Carcinoma of the Exocrine Pancreas
Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

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

NEOADJUVANT THERAPY (Note 1)

- ◯ Information not provided
- ◯ Not administered
- ◯ Administered (select all that apply)
  - ☐ Chemotherapy
  - ☐ Radiotherapy
  - ☐ Other, *specify*

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

- ☐ Whipple pancreatoduodenectomy
- ☐ Pylorus-preserving pancreatoduodenectomy
- ☐ Distal pancreatectomy
- ☐ Total pancreatectomy
- ☐ Subtotal pancreatectomy
- ☐ Pancreatic resection (tick one of the options above) extended with one or more of the following additionally resected organs/structures:
  - ☐ Vein
    - ☐ Superior mesenteric vein
    - ☐ Portal vein
  - ☐ Artery(s)
    - ☐ Superior mesenteric artery
    - ☐ Common hepatic artery
    - ☐ Coeliac trunk
  - ☐ 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)

mm

Additional dimensions (largest tumour)

mm x mm

Dimensions of additional smaller tumour foci

mm x mm x mm

mm x mm x mm

Method of measurement (in case of neoadjuvant treatment)[a]

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

[a] *See Note for an explanation of the approaches to the method of measurement following neoadjuvant treatment.*

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HISTOLOGICAL TUMOUR TYPE (Note 6)

(Value list from the World Health Organization Classification of Tumours of the Gastrointestinal Tract (2019))

- ◯ Ductal adenocarcinoma
  - ◯ Ductal adenocarcinoma not otherwise specified (NOS)
  - ◯ Adenosquamous carcinoma
  - ◯ Colloid carcinoma
  - ◯ Signet-ring cell (poorly cohesive cell) carcinoma
  - ◯ Medullary carcinoma NOS
  - ◯ Hepatoid carcinoma
  - ◯ Invasive micropapillary carcinoma
  - ◯ Large cell carcinoma with rhabdoid phenotype
  - ◯ Carcinoma, undifferentiated, NOS
  - ◯ Undifferentiated carcinoma with osteoclast-like giant cells
- ◯ Acinar cell carcinoma
  - ◯ Acinar cell cystadenocarcinoma
  - ◯ Mixed acinar-neuroendocrine carcinoma
  - ◯ Mixed acinar-endocrine-ductal carcinoma
  - ◯ Mixed acinar-ductal carcinoma
  - ◯ Acinar cell carcinoma, NOS
- ◯ 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
- ◯ Other, *specify*

HISTOLOGICAL TUMOUR GRADE (Note 7)

- ◯ Not applicable
- ◯ Grade X: 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 8)

- ◯ 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

    Specify maximum depth of invasion
    - ◯ Tunica adventitia
    - ◯ Tunica media
    - ◯ Tunica intima
    - ◯ Vascular lumen
  - ☐ Invasion into arterial resection

    Specify which artery(s)

    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 9)

- ◯ Not identified
- ◯ Present
  - ☐ Lymphatic invasion
  - ☐ Venous invasion

PERINEURAL INVASION (Note 10)

- ◯ Not identified
- ◯ Present

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RESPONSE TO NEOADJUVANT THERAPY (Note 11)

- ◯ No neoadjuvant treatment
- ◯ Complete response – no viable cancer cells (score 0)
- ◯ Near complete response – single cells or rare groups of cancer cells (score 1)
- ◯ Partial response – residual cancer with evident tumour regression (score 2)
- ◯ Poor or no response – extensive residual cancer with no evident tumour regression (score 3)
- ◯ Cannot be assessed, *specify*

MARGIN STATUS[b] (Note 12)

Pancreatic transection margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
  - ◯ Invasive carcinoma
  - ◯ High grade dysplasia
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Bile duct transection margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Gastric/proximal duodenal transection margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Posterior dissection margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Superior mesenteric artery (SMA) dissection margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Superior mesenteric vein (SMV) dissection margin

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Anterior pancreatic surface

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Transection margins of venous resection

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Transection margins of arterial resection

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

Other margin(s), *specify*

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance of tumour from closest margin ____ mm

[b] *See Note for the definition of margin involvement and for an explanation of the various specimen margins and surfaces.*

