

Carcinoma of the Pancreas Histopathology Reporting Guide



Family/Last name		Date of birth	DD - MM - YYYY
Given name(s)			

Patient identifiers	Date of request	Accession/Laboratory number
	DD - MM - YYYY	

Elements in **black text** are **CORE**. Elements in **grey text** are **NON-CORE**.

☐ indicates multi-select values ☐ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

- ☐ Information not provided
☐ Information provided

Neoadjuvant therapy

- ☐ Information not provided
☐ No
☐ Yes (select all that apply)

- ☐ Chemotherapy
☐ Radiotherapy
☐ Other, *specify*

Other clinical information, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- ☐ Not specified
☐ Whipple pancreatoduodenectomy
☐ Pylorus-preserving pancreatoduodenectomy
☐ Distal pancreatectomy with splenectomy
☐ Spleen-preserving distal pancreatectomy
☐ Total pancreatectomy
☐ Subtotal pancreatectomy
☐ Pancreatic resection (select one of the options above)
extended with one or more of the following additionally
resected organ(s)/structure(s)

- ☐ Vein
☐ Superior mesenteric vein
☐ Portal vein

- ☐ Artery(s)
☐ Superior mesenteric artery
☐ Common hepatic artery
☐ Coeliac axis

☐ Other, *specify*

☐ Other, *specify*

TUMOUR FOCALITY (Note 3)

- ☐ Unifocal
☐ Multifocal

Specify number of tumours
in specimen

☐ Cannot be assessed, *specify*

TUMOUR SITE (select all that apply) (Note 4)

- ☐ No macroscopically visible tumour
☐ Pancreatic head
☐ Pancreatic body
☐ Pancreatic tail
☐ Other, *specify*

TUMOUR DIMENSIONS (Note 5)

Maximum tumour dimension (largest tumour)

Additional dimensions (largest tumour)

 x

Dimensions of additional smaller tumour foci

 x x x x

Method of measurement (in case of neoadjuvant treatment)^a

- ☐ Approach 1 (largest overall dimensions)
☐ Approach 2 (summation of dimensions of each tumour
focus)

☐ Cannot be assessed, *specify*

^a Refer to the Note for an explanation of the approaches to the method of measurement following neoadjuvant treatment.

BLOCK IDENTIFICATION KEY (Note 6)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (Note 7)

(Value list based on the World Health Organization Classification of Digestive System Tumours, 6th Edition (2026))

- ☐ Ductal adenocarcinoma
- ▼ ☐ Ductal adenocarcinoma, not otherwise specified (NOS)
- ☐ Adenosquamous carcinoma
- ☐ Colloid carcinoma
- ☐ Hepatoid carcinoma
- ☐ Medullary carcinoma
- ☐ Poorly cohesive/signet-ring cell carcinoma
- ☐ Undifferentiated carcinoma
- ☐ Undifferentiated carcinoma with osteoclast-like giant cells
- ☐ Acinar cell carcinoma
- ▼ ☐ Acinar cell cystadenocarcinoma
- ☐ Mixed acinar-ductal carcinoma
- ☐ Intraductal papillary mucinous neoplasm with associated invasive carcinoma
- ☐ Intraductal oncocytic papillary neoplasm with associated invasive carcinoma
- ☐ Intraductal tubulopapillary neoplasm with associated invasive carcinoma
- ☐ Mucinous cystic neoplasm with associated invasive carcinoma
- ☐ Neuroendocrine neoplasms^b
- ▼ ☐ Neuroendocrine carcinoma, NOS
- ☐ Large cell
- ☐ Small cell
- ☐ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)
- ▼ ☐ Mixed ductal adenocarcinoma-neuroendocrine carcinoma
- ☐ Mixed acinar-neuroendocrine carcinoma
- ☐ Mixed acinar-neuroendocrine-ductal carcinoma
- ☐ Other, *specify*
- ▼

^b Neuroendocrine tumours are not covered in this dataset; refer to the ICCR Neuroendocrine tumours dataset.

