy

Positive/malignant

2. Record findings (e.g., grade of atypia), or presumptive diagnosis

2) Classification of intraoperative peritoneal washing cytology (CY)

CYX: Peritoneal washing cytology not performed

CY0: Peritoneal washing cytology negative for carcinoma cells

CY1: Peritoneal washing cytology positive for carcinoma cells

3) Pancreatic neoplasms

(1) Intraductal papillary mucinous neoplasms (IPMNs)

The most important point in cytologic diagnosis for IPMN is the identification of non-invasive/high-grade cells.

i. [Cytological classification] Negative/benign

In this category, the large mass with a smooth margin shows no irregular overlapping. The nuclei are at a uniform distance and have a regular arrangement. Mucous cells are aligned regularly, retain cell adhesion, and have no nuclei with irregular shapes or chromatin abnormalities. Background mucus is abundant. IPMA (IPMN with low-grade dysplasia) is suggested.

ii. [Cytological classification] Atypical/indeterminate (favor benign)

The large- to medium-sized mass with a slightly indented smooth margin retains cell adhesion, and shows partial overlapping and rare, irregular nuclei. Small exfoliative cell clusters might be observed in the pancreatic fluid. IPMA (IPMN with intermediate-grade dysplasia) is suggested.

iii. [Cytological classification] Atypical/indeterminate (others)

Medium- to small-sized mass with a moderately indented margin shows irregular overlapping. Irregular internuclear distance and disturbed nuclear arrangement are visible, and cell adhesion is weaker. An irregular nuclear shape is often seen and chromatin is increased. Cases of this category show cellular atypia, but no apparent positive/malignant cells are observed. It is desirable to classify the cases as atypical/indeterminate (others) and report detailed cytological findings to the clinicians.

iv. [Cytological classification] Positive/malignant

Cellular findings of non-invasive carcinoma generally satisfy the criteria of malignancy. Clusters are mostly small, but the margin is distinctively indented, even in large clusters. Characteristics include irregular overlapping, disturbed internuclear distance and nuclear arrangement, tendency of nuclei to protrude out into the margin, irregular size of nuclei, increased N/C rate, coarse structure of nuclear chromatin, and a higher grade of nuclear atypia, including a more distinct nucleolus. When the background is mostly necrotic and clusters of differently sized, atypical cells appear, invasive cancer is the likely diagnosis, but it is difficult to clearly distinguish between images of non-invasive and invasive cancers. IPMC non-invasive/invasive is suggested.

Note: Pancreatic intraepithelial neoplasia (PanIN)

When differentiating between IPMN and PanIN, IPMN should be suspected when duct ectasia and mucus pools can be observed clinically and on imaging, because PanIN occurs in the non-dilated pancreatic duct. However, it is difficult to differentiate between IPMN and PanIN based only on cytological findings.

(2) Invasive ductal carcinomas (IDCs)

[Cytological classification] Positive/malignant

Cell clusters of various sizes can be observed. The grade of cellular atypia might appear to be low with low magnification. However, with high magnification, characteristics of adenocarcinoma can be observed, including overlapping cells/nuclei, sheet-shaped arrangement, tubular gland-like structure,

irregular nuclear size, disturbed internuclear distance, multiple and more distinct nucleoli, tendency of nuclei to protrude outwards into the margin, increased N/C rate, and rough nuclear chromatin structure. In addition to the necrotic or inflammatory background, adenocarcinoma cells producing mucus or showing various atypia can be seen scattered separately or in clusters of varied sizes.

Note: IDCs include adenosquamous carcinoma, wherein adenocarcinoma and squamous carcinoma components consisting of abnormal keratinocytes coexist; mucinous carcinoma with adenocarcinoma cells floating in large amounts of mucus; and anaplastic carcinoma with atypical giant cells, atypical spindle-shaped cells, and large irregular atypical cells in addition to various adenocarcinoma components.

(3) Acinar cell carcinoma (ACC)

[Cytological classification] Positive/malignant

Cytology shows that the tissue comprises masses of solid tumor cells showing acinar structure, tubular-gland like component, or overlapped cells. Loose or isolated clusters appear and rosette formations can be partially seen. Oval-shaped nuclei show eccentric distinct nucleoli and relatively irregular fine granular chromatin patterns. Cytoplasm is abundant because of the zymogen granules that are characteristic of acinar cells; it is composed of eosinophilic fine to rough granules. When differentiation from neuroendocrine neoplasm is indeterminate or various tissue types including neuroendocrine neoplasm can coexist in a tumor, immunostaining is required to confirm differentiation into acinar cells. In immunostaining for acinar cell carcinoma, trypsin and BCL10 are considered to be specific markers and the reaction can be confirmed with a cytology sample.

Note: Some cases require differentiation from SPN or NET. It is recommended to determine the case as suspicious for malignancy/at least low-grade malignancy and describe the detailed findings in the report. Diagnosis by immunostaining may sometimes be required.

(4) Neuroendocrine neoplasms (NENs)

The important role of cytology here is to judge if the cell morphology shows the characteristics of neuroendocrine neoplasms.

i. [Cytological classification] Suspicious for malignancy/at least low-grade malignancy

The tumor cells have relatively uniform and small to medium sized oval-shaped nuclei. Nuclei tend to be naked during preparation. Cells show relatively scarce adhesion and arrangements reflecting the histological picture including rosette formation, trabecular structure, solid alveolar arrangement, and alignment around the blood vessels. Some cells may appear scattered and isolated. Nuclei of tumor cells are regular and include clusters of so-called “salt and pepper” chromatin that looks like sand or rough granules. Eccentric nuclei such as those in plasmacytes might also be seen. Various degrees of polymorphism are present with no correlation with malignancy grade. The sizes of nucleoli are varied and the cytoplasm is fine, granular, and relatively abundant. Neuroendocrine tumors (NETs: NET G1, NET G2) are suggested. If amyloid is observed in the background, insulinoma is suspected.

ii. [Cytological classification] Positive/malignant

When necroses or mitoses are evident in addition to the cytological findings of NET, the possibility of neuroendocrine carcinoma (NEC) should be considered. Frequency of NEC is low and the cytological findings are similar to those of small cell lung cancer or large cell endocrine carcinoma. For diagnosis, it is extremely effective to perform immunostaining using the cytology sample or cell block technique to confirm differentiation into neuroendocrine cells. Note that results by Ki67 index by immunostaining might not necessarily match the cytological results or histological results using biopsy/surgical specimen. NEC is suggested.