LYMPH NODE STATUS (Note 13)

- ◯ Cannot be assessed
- ◯ 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 14)

- ☐ Chronic pancreatitis
- ☐ Pancreatic intraepithelial neoplasia, *specify highest grade*
- ☐ Intraductal papillary mucinous neoplasia, *specify highest grade*
- ☐ Neuroendocrine tumour, *specify grade*
- ☐ Other, *specify*

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ANCILLARY STUDIES (Note 15)

- ◯ Not performed
- ◯ Performed, *specify*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 16)

- ◯ Not assessed
- ◯ Not identified
- ◯ Present, *specify site(s)*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[c] (Note 17)

TNM Descriptors (only if applicable) (select all that apply)

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

Primary tumour (pT)

- ◯ TX Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ Tis Carcinoma in situ[d]
- ◯ 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 more than 4 cm in greatest dimension
- ◯ T4 Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery

[d] *Tis also includes the 'PanIN–III' classification.*

Regional lymph nodes (pN)

- ◯ No nodes submitted or found
- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Metastases in 1 to 3 regional lymph nodes
- ◯ N2 Metastases in 4 or more regional lymph nodes

[c] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley-Blackwell.*

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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 III-2 or above (based on prognostic factors in the National Health and Medical Research Council levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

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 III-2 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 Dataset Authoring Committee.

Scope of this dataset

The dataset has been developed for pancreatic resection specimens with carcinomas of the exocrine pancreas, i.e., ductal adenocarcinoma and acinar cell carcinoma.

Carcinoma of the ampulla of Vater, common bile duct and duodenum, neuroendocrine neoplasia, 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. 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.[2-4] 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.[5] Furthermore, colonisation of non-neoplastic epithelial surfaces (of pancreatic ducts or the duodenum) by adenocarcinoma (so-called 'cancerisation') may mimic dysplasia.[6,7] Microscopically, intestinal type morphology of the adenocarcinoma and expression of intestinal markers (CK20+, CDX2+, MUC2+) may help with distinguishing ampullary cancer from carcinoma arising in the pancreas or bile duct, which is predominantly of pancreatobiliary type (CK20-, CDX2-, MUC2-, CK7+, MUC1+).[8] While duodenal cancer usually exhibits more extensive growth along the duodenal wall than into the pancreatic head, its morphology and immunohistochemical phenotype 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.

⬆ **Back**

Note 1 – Neoadjuvant therapy (Core)

Neoadjuvant treatment can have a profound effect on the morphological findings and has implications for both specimen sampling and histological interpretation. Information regarding the administration of neoadjuvant therapy should therefore always be provided to and recorded by the pathologist.

Back

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 depends on the site, size and extent of the tumour.

Back

Note 3 – Tumour focality (Core)

The vast majority of tumours are solitary, but multifocal disease can occur. 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.

Back

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”.

Back

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

Assessment is based on macroscopic evaluation and microscopic confirmation/correction. The latter is important, because ductal adenocarcinoma of the pancreas often has a highly dispersed growth pattern,[10] 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,[11] 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. Similar considerations apply to the measurement of tumours in the pancreatic head.

Measurement of the tumour dimensions may be difficult following neoadjuvant treatment, especially when two or more foci of residual tumour tissue are present.[12] 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 structures
- **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. Moreover, the accuracy of measurement is also dependent on the extent of tissue sampling. Given the lack of evidence on how to best measure tumour size, there is currently no international consensus. The approach that is used, based on local practice or dependent on the particular case, should be recorded.

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.

Back

Note 6 – Histological tumour type (Core)

Tumours should be typed according to the World Health Organization (WHO) Classification of Tumours of the Gastrointestinal Tract, 5th edition, 2019.[13]

Ductal adenocarcinoma, including its subtypes, account for 90% of all pancreatic malignancies, whereas acinar cell carcinoma makes up less than 2% of all pancreatic cancers in adults. Correct diagnosis of the various subtypes of ductal adenocarcinoma 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.[13]

Back

Note 7 – Histological tumour grade (Core)

While the WHO and the Union for International Cancer Control (UICC)[11]/American Joint Committee on Cancer (AJCC)[14] each propose a different system for grading of the histological tumour differentiation,[11,13-15] grading is highly concordant between both and has a similar predictive value.[16] Grading according to the UICC[11]/AJCC[14] 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. The UICC[11]/AJCC[14] 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.[17-19]

By consensus, the histological grade of tumour differentiation is not given for acinar cell carcinoma and acinar cell cystadenocarcinoma or for tumours following neoadjuvant treatment.