HISTOLOGICAL TUMOUR GRADE (Note 8)

- ☐ Not applicable
- ☐ Cannot be assessed
- ☐ Grade 1: Well differentiated
- ☐ Grade 2: Moderately differentiated
- ☐ Grade 3: Poorly differentiated or undifferentiated

EXTENT OF INVASION (select all that apply) (Note 9)

- ☐ Cannot be assessed
- ☐ No evidence of primary tumour
- ☐ Tumour is confined to pancreas
- ☐ Invasion into ampulla of Vater
- ☐ Invasion into duodenum
- ☐ Invasion into common bile duct
- ☐ Invasion into peripancreatic soft tissues
- ☐ Invasion into spleen
- ☐ Invasion into splenic vein/artery

☐ Invasion into vascular resection

▼ ☐ Invasion into venous resection, *specify which vein(s)*

Maximum depth of invasion

- ☐ Tunica adventitia
- ☐ Tunica media
- ☐ Tunica intima
- ☐ Vascular lumen

☐ Invasion into arterial resection (select all that apply)

- ☐ Coeliac axis
- ☐ Superior mesenteric artery
- ☐ Common hepatic artery
- ▼ ☐ Other, *specify*

Maximum depth of invasion

- ☐ Tunica adventitia
- ☐ Tunica media
- ☐ Tunica intima
- ☐ Vascular lumen

☐ Invasion into other adjacent structure(s)/organ(s), *specify*

LYMPHATIC AND VENOUS INVASION (Note 10)

- ☐ Not identified
- ▼ ☐ Present (select all that apply)
- ☐ Lymphatic invasion
- ☐ Venous invasion
- ☐ Uncertain whether lymphatic invasion or venous invasion

PERINEURAL INVASION (Note 11)

- ☐ Not identified
- ☐ Present

RESPONSE TO NEOADJUVANT THERAPY (Note 12)

Specify which system used

- ☐ No neoadjuvant treatment
- ☐ Complete response
- ☐ Near complete response
- ☐ Partial, poor or no response
- ▼ ☐ Cannot be assessed, *specify*

MARGIN STATUS^c (Note 13)**Pancreatic transection margin**

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☒ Involved
☐ Invasive carcinoma
☐ High grade dysplasia

Bile duct transection margin

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

Gastric/proximal duodenal transection margin

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

Posterior dissection margin

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

Superior mesenteric artery (SMA) dissection margin

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

Superior mesenteric vein (SMV) dissection margin

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

Anterior pancreatic surface

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

^c Refer to the Note for the definition of margin involvement and for an explanation of the various specimen margins and surfaces.

Transection margins of venous resection

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

Transection margins of arterial resection

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

Other margin(s), specify

- ☐ Not applicable
☐ Cannot be assessed
☒ Not involved

Distance of tumour from closest margin mm

- ☐ Involved

LYMPH NODE STATUS (Note 14)

- ☐ No nodes submitted or found

Number of lymph nodes examined

- ☐ Not involved

- ☒ Involved

Number of involved lymph nodes

ADDITIONAL FINDINGS (select all that apply) (Note 15)

- ☐ Chronic pancreatitis
☒ Pancreatic intraepithelial neoplasia, *specify highest grade*

- ☐ Intraductal papillary mucinous neoplasm, *specify highest grade*

- ☐ Other, *specify*

ANCILLARY STUDIES (Note 16)

- ☐ Not performed
- ☐ Performed
- ▼ ☐ Mismatch repair (MMR) immunohistochemistry
- ☐ Not interpretable
- ☐ Proficient
- ☐ Deficient, *specify*

- ☐ Other, *record test(s), methodology and result(s)*

Representative blocks for ancillary studies, specify those blocks best representing tumour and/or normal tissue for further study

ACINAR CELL CARCINOMAS ONLY**Acinar markers**

- ☐ Not performed
- ☐ Performed (select all that apply)
- ▼ ☐ BCL10
- ☐ Trypsin
- ☐ CPA1
- ☐ Other, *specify*

HIGH GRADE NEUROENDOCRINE NEOPLASMS ONLY^a**Neuroendocrine markers**

- ☐ Not performed
- ☐ Performed (select at least two of the following core options)
- ▼ ☐ Synaptophysin
- ☐ Chromogranin-A
- ☐ INSM1
- ☐ Other, *specify*

Specify test(s) performed and result(s) if available

Ki-67 proliferation index

- ☐ Not performed
- ☐ Performed

 %
p53

- ☐ Not performed
- ☐ Performed
- ▼ ☐ Abnormal, *specify test(s) performed and result(s) if available*

- ☐ Wildtype pattern

^a Neuroendocrine tumours are not covered in this dataset; refer to the ICCR Neuroendocrine tumours dataset.