Note 1: When it is difficult to differentiate between NET G3-NEC and NET G1 or G2 based on cytology, report it as suspicious for malignancy/at least low-grade malignancy. If the cytological findings clearly show it is NEC, report it as positive/malignant (presumptive diagnosis: NEC).

Note 2: When it is challenging to distinguish between NEN and acinar cell carcinoma or SPN by cytology, clinical information including patient age and sex is important. Immunostaining or electron microscopy may be sometimes required for differentiation of the cells.

(5) Solid-pseudopapillary neoplasm (SPN)

[Cytological classification] Suspicious for malignancy/at least low-grade malignancy

In fine-needle aspiration cytology, the sample contains a large volume of collected cells and hemorrhage or necrotic substances might be found in the background. Tumor cells are small, quasi-round, and relatively uniform, and they form clusters or pseudopapillary structures around the vessels, or appear separately. Relatively abundant fine vessel structure is observed but cell adhesion is weak. Tumor cells have fine granular nuclear chromatin. Oval-shaped nuclei may show cuts or grooves. Nucleolus may be seen but is normally indistinct. The cytoplasm is fine granular and a long protruding structure might be observed. Mitoses are rare. Some hyaline globules may show metachromasia in Giemsa stain. Cytology shows foam cells, multinucleated giant cells, and/or cholesterol crystals as well as hemorrhage and background necrosis. These are useful in giving presumptive diagnosis.

Note: For cytological differentiation of SPN from acinar cell carcinoma or NET, clinical information including patient age and sex is important. In some cases, immunostaining or electron microscopy might be required for differentiation.

Pancreatic cytology guideline working group committee members:

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■ Cytological Atlas

This section demonstrates representative cytological pictures of cases of definite histopathological diagnosis. For practical diagnosis, sufficient clinical findings should be considered to determine and report cytodiagnosis.

Fig. 119 Cancerous peritonitis in pancreatic ductal carcinoma

[Cytological classification] CY1

Mucus producing clear cell cluster is shown. Nucleoli are distinct with nucleus atypia. Inflammatory reaction of lymphocytes can be seen in the background. Ascites, Papanicolaou stain.

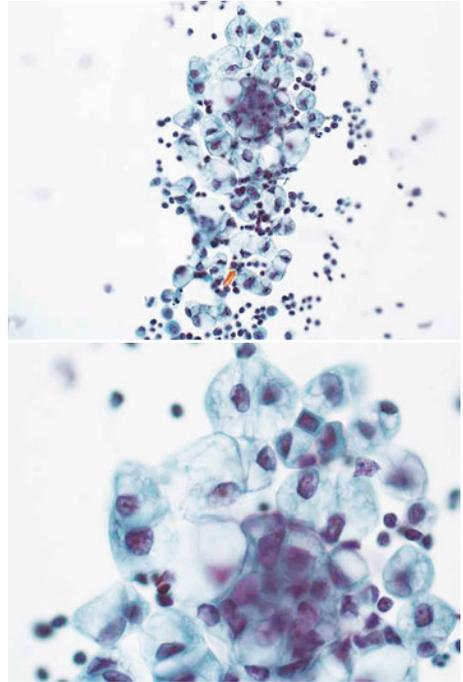
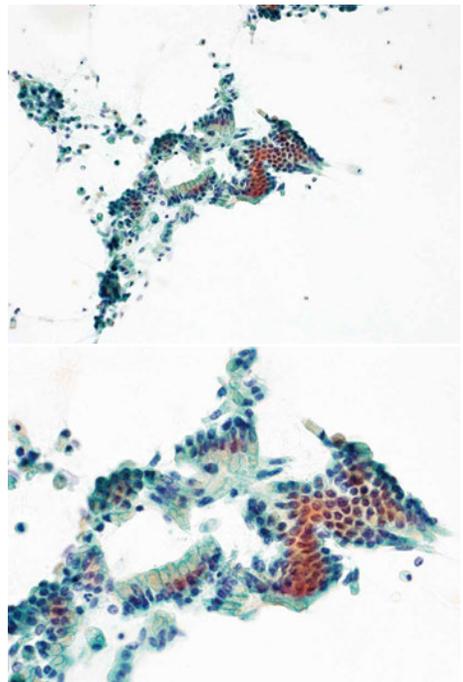


Fig. 120 IPMA (corresponds to IPMN with low-grade dysplasia)

[Cytological classification] Negative/benign

Cluster in a sheet form of cells with increased density. The margin is smooth, retaining cytoplasm in the outermost layer. The cytoplasm contains mucus with moderately enlarged nucleus. The nuclei are arranged regularly on the basal side. Pancreatic juice, Papanicolaou stain.