Back

Note 8 – Extent of invasion (Core and Non-core)

The anatomical extent of tumour invasion, assessed by a combination of macroscopic and microscopic assessment, formed the basis for pT-staging according to the UICC[20]/AJCC[21] TNM 7th editions. In pancreatic ductal adenocarcinoma, tumour extension beyond the pancreas is present in up to 90% of cases.[22] 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/AJCC TNM 8th editions have introduced tumour size as the exclusive criterion for stages pT1-3.[11,14] 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.[23]

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.[24] 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. According to some, but not all studies, tumour invasion of named vessels is associated with worse patient outcome,[25-28] and the depth of invasion into the vessel wall (tunica adventitia, media, intima, or vascular lumen) is prognostically relevant.[29,30]

Back

Note 9 – Lymphatic and venous invasion (Core and Non-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 8th edition.[11]

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 or podoplanin/D2-40, may also assist the distinction.[31] The latter immunohistochemical stains may also be useful to identify the occasional examples of vascular invasion that mimic pancreatic intraepithelial neoplasia.[32]

While invasion of lymphatic or vascular vessels has been correlated with survival, both in patients who receive neoadjuvant treatment and those who do not, their prognostic value is weaker than that of tumour stage.[13,31-34]

⬆ Back

Note 10 – 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-naive tumours and following neoadjuvant therapy.[35-37]

⬆ Back

Note 11 – Response to neoadjuvant therapy (Core)

In the past several years, neoadjuvant treatment of pancreatic cancer has 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.[38]

Several different scoring systems have been proposed.[12] The modified Ryan scheme (which is included in the guidelines of the College of American Pathologists[39]) is recommended, because the 4-point scoring scale[40] 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 current evidence does not show a difference in patient outcome between score 2 and score 3,[41] 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,[38] which has merged score 2 and 3 into a single group, is not recommended. The introduction of an arbitrary and difficult to implement 5% threshold value is a further disadvantage of the Chatterjee scoring system.

Accurate evaluation of tumour regression requires extensive sampling of lesional tissue. In case of complete tumour regression, the entire tumour bed and any adjacent, macroscopically abnormal-looking tissues should be processed for histological examination.

⬆ Back

Note 12 – 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.[42] The need for extensive tissue sampling to detect microscopic margin involvement is also supported by molecular studies.[43]

"R1" is defined by UICC[11]/AJCC[14] 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). Involvement of these surfaces increases the risk of local tumour recurrence and is therefore of prognostic relevance.[44] Studies based on a fully standardised, detailed pathology examination protocol that includes evaluation of all surfaces report on a high R1-rate (>70%) that correlates with survival.[45-47]

Currently, a margin is considered positive if the tumour is at or within 1 millimetre (mm) of the margin (R1). 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,[10] a definition based on larger clearances (e.g., 1.5 mm) was proposed and found to be prognostically significant in some studies,[48,49] 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.[14,39,50,51]

An appropriate definition of microscopic margin involvement (R1) following neoadjuvant treatment has not been established yet.[52] 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 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, which has a different, often less dispersed growth pattern. It is therefore recommended to record the minimum distance to the closest margin(s).

By consensus, 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).