RB1

- ☐ Retained
- ☐ Deficient

Low molecular weight cytokeratin(s)

- ☐ Positive
- ☐ Negative

HISTOLOGICALLY CONFIRMED DISTANT METASTASES

(Note 17)

- ☐ Not applicable
- ☐ Not identified
- ☐ Present (M1), *specify site(s)*

PATHOLOGICAL STAGING (UICC TNM 9th edition)^d (Note 18)**TNM Descriptors** (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ y - post-therapy
- ☐ r - recurrent

Primary tumour (pT)

- ☐ TX^e Primary tumour cannot be assessed
- ☐ T0 No evidence of primary tumour
- ☐ Tis Carcinoma in situ^f
- ☐ 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 not more than 1 cm in greatest dimension
- ☐ T1c Tumour greater than 1 cm but not more than 2 cm in greatest dimension
- ☐ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
- ☐ T3 Tumour more than 4 cm in greatest dimension
- ☐ T4 Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery

Regional lymph nodes (pN)

- ☐ NX^e Regional lymph nodes cannot be assessed
- ☐ N0 No regional lymph node metastasis
- ☐ N1 Metastases in 1 - 3 regional lymph node(s)
- ☐ N2 Metastases in 4 or more regional lymph nodes

^d Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 9th Edition, eds by James Brierley, Meredith Giuliani, Brian O'Sullivan, Brian Rous, Elizabeth Van Eycken. 2025, Publisher Wiley (incorporating any errata published up until 21 August 2026).

^e TX and NX should be used only if absolutely necessary.

^f Tis also includes the 'PanIN-III' classification.

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level P2 or above (based on the Hierarchy of Research Evidence for Tumour Pathology¹). In rare circumstances, where level P2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the Dataset Authoring Committee (DAC). An appropriate staging system, e.g., Pathological TNM staging would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level P2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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Scope of this dataset

The dataset has been developed for pancreatic resection specimens with carcinomas of the pancreas, i.e., ductal adenocarcinoma, acinar cell carcinoma and neuroendocrine carcinoma (NEC) as well as tumours with mixed lineage differentiation, i.e., mixed ductal adenocarcinoma-neuroendocrine carcinoma, mixed acinar-neuroendocrine carcinoma, mixed acinar-neuroendocrine-ductal carcinoma, mixed acinar-ductal carcinoma.²

Carcinoma of the ampulla of Vater, common bile duct and duodenum, neuroendocrine tumours (NETs), lymphoma, sarcoma and secondary tumours are excluded from this dataset.

The distinction between adenocarcinoma arising in the pancreatic head, ampulla, distal bile duct and duodenum may at times be difficult.³ However, because the pTN-staging of these tumours differs, and patient treatment and prognosis may be different, correct identification of the cancer origin is important and primarily based on the location of the centre of the tumour mass.^{4,5} While the presence of precursor lesions (e.g., dysplasia in the ampulla or duodenum, high grade pancreatic intraepithelial neoplasia (PanIN)) may be helpful in identifying the cancer origin, these are often lacking or, as in the case of low grade PanIN,

of no evidentiary support.⁶ Furthermore, colonisation of non-neoplastic epithelial surfaces (of pancreatic ducts or the duodenum) by adenocarcinoma (so-called 'cancerisation') may mimic dysplasia.^{7,8} Of note, the morphology and immunohistochemical phenotype of ampullary and duodenal adenocarcinoma are known to be heterogeneous and may overlap with those of pancreatobiliary cancer.⁹ Nevertheless, in many cases a confident decision can be reached based on detailed macroscopic and microscopic assessment.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Digestive System Tumours, 6th edition, 2026.²

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Note 1 – Clinical information (Core and Non-core)

Clinical information can be provided by the clinician on the pathology request form. Pathologists can search for additional information from previous pathology reports, if any, or accessible medical records. Of particular relevance is information on neoadjuvant treatment, as it can have a significant effect on the morphological findings. Moreover, it has implications for both specimen sampling, histological interpretation, reporting and staging. Information regarding the administration of neoadjuvant therapy should therefore always be provided to and recorded by the pathologist (core).