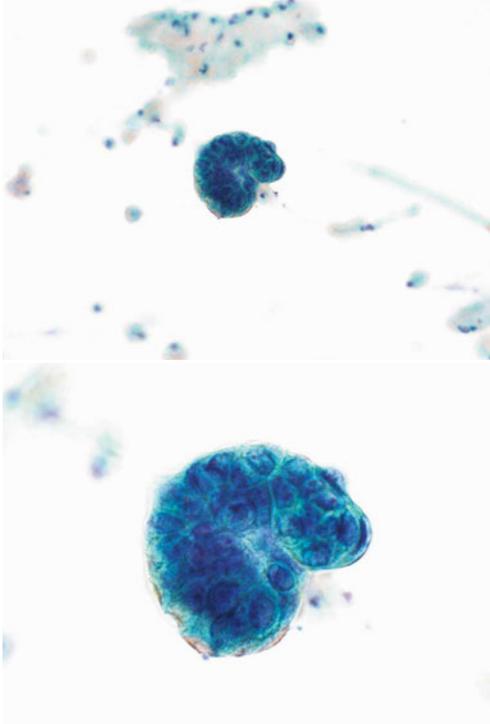


Fig. 121 IPMA (corresponds to IPMN with intermediate-grade dysplasia)

[Cytological classification] Atypical/indeterminate (favor benign)

Adhesion is retained and a small cluster with smooth outermost layer is observed. Almost no nucleus protrusions are observed. Increased cell density, irregular nucleus overlapping, and disturbed nuclear arrangements are observed. Pancreatic juice, Papanicolaou stain.

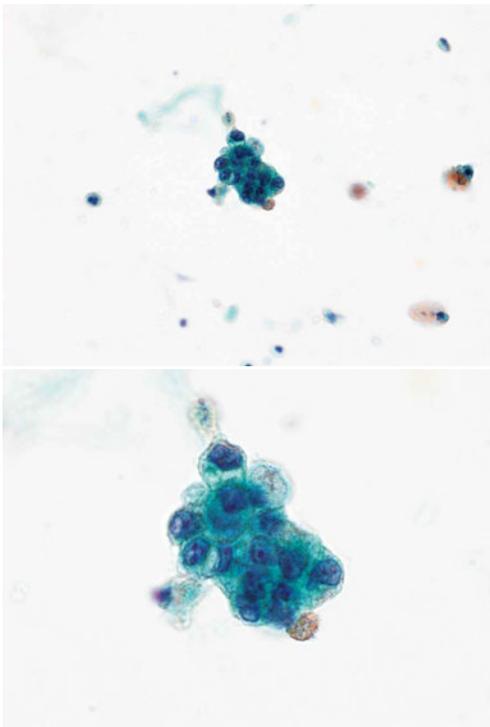


Fig. 122 IPMA (corresponds to IPMN with intermediate-grade dysplasia)

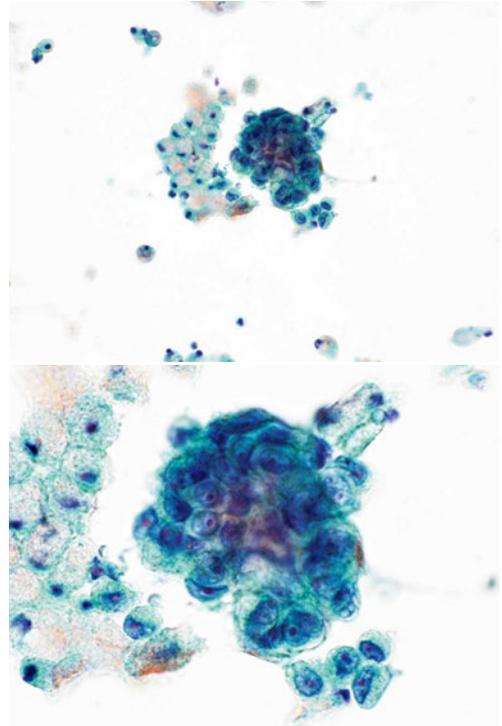
[Cytological classification] Atypical/indeterminate (others)

A small cluster with indented margin is shown. The nuclei have disturbed arrangements and varied distances between them. Nuclear chromatin is fine granular. Irregular nuclei are conspicuous. Pancreatic juice, Papanicolaou stain.

Fig. 123 IPMC

[Cytological classification] Positive/malignant

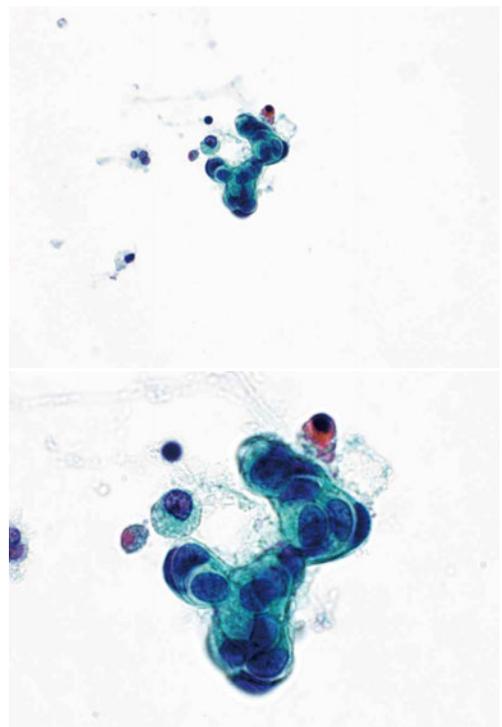
Tumor cells form a cluster of irregular shape. Nuclei are enlarged and show disturbed arrangement and internuclear distance. Cell borders are indistinct with distinct nucleolus and conspicuous irregularity in nucleus. Pancreatic juice, Papanicolaou stain.

**Fig. 124** Reference

[Cytological classification] Positive/malignant

This is a cytological picture of a case of histopathological and cytological definite diagnosis of high-grade PanIN.

The low power image shows a cluster of atypical cells with abundant nuclear chromatin and oval-shaped nuclei in a clear background. Atypical cells show nucleolus and increased nuclear chromatin. The nuclei tend to be eccentric. The high-power view shows irregular nuclei of varied sizes, distinct nucleoli, and coarse chromatin structure. Pancreatic juice, Papanicolaou stain.