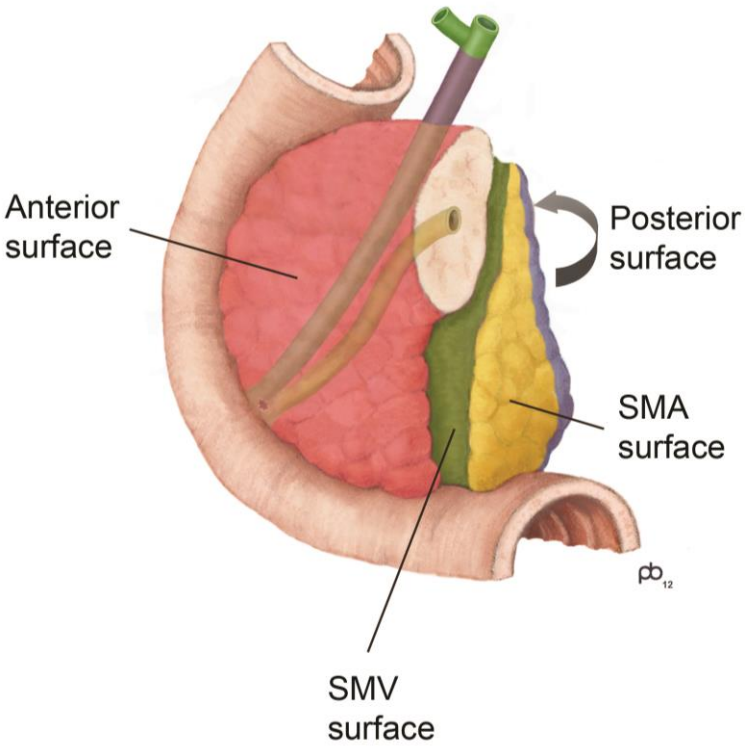

Figure 1: Circumferential surfaces of a pancreatoduodenectomy specimen to be included in the assessment of the margin status: anterior pancreatic surface (red), superior mesenteric vein (SMV) dissection margin (green), superior mesenteric artery (SMA) dissection margin (yellow), posterior dissection margin (blue). Permission courtesy of Mr Paul Brown.[53]

⬆ **Back**

Note 13 – 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 predictors of survival for ductal adenocarcinoma of the pancreas.[34,54-58] Based on outcome data, tumours with positive lymph nodes are now categorised as N1 (1-3 positive regional lymph nodes) or N2 (4 or more regional lymph node metastases).[11,14,59,60]

All lymph nodes in the resection specimen should be examined histologically. The lymph node yield from Whipple resection specimens should be at least 12.[61-63] For distal pancreatectomy specimens, the minimum lymph node yield has not been established.

In accordance with the UICC[11]/AJCC[14] 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[11] and AJCC[14] 8th edition staging systems regarding the assignment of coeliac lymph nodes. While these are considered regional lymph nodes only for cancer in the head of the pancreas by UICC,[11] the AJCC regards them as regional lymph nodes exclusively for tumours in the body and tail of the pancreas.[14]

⬆ **Back**

Note 14 – 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).

Back

Note 15 – Ancillary studies (Non-core)

Any ancillary studies should be recorded and specified. Ancillary investigations based on immunohistochemistry or molecular analysis are not recommended for routine diagnostics and are currently considered investigational.

Back

Note 16 – 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 prognosis[64-66] and should be recorded as distant metastasis.

Back

Note 17 – Pathological staging (Core)

TNM staging should be assessed according to the agreed criteria of the UICC[11] and AJCC[14] 8th edition staging systems.

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

In case of multiple synchronous cancers, the stage should be based on the largest tumour (and recorded as "pTm") and the overall lymph node status.

The shift of stage criteria for pT1-3 from tumour size and tumour extent (TNM 7th edition)[20,21] to tumour size alone (TNM 8th edition)[11,14] was prompted by concerns regarding the reproducibility of the criterion "extension beyond the pancreas".[67] In addition, extrapancreatic tumour extension is observed in over 80% of tumours smaller than 20 mm in size, and yet, the associated survival is closer to that of tumours without extrapancreatic extension.[68-71] The changes introduced by the UICC[11]/AJCC[14] 8th edition staging systems aimed at improving reproducibility of T-stage and a more even stratification of patients across stages without sacrificing prognostic accuracy.[72] In addition, an N2 category was added, similar to the pN-staging for other gastrointestinal cancer sites. Several

validation studies of the UICC/AJCC 8th edition staging systems have been published.[72-75] Whereas most find the revised N-stage to be highly prognostic, only a modest increase in prognostic accuracy is observed for the revised T-stage, which remains a fairly poor predictor of survival.[73,74] Future studies will be needed to evaluate the prognostic significance of tumour size following neoadjuvant therapy.[76]

Back

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