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Note 2 – Operative procedure (Core)

Information regarding the type of surgical specimen should be recorded. For so-called extended resection specimens, the tissue(s) or organ(s) that are resected en bloc, for example a segment of the superior mesenteric vein or the left adrenal gland, should be clearly indicated. The type and extent of the surgical procedure depend on the site, size and extent of the tumour.

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Note 3 – Tumour focality (Core)

The vast majority of tumours are solitary, but multifocal disease can occur. Identification of tumour focality is based on combined macroscopic and microscopic assessment.

In case of multiple synchronous tumours in a specimen, the number of tumours should be recorded. A single dataset should be completed, in which the site and dimensions of the individual tumours are recorded, while staging should be based on the largest tumour and the overall lymph node status.

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Note 4 – Tumour site (Core)

Determination of the tumour site is based on clinical information combined with specimen assessment by the pathologist.

The uncinate process is considered part of the pancreatic head.

In cases where a single tumour involves more than one anatomical region, each site should be recorded.

In case of multifocal cancer, the location of the largest tumour should be selected, while the sites of further smaller tumours should be specified under 'other'.

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Note 5 – Tumour dimensions (Core and Non-core)

Assessment is based on macroscopic evaluation and microscopic confirmation/correction.¹⁰⁻¹⁵ The latter is important, because ductal adenocarcinoma of the pancreas often has a highly dispersed growth pattern,¹⁶ and small clusters of cancer cells that are widely separated from the main tumour mass will be missed on macroscopic assessment. Conversely, the microscopic extent may sometimes be less than the apparent macroscopic maximum size because of peritumoural fibrosis.

As pT-staging is based on tumour size,^{17,18} it is important that a tumour is measured in three dimensions such that the largest dimension can be correctly identified. Tumours of the body or tail of the pancreas often have their largest dimension along the length of the pancreas. In case of serial sagittal slicing of the pancreatic body and tail, this means that this tumour dimension must be assessed across specimen slices.¹⁰ Similar considerations apply to the measurement of tumours in the pancreatic head.

Measurement of the tumour dimensions may be difficult following neoadjuvant treatment, as the distribution of residual cancer cells may be even more scattered and two or more foci of residual tumour tissue may be present.^{12,14,15,19} Two approaches are being used:

- **Approach 1:** measurement of the largest linear dimension of the entire area involved by viable residual tumour cells including intervening non-cancerous tissue, e.g., stroma and/or pancreatic parenchyma or other tissue structures¹⁵
- **Approach 2:** measurement of the maximum dimension of each tumour focus and calculation of the sum of these.

Both approaches have disadvantages that may lead to incorrect assessment of tumour size. Given the lack of evidence on how to best measure tumour size and how to define individual tumor foci in treated tumor bed, there is currently no international consensus. The approach that is used, based on local practice or dependent on the particular case, should be recorded. Approach 2 may be better suited for cases with a near-complete tumor response, in which only few scattered foci of viable tumor remain.

Because the accuracy of tumour size measurement is dependent on the extent of tissue sampling, thorough sampling, including mapping sections also beyond the macroscopically assumed tumour bed, is important, in particular following neoadjuvant treatment.^{11,12,15,20}

In case of intraductal papillary mucinous neoplasm with associated invasive carcinoma, only the dimensions of the invasive carcinoma are to be recorded. This rule also applies to invasive carcinoma associated with intraductal oncocytic papillary neoplasm, intraductal tubulopapillary neoplasm, or mucinous cystic neoplasm.

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Note 6 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important when further internal or external review arises. The reviewer needs to have unequivocal description of the origin of each block to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It is highly encouraged to have a digital image (photograph) of the specimen and record of the key of the tumour blocks.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

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Note 7 – Histological tumour type (Core)

Tumours should be typed according to the World Health Organization (WHO) Classification of Digestive System Tumours, 6th edition, 2026 (Table 1).²

Ductal adenocarcinoma, including its subtypes, account for 90% of all pancreatic malignancies, whereas acinar cell carcinoma and NEC make up less than 2% and 1%, respectively, of all pancreatic cancers in adults. Mixed neuroendocrine-non-neuroendocrine carcinomas (MiNENs) of the pancreas are rare. Correct diagnosis of the various tumour entities is important, as they may differ in terms of prognosis, response to treatment and molecular profile.