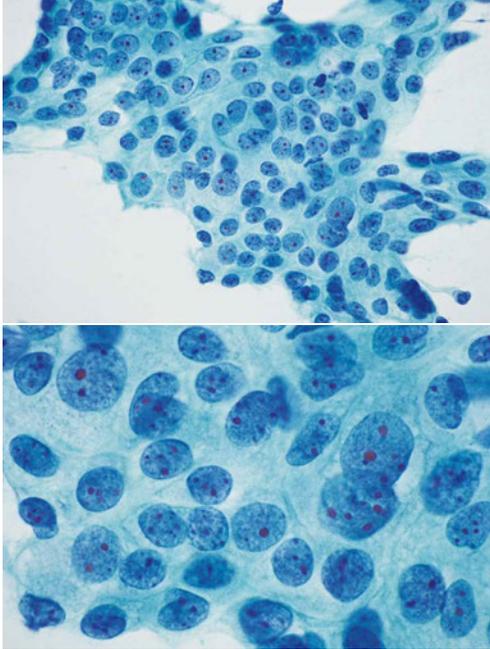


Fig. 125 Invasive ductal carcinomas (IDCs)

[Cytological classification] Positive/malignant

The image shows sheet-form cell arrangement, lumina, overlapping nuclei, various sizes of nuclei, irregular internuclear distances, and a tendency of nucleus protrusion to the cell margin. The high-power view shows conspicuous nuclear atypia including irregular nuclei, distinct nucleoli, and coarse nuclear chromatin structure. EUS-FNAC, Papanicolaou stain.

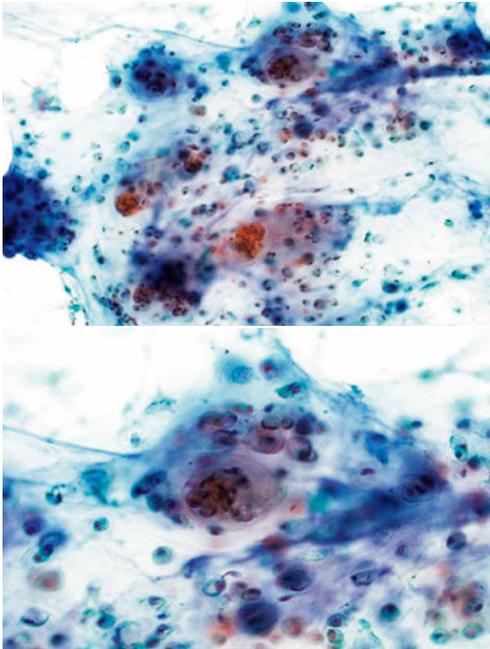


Fig. 126 Invasive ductal carcinomas (IDCs)

Mucinous carcinoma

[Cytological classification] Positive/malignant

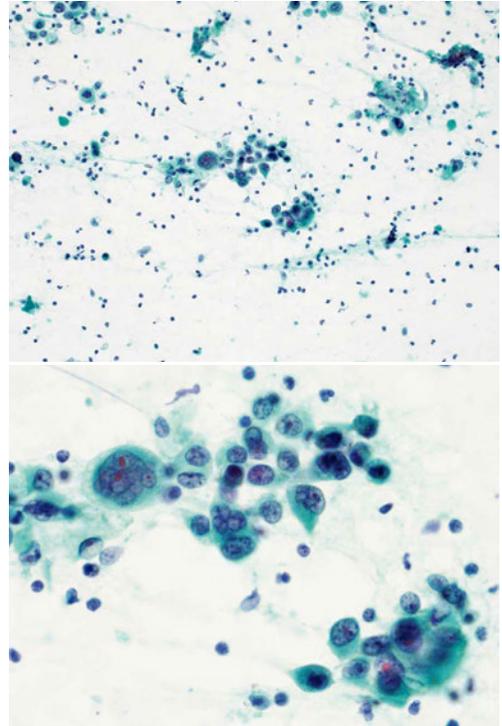
Atypical mucus producing cells are shown in abundant mucus with necrotic or degenerated cells. The high-power view shows a high grade of nucleus atypia with atypical mucus producing cells and inflammatory cells. EUS-FNAC, Papanicolaou stain.

Fig. 127 Invasive ductal carcinomas (IDCs)

Anaplastic carcinoma

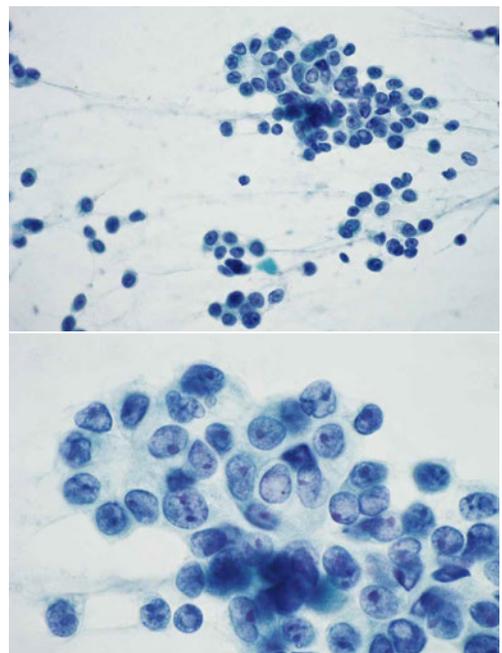
[Cytological classification] Positive/malignant

Clusters of atypical cells of various sizes with decreased adhesion are shown with necrotic and/or degenerated cells. The high-power view shows atypical tumor cells with multiple nuclei and high grade of nucleus atypia including irregular nucleus and distinct nucleoli. EUS-FNAC, Papanicolaou stain.

**Fig. 128** Acinar cell carcinoma

[Cytological classification] Positive/malignant

Solid acinar structure, tubular component, and overlapped cells are shown. Rosette formation comprises numerous tumor cells. Loose or isolated clusters are also seen. The high-power view shows eccentric oval-shaped nuclei and distinct nucleoli. Fine granular chromatin patterns are irregular and granular nuclear pseudoinclusion is also observed. Relatively abundant cytoplasm is eosinophilic and has fine to coarse granularity. EUS-FNAC, Papanicolaou stain.



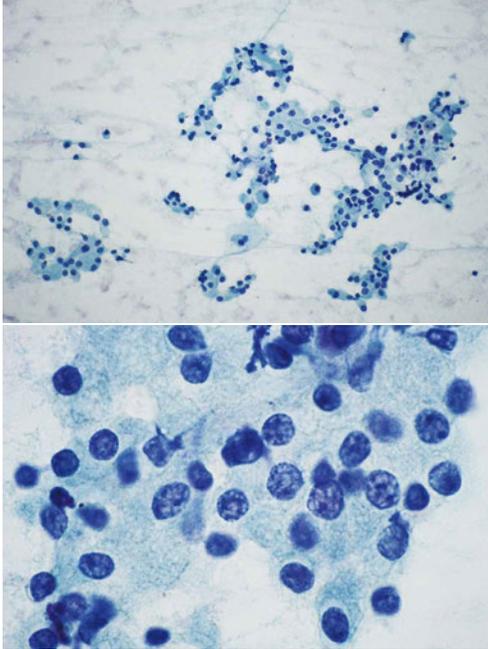


Fig. 129 Neuroendocrine tumor (NET G2)
[Cytological classification] Suspicious for malignancy/at least low-grade malignancy
Tumor cells with relatively uniform and small to medium sized oval-shaped nuclei form clusters of varied sizes. The high-power view shows tumor cells with a “salt and pepper” pattern and/or coarse granular chromatin. These are arranged in rosette, tubular, trabecular, and/or solid nest forms. Relatively abundant cytoplasm has a fine granular appearance. EUS-FNAC, Papanicolaou stain.

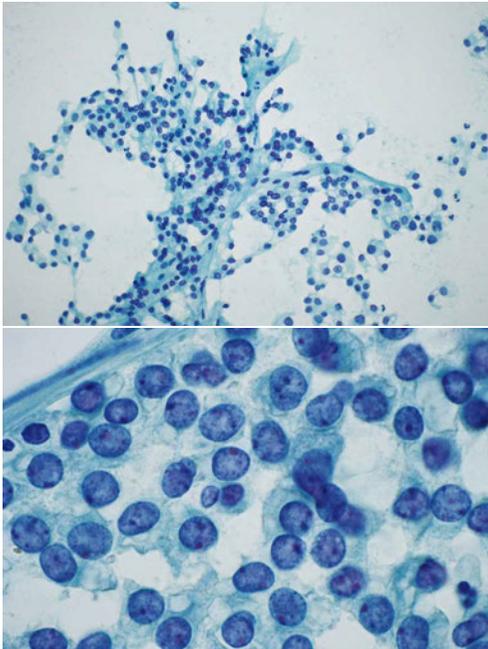


Fig. 130 Solid-pseudopapillary neoplasm
[Cytological classification] Suspicious for malignancy/at least low-grade malignancy
Tumor cells appear in clusters, grow in pseudopapillary forms around the vessel, or appear separately. The high-power view shows relatively uniform and small oval-shaped tumor cells with low adhesion and fine-granular chromatin. Nucleoli are not remarkable. Tumor cells have fine granular cytoplasm. EUS-FNA, Papanicolaou stain.

IX. Histological Assessment of Preoperative Therapeutic Effects

Criteria for histological response to drug therapy/radiotherapy

In pancreatic cancer cases for which radiotherapy and drug therapy (including chemotherapy and molecular target treatment) is administered, the tumor tissues show a wide range of responses in accordance with factors such as tumor cell sensitivity to therapeutics, type/dose/administration route of the drug, quality/dose/administration method of radiation, therapy period, and interval between the final therapeutic session and surgery. The histological response to these preoperative therapies is assessed on the basis of the following criteria depending on the level of response.

The subject is a surgery case of primary pancreatic carcinoma following preoperative therapy. The response is classified based on the residual rate of viable cancer cells in post-treatment pancreatectomy specimens. Stromal findings (host responses) associated with tumor cell destruction and/or disappearance may be helpful, although it is challenging to estimate the pre-existing tumor area. In principle, only changes in invasive lesions are assessed as a response. Therefore, a case where only the intraductal components remain in the post-treatment tissue is classified as Grade 4.

[Grading of histological response to preoperative therapy]

Grade 1: Poor or no response:

Therapeutic response is poor (estimated residual rate $\geq 50\%$)

Grade 1a: Estimated residual rate $\geq 90\%$

Grade 1b: $50\% \leq$ estimated residual rate $< 90\%$

Grade 2: Moderate response:

A moderate amount of viable cancer cells is found ($10\% \leq$ estimated residual rate $< 50\%$)

Grade 3: Marked response:

Only a small amount of viable cancer cells is found (estimated residual rate $< 10\%$).

Grade 4: Complete response:

No viable cancer cells are found.

Notes:

1. Response may vary depending on the site. Therefore, biopsy samples are not used for assessment.
2. Estimated residual cancer rate is defined as the ratio of viable cancer cell volume against estimated pretreatment cancer volume.
3. Necrosis, particularly coagulative necrosis considered to be an ischemic change, is often observed even in non-treated pancreatic cancer. A response that is difficult to classify should not be overestimated.
4. In adenocarcinoma, the stromal findings associated with tumor cell destruction/disappearance include xanthogranuloma-like reactions accompanied by numerous foamy histiocytes, mucus pools with no cancer cells (a type of mucinous degeneration), and inflammatory cell infiltration or fibrosis of various degrees. Presence of xanthogranuloma-like reactions and mucus pools are key findings to estimate the pre-existing

cancer area, whereas inflammatory cell infiltration or fibrosis are less specific.