Invasive carcinoma that has arisen from a neoplastic precursor lesion, for example from a mucinous cystic neoplasm or intraductal papillary mucinous neoplasm, should be recorded under the corresponding histological tumour type in accordance with the WHO Classification.²

Amphicrine-like carcinoma, which is defined by the intimate admixture of tumours cell with acinar and neuroendocrine differentiation,² may be recorded under 'other, specify'.

Table 1: 6th edition of the World Health Organization Classification of tumours of the pancreas.²

Descriptor	ICD-O codes ^a
Malignant epithelial tumours	
Duct adenocarcinoma, NOS	85000/3
Adenosquamous carcinoma	85600/3
Colloid carcinoma	84800/3
Hepatoid carcinoma	85760/3
Medullary carcinoma	85100/3
Poorly cohesive carcinoma / signet-ring cell carcinoma	84901/3
Undifferentiated carcinoma	80200/3
Undifferentiated carcinoma with osteoclast-like giant cells	80352/3
Acinar cell carcinoma	85500/3
Acinar cell cystadenocarcinoma	85510/3
Mixed acinar–neuroendocrine carcinoma	81542/3
Mixed acinar–neuroendocrine–ductal carcinoma	81543/3
Mixed acinar–ductal carcinoma	85520/3

^a These morphology codes are from the International Classification of Diseases for Oncology, fourth edition (ICD-O-4.0).²¹ Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

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Note 8 – Histological tumour grade (Core)

While the WHO² and the Union for International Cancer Control (UICC)¹⁷ /American Joint Committee on Cancer (AJCC)¹⁸ each propose a different system for grading of the histological tumour differentiation, grading is highly concordant between both and has a similar predictive value.²² Grading according to the UICC¹⁷/AJCC¹⁸ Staging Systems is recommended because it is more widely used and less complex than the WHO grading system (i.e., it does not require assessment of mucin production and mitotic activity). Other grading systems have been proposed but have not been adopted widely.^{23,24}

The UICC¹⁷/AJCC¹⁸ system is as follows:

- Grade 1: >95% of the tumour is composed of glands
- Grade 2: 50-95% of the tumour is composed of glands
- Grade 3: <50% of the tumour is composed of glands.

Histological tumour grade has been shown to have prognostic significance, with grade 3 being an adverse prognostic factor.²⁵⁻²⁹

By convention, the histological grade of tumour differentiation is not given for acinar cell carcinoma, acinar cell cystadenocarcinoma, and NEC.

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Note 9 – Extent of invasion (Core and Non-core)

In pancreatic ductal adenocarcinoma, tumour extension beyond the pancreas is present in up to 90% of cases.^{11,30} Extrapancreatic invasion may also be seen in acinar cell carcinoma and NEC.

Following controversy as to whether infiltration of the intrapancreatic common bile duct should be regarded as extrapancreatic extension and difficulties related to the identification of infiltration into the peripancreatic soft tissue, UICC 9th edition/AJCC TNM 8th edition have introduced tumour size as the exclusive criterion for stages pT1-3.^{17,18} T4 tumours remain defined by invasion of the common hepatic artery, superior mesenteric artery and/or coeliac axis, which may be considered resectable in highly selected cases with favourable response to neoadjuvant treatment.³¹

Tumours that infiltrate named blood vessels or other organs, for example the adrenal gland, stomach or colon, may be resected by an extended surgical procedure.³² The presence or absence of tumour infiltration into these additionally resected structures should be recorded, because it allows correlation with preoperative imaging and intraoperative surgical assessment.^{33,34} According to some, but not all studies, tumour invasion of named vessels is associated with worse patient outcome,^{33,35-40} and the depth of invasion into the vessel wall (tunica adventitia, media, intima, or vascular lumen) is prognostically relevant.^{35,40-42}

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Note 10 – Lymphatic and venous invasion (Core)

Tumour invasion of lymphatic and venous vessels represents different biological processes with a different outcome, i.e., lymph node metastasis or distant, blood-borne metastasis. Hence, these features should be recorded separately, in accordance with the UICC TNM 9th edition.¹⁷

It may be difficult to distinguish between small lymphatics and venous blood vessels, in which case the 'orphan arteriole' sign may help with identifying venous invasion. Special stains, in particular elastin stains or immunohistochemistry for caldesmon, podoplanin/D2-40 or desmin, may also assist the distinction.^{43,44} The latter immunohistochemical stains may also be useful to identify the occasional examples of vascular invasion that mimic PanIN.⁴⁵