5. Cases with a complete response to invasive cancer components are known to have an extremely good prognosis indifferent to the presence of residual intraductal components. These cases are diagnosed as a pathologically complete response. However, the presence of intraductal components should be noted in remarks because the significance of residual intraductal components requires further investigation. Note that assessment of the whole mounted sections of the extracted pancreas is desirable to classify a case as Grade 4.
6. A case challenging to classify should be categorized as a lower response grade.
7. Surgical radicality may not be considered. Therefore, when there are distinctive clinical or pathohistological residual cancer cells, therapeutic response is assessed in the field of observation if a certain level of lesions is included in the resected range.
8. To date, several classifications have been reported regarding the histological response to preoperative therapy of pancreatic neoplasms. This Classification uses the widely-used Evans classification¹⁾ and CAP classification²⁾ as their basis because their clinical significance has been demonstrated. In addition, this Classification attempts to clarify the area that these two classification systems left rather obscure, namely the handling of the stroma where the therapy caused the cancer to completely disappear and intraductal lesions, while keeping the conformity to the two classification schemes³⁾.

1) Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg.* 1992; 127: 1335–9.

2) Washington K, Berlin J, Branton P, et al. Protocol for the Examination of Specimens from Patients with Carcinoma of the Exocrine Pancreas. College of American Pathologists. 2010.

3) Chatterjee D, Katz MH, Rashid A, et al. Histologic grading the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. *Cancer.* 2012; 118: 3182–90.

[Evans Classification]

- Grade I Characteristic cytologic changes of malignancy are present, but little (<10%) or no tumor cell destruction is evident.
- Grade II In addition to characteristic cytologic changes of malignancy, 10%–90% of tumor cells are destroyed.
 - Grade IIa Destruction of 10%–50% of tumor cells.
 - Grade IIb Destruction of 51%–90% of tumor cells.
- Grade III Few (<10%) viable-appearing tumor cells are present.
- Grade III M Sizable pools of mucin are present.
- Grade IV No viable tumor cells are present.
- Grade IV M Acellular pools of mucin are present.

[CAP System]

- Grade 0 Complete response:
- Grade 1 Marked response
- Grade 2 Moderate response
- Grade 3 Poor or no response

Table 6 Comparison table of this Classification, Evans classification, and the CAP system

This Classification	Evans Classification	CAP System
Grade 1a	Grade I	Grade 3
Grade 1b	Grade IIa	
Grade 2	Grade IIb	Grade 2
Grade 3	Grade III	Grade 1
Grade 4	Grade IV	Grade 0

Histological findings following drug therapy/radiotherapy

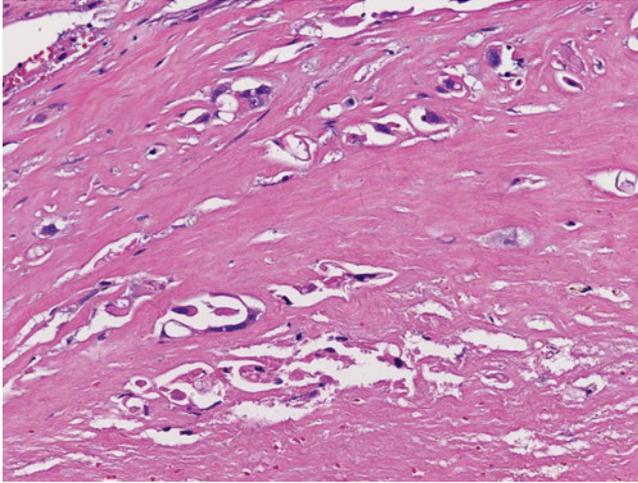


Fig. 131 Post therapeutic response of cancer cells
Cancer cells with pyknosis, loss of nuclei, indistinct cell border, etc., are coexisting.

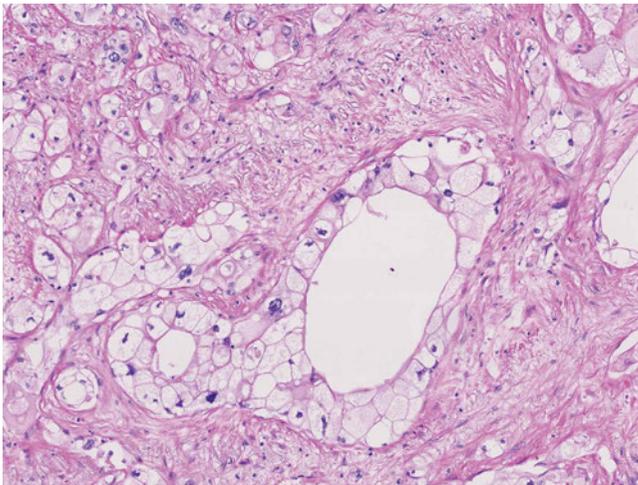


Fig. 132 Post therapeutic response of cancer cells
The cancer cells show distinctively clear cytoplasm but most of these cancer cells are considered viable. Lighter and clearer cells are often observed in post-therapy pancreatic cancer tissues.

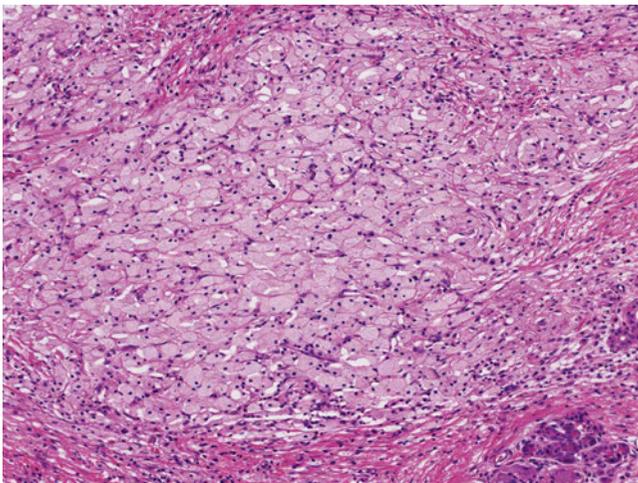


Fig. 133 Host tissue response to the tumor cell destruction/disappearance
Xanthogranuloma-like features accompanied by numerous foamy cells.