While invasion of lymphatic or vascular vessels has been correlated with survival, both in patients who received neoadjuvant treatment and those who did not, their prognostic value is weaker than that of tumour stage.^{2,27,43,45-47}

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Note 11 – Perineural invasion (Core)

Perineural invasion of intrapancreatic nerves and the extrapancreatic neural plexus is a common finding in pancreatic ductal adenocarcinoma. It is an adverse prognostic factor both in treatment-naïve tumours and following neoadjuvant therapy.^{48-50 25,28,37,51-55}

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Note 12 – Response to neoadjuvant therapy (Core and Non-core)

In the past several years, neoadjuvant treatment of pancreatic ductal adenocarcinoma has increasingly entered routine clinical practice. The response to neoadjuvant treatment should be recorded, because it reflects the tissue-based result of clinical intervention. Moreover, complete and near complete response correlate with better patient outcome.⁵⁶

Several different scoring systems have been proposed.^{19,57} None of these has been universally accepted, and interobserver variation has been reported for the most commonly used systems.⁵⁸⁻⁶² The modified Ryan scheme (which is included in the guidelines of the College of American Pathologists⁶³) is recommended, because the 4-point scoring scale⁶⁴ is based on non-numeric criteria and on the evaluation of the residual cancer (not the proportion of the tumour that has been destroyed), which makes it easier to use. While many, but not all, studies do not show a difference in patient outcome between score 2 and score 3,^{65,66} it is deemed important to distinguish between patients with a treatment response that is poorer than score 1 but definitely better than score 3, in order to risk-stratify the large number of patients (>80%) who fall into both these categories. For that reason, the modified three-tiered system proposed by Chatterjee,⁵⁶ which has merged score 2 and 3 into a single group, is not recommended. One of the drawbacks of this system is a 5% threshold value, which is difficult to determine, because assessment of the denominator (the size of the tumour bed) may be difficult and subjective.^{12,62} The advantage of the Ryan system is that it is based on residual viable tumour.

Accurate evaluation of tumour regression requires extensive sampling of lesional tissue.^{15,20,67} If there is no grossly identifiable tumour, or the initially submitted sections do not contain viable cancer cells, entire embedding or extensive sampling of the pancreas and peripancreatic/adjacent tissues is recommended.¹⁵

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Note 13 – Margin status (Core and Non-core)

Margin assessment is based on combined macroscopic and microscopic measurement. Because margin involvement may be a focal, macroscopically indiscernible finding, extensive sampling is important for accurate assessment of the margin status.⁶⁸ The need for extensive tissue sampling to detect microscopic margin involvement is also supported by molecular studies.⁶⁹

‘R1’ is defined by UICC¹⁷/AJCC¹⁸ TNM as *microscopic residual disease*, i.e., irrespective of whether tumour is left behind at a surgical resection margin or at a non-surgical tissue plane. Assessment of the R-status should therefore be based on evaluation of all surfaces of the resection specimen, including the anterior pancreatic surface and the surface of the superior mesenteric vein groove (Figure 1).

Currently, a margin is considered positive if the tumour is at or within 1 millimetre (mm) of the margin. This definition was originally adopted from the protocols for the assessment of rectal cancer, for which a clearance of ≤ 1 mm was found to be predictive of local recurrence and poor survival. Based on the dispersed growth pattern that is characteristic of pancreatic ductal adenocarcinoma and more pronounced than in rectal cancer,¹⁶ a definition based on larger clearances (e.g., 1.5 mm) was proposed and found to be prognostically significant in some studies,^{70,71} but has not been implemented in diagnostic practice. Because the anterior surface of the pancreas is a peritonealised anatomical surface, involvement of that surface is defined by breaching of the surface, i.e., a clearance of 0 mm. While further evidence is awaited, assessment of the margin status based on R1 defined as 1 mm clearance (0 mm for the anterior surface) is now also recommended by the AJCC and other professional bodies.^{18,63,72,73}

An appropriate definition of microscopic margin involvement (R1) following neoadjuvant treatment has not been established yet.⁷⁴ Because a clearance of >1 mm does not necessarily reflect absence of microscopic residual disease, it is recommended to record the minimum distance to the relevant margins.