Fig. 134 Host tissue response to the tumor cell destruction/disappearance
Viable cancer cells are observed (arrow heads), but a mucin pool as a therapeutic response is found around the nerve (asterisk).

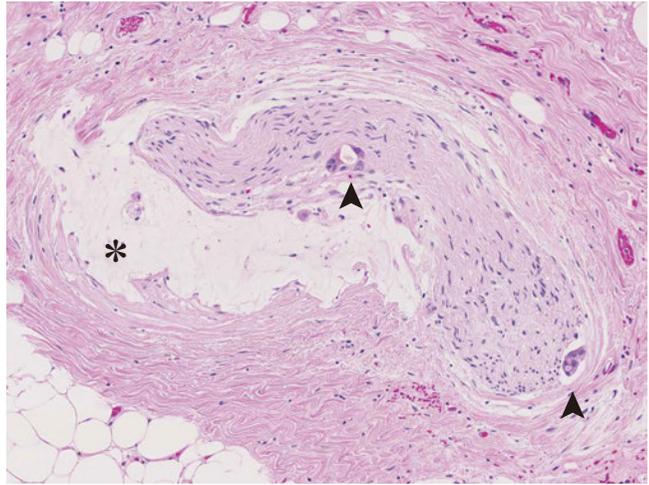


Fig. 135 Host tissue response to the tumor cell destruction/disappearance
In the area showing tumor destruction/disappearance, some inflammatory cells are floating.

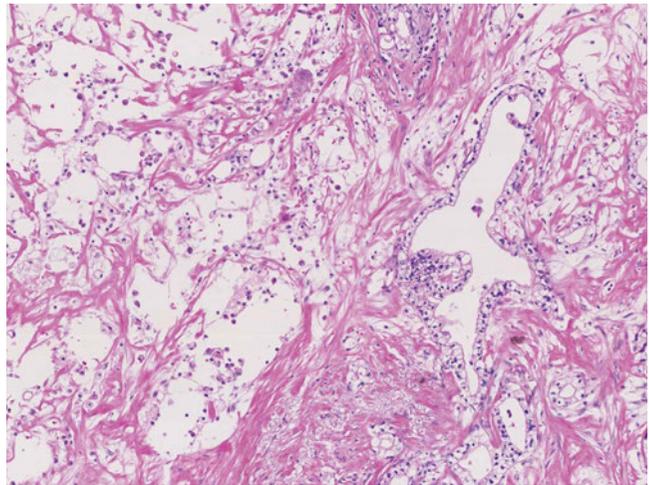
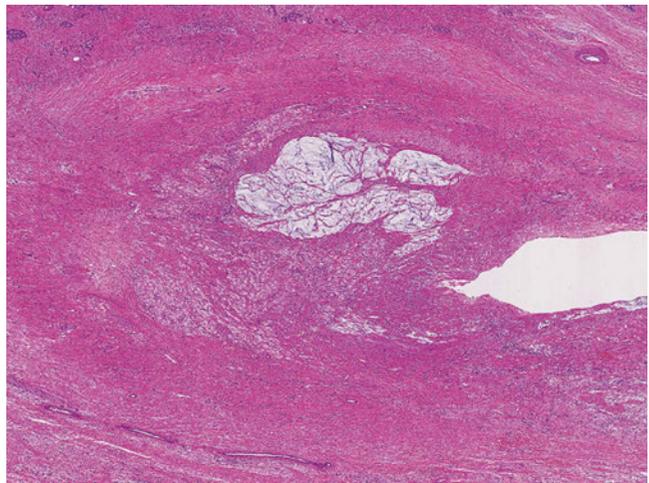


Fig. 136 Host tissue response to the tumor cell destruction/disappearance
Fibrosis and a mucin pool without cancer cells are observed within the tunica interna of PV.



Example of histological assessment of preoperative therapeutic effects (Grade 2, same case, Figs. 137–142)

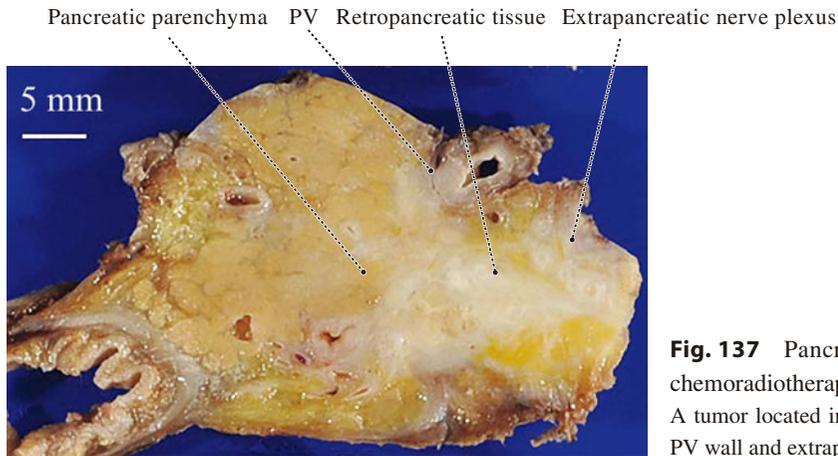


Fig. 137 Pancreatic cancer following chemoradiotherapy (macroscopic view)
A tumor located in UP that is involving the PV wall and extrapancreatic nerve plexus.