The detection of microscopic margin involvement (R1) is also strongly affected by the specimen dissection technique.⁷⁵ The current divergence in specimen grossing, including the extent of tissue sampling, along with the continued use of 0 mm clearance as the definition of R1 in some centres, are likely important reasons for the marked variation in published R1-rates. Studies based on a fully standardised, detailed pathology examination protocol that includes evaluation of all surfaces and the use of 1 mm clearance report on a high R1-rate (>70%).⁴⁵⁻⁴⁷

The variation in R1-rates among studies hampers comparison of data and identification of the prognostic significance of margin status.⁷⁶ In patients with resected pancreatic ductal adenocarcinoma without neoadjuvant treatment, microscopic margin involvement is found to correlate with poorer outcome in most studies.^{51,77,78} Following neoadjuvant treatment, the prognostic impact of R1 remains unclear.^{51,79-82}

The definition of R1 based on 1 mm clearance applies to ductal adenocarcinoma of the pancreas only. There is no evidence that this definition is also appropriate for acinar cell carcinoma and NEC, which have a different, often less dispersed growth pattern. It is therefore recommended to record the minimum distance to the closest margin(s).

By convention, diagnosing macroscopic residual disease (R2) is the surgeon's responsibility, and therefore this data item is not included in the pathology reporting document.

The distance of a carcinoma to some of the margins may be large, such that this information is of limited clinical relevance. However, it is recommended to record the clearance to the margins that are closest to, but not involved by, the tumour (non-core).

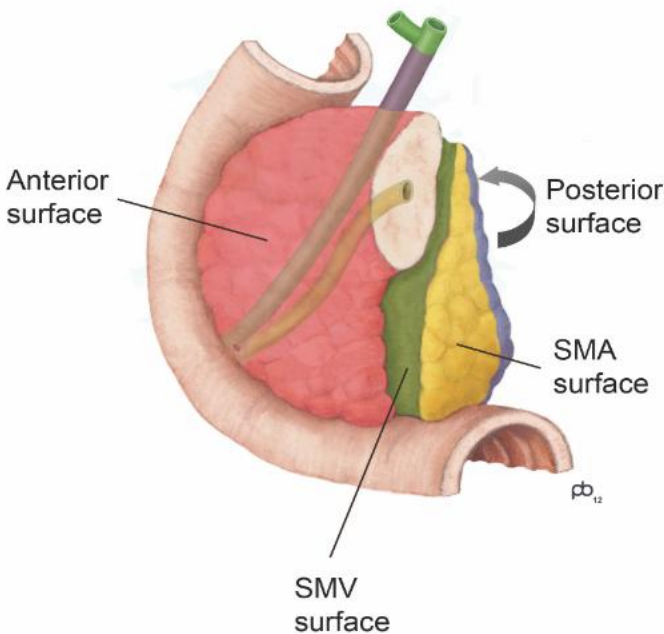


Figure 1: Circumferential surfaces of a pancreatoduodenectomy specimen to be included in the assessment of the margin status: anterior pancreatic surface (red), superior mesenteric vein (SMV) dissection margin (green), superior mesenteric artery (SMA) dissection margin (yellow), posterior dissection margin (blue). Adapted with permission courtesy of Mr Paul Brown.⁸³

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Note 14 – Lymph node status (Core)

Regional lymph nodes that are submitted separately should be reported individually, but the numbers should be included in the above response.

Lymph node status is one of the most potent prognostic factors for ductal adenocarcinoma of the pancreas, both for overall and disease-free patient survival in surgery-first and neoadjuvant treatment settings.

^{26,27,29,51,84-86} Based on outcome data, tumours with positive lymph nodes are categorised as N1 (1-3 positive regional lymph nodes) or N2 (4 or more regional lymph node metastases).^{17,18}

Lymph node status is also found to be prognostically relevant for acinar cell carcinoma.⁸⁷⁻⁹⁰ Lymph node status is one of the most important prognostic factors for localised NEC, and it may guide adjuvant treatment for MiNEN.

All lymph nodes in the resection specimen should be examined histologically. While various thresholds of the lymph node yield have been proposed,⁹¹⁻⁹⁷ the 6th edition WHO Classification of Digestive System Tumours,² as well as the CAP and NCCN guidelines recommend retrieving at least 12 lymph nodes from pancreatoduodenectomy specimens.^{2,98,99} For distal pancreatectomy specimens and for pancreatic cancer after neoadjuvant treatment, the minimum lymph node yield has not been established.^{84,100-102} Neither has the lymph node yield for resection specimens with acinar cell carcinoma or NEC been identified.

In accordance with the UICC 9th edition¹⁷/AJCC 8th edition Staging Systems, direct invasion of a lymph node by the primary tumour should also be reported as lymph node involvement and included in the above information.

It should be noted that there is a discrepancy between UICC 9th edition¹⁷ and AJCC 8th edition¹⁸ Staging Systems regarding the assignment of coeliac lymph nodes. While these are considered regional lymph nodes for cancer in the head, body and tail of the pancreas by UICC,¹⁷ the AJCC regards them as regional lymph nodes exclusively for tumours in the pancreatic body and tail.¹⁸

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Note 15 – Additional findings (Non-core)

The information recorded in this element refers to any diagnostic lesion that is found in addition to the index lesion. In particular, in case of ductal adenocarcinoma arising from an intraductal papillary mucinous neoplasm, the latter should *not* be recorded as an additional finding but rather the tumour should be documented as ‘intraductal papillary mucinous neoplasm with associated invasive carcinoma’ under ‘Histological tumour type’.

If a preinvasive lesion is present, the highest grade of dysplasia should be recorded (low or high grade).

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Note 16 – Ancillary studies (Core and non-core)

Ancillary studies, including immunohistochemistry and molecular testing, may be performed where clinically indicated. While not always required for diagnosis, they may provide prognostic, predictive, or therapeutic information and should be recorded and specified.

For ductal adenocarcinoma of the pancreas, targetable molecular alterations may include, for example, mismatch repair (MMR)/microsatellite instability (MSI), KRAS, BRCA1/BRCA2 or PALB2 mutations.

Immunohistochemical confirmation of acinar differentiation by specific markers (BCL10, trypsin, CPA1 or CPA2) is essential for the diagnosis of acinar cell carcinoma.²

If a pure or mixed neuroendocrine neoplasm is suspected on morphology, positivity for at least two markers of neuroendocrine differentiation by immunohistochemistry is required (core) to confirm neuroendocrine differentiation, usually synaptophysin, chromogranin A and/or INSM1. As with other gastrointestinal tract and pancreatic neuroendocrine neoplasms, assessment of proliferation index by Ki-67 immunohistochemistry is a core component as it is fundamental to grading of the neuroendocrine component.² For the differential diagnosis with grade 3 NET, p53 (core) and Rb1 (non-core) can be applied. Low molecular weight cytokeratins can be used (non-core). MMR stains may also be considered for NECs (non-core). A Ki-67 proliferation index <55% is associated with better overall survival in NECs.¹⁰³ TP53 mutations are found in over 69% of NEC compared to 10-15% of NET grade 3 (G3),^{104,105} RB1 loss is found in 40-60% of NEC and only very rarely in NET G3.¹⁰⁶

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Note 17 – Histologically confirmed distant metastases (Core)

Distant metastasis is a strong adverse prognostic factor. Metastasis to extraregional lymph nodes (e.g., paraaortic lymph nodes) is also associated with poor prognosis¹⁰⁷⁻¹⁰⁹ and should be recorded as distant metastasis.

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Note 18 – Pathological staging (Core)

TNM staging should be assessed according to the agreed criteria of the UICC 9th edition¹⁷ and AJCC¹⁸ 8th edition Staging Systems.

The staging system for acinar cell carcinoma, NEC and MiNEN is the same as the one used for pancreatic ductal adenocarcinoma.

In case of multiple synchronous cancers – arising de novo or in association with intraductal papillary mucinous neoplasia or other precursor lesions – the pT category should be based on the largest tumour (not the total sum of all invasive foci¹¹⁰) and recorded as ‘pTm’, while the pN category should be based on the overall lymph node status.

N category is strongly associated with survival for pancreatic ductal adenocarcinoma, both in patients who were treated neoadjuvantly and those who were not.^{28,51,111,112} The prognostic significance of T category is weaker than that of N-category in a surgery-first setting, while results are conflicting following neoadjuvant therapy.^{7625,28,51,52,112,113} TNM stage provides prognostic stratification both in treatment-naïve and neoadjuvantly treated pancreatic ductal adenocarcinoma, although with variable discrimination between the various stage groups.^{111,113,114}

Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM9 and AJCC TNM8,^{17,18} the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

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