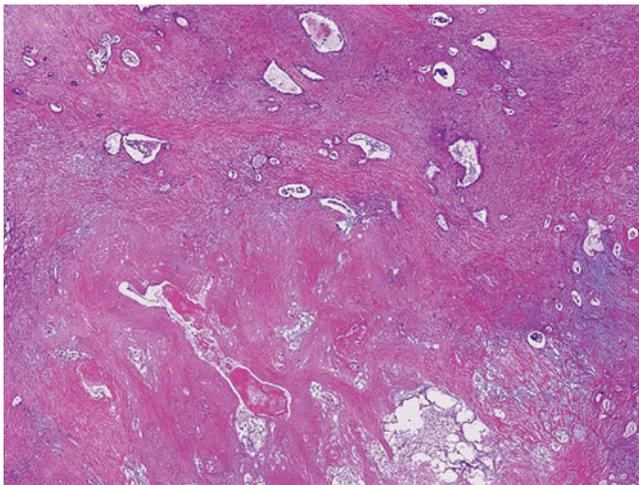


Fig. 138 Within the pancreatic parenchyma (low-power view)
Viable adenocarcinoma (upper half) is observed in contact with the coagulative necrosis area (lower half). Coagulative necrosis may be an area of ischemic change that cannot be identified immediately as a therapeutic response.

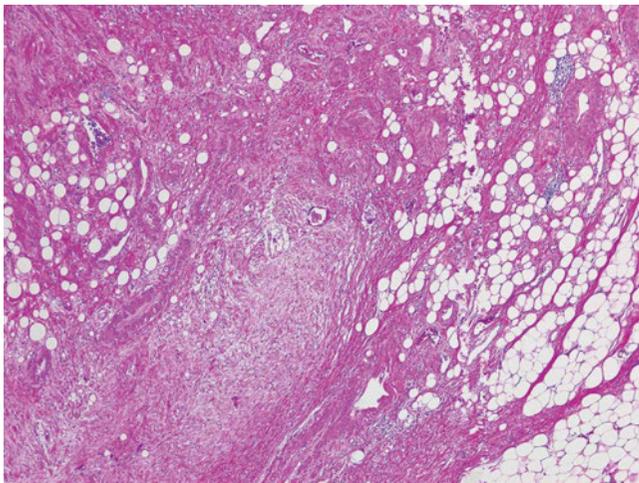


Fig. 139 Retropancreatic tissue (low-power view)
Scattered viable adenocarcinoma cells and glands are observed in the fibrous lesion.

Fig. 140 Retropancreatic tissue (high-power view)

A few cancer cells (arrow heads) are seen in the background of coarse fibrosis and inflammatory cell infiltration.

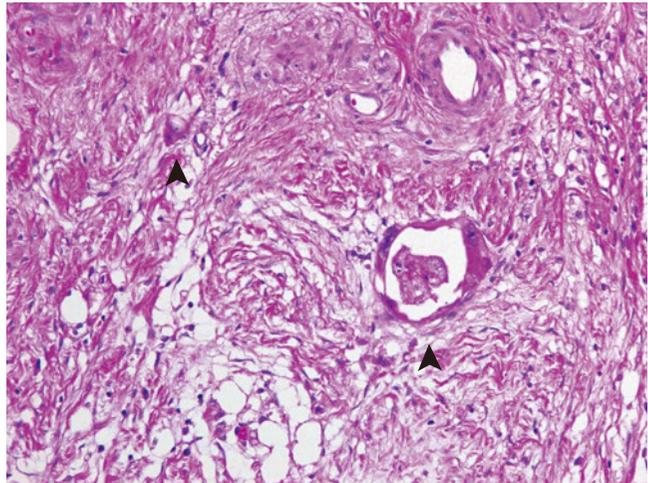


Fig. 141 PV wall (low-power view)

A few cancer cells (encircled, inset) in the tunica media are found to be replaced by fibrosis.

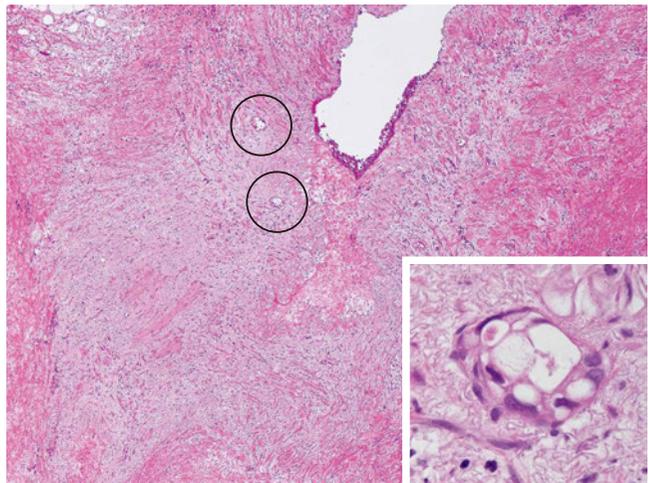
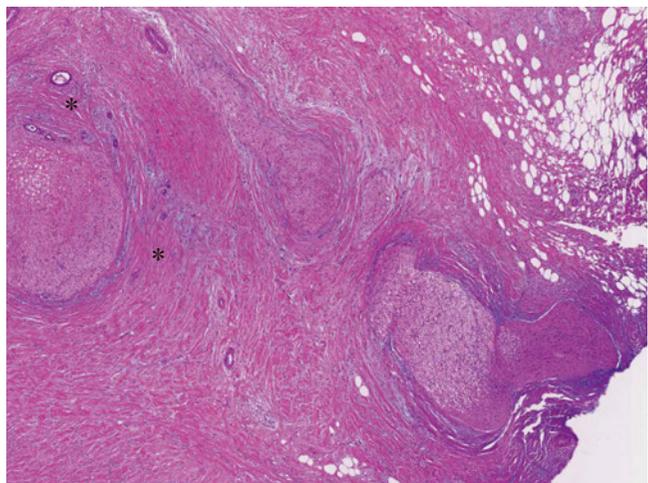


Fig. 142 Extrapancreatic nerve plexus (low-power view)

Dense fibrosis is observed in the nerve plexus, which suggests a high degree of nerve plexus invasion. A few cancer glands (asterisks) are observed.



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