The Royal College of Pathologists
Pathology: the science behind the cure

Dataset for histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct

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Foreword

The cancer datasets published by the Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients, and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see Appendices E–J) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Dataset) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- British Society of Gastroenterology – Pancreas Section (www.bsg.org.uk)
- British Society of Gastroenterology – Pathology Section (www.bsg.org.uk)
- Pancreatic Society of Great Britain and Ireland (www.psgbi.org).

Evidence for the revised dataset was obtained from updates to classification systems and by electronically searching medical literature databases for relevant research evidence, systemic reviews and national or international publications on pancreatic/ampullary/bile duct cancer up to and including December 2016. The level of evidence for the recommendations has been summarised (see Appendix K). Unless otherwise stated, the level of evidence corresponds to “Good practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing group”. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in Appendix L.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset for the core items.

A formal revision for all cancer datasets takes place on a three-year cycle. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant subspecialty advisor to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members’ attention. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness department and the Working Group on Cancer Services. It was placed on the College website for an abridged consultation with the membership from 9 to 23 May 2019. All comments received from the Working Group and the

membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

Careful and accurate pathology reporting of pancreatic, ampulla of Vater and common bile duct cancers is important because pathology reports are used to:

- confirm the diagnosis
- inform prognosis
- select potential patients for future trials of adjuvant therapy
- audit pathology services
- evaluate the quality of other clinical services, e.g. radiology and surgery
- collect accurate data for cancer registration and epidemiology
- facilitate high-quality research
- plan service delivery.

In pancreatic/ampullary/bile duct cancer, the key reasons for high-quality pathology reporting include the following:[1]

- to identify the primary origin of the tumour, which, in turn, may determine further therapy and/or entry into clinical trials
- to determine the type, grade and stage of the tumour correctly
- to assess resection margin status accurately and comprehensively
- to document the presence of significant precursor lesions
- to provide accurate, good quality prognostic information
- to determine the effects of preoperative (neoadjuvant) therapy
- to evaluate any changes in surgical technique
- to provide information that will facilitate investigations into the epidemiological, biological and molecular characteristics of these tumours.

Communication of pathology information to the patient and the multidisciplinary team (MDT) is essential for optimal clinical management. Each department should have, as a minimum, a lead and deputy gastrointestinal pathologist, one of whom should attend MDT meetings. All reporting pathologists should provide pathology reports that are accurate, complete, understandable, timely and transferable. There is evidence that the use of proformas facilitates these requirements[2] and their use is strongly recommended, supplemented as necessary by free text. It is appreciated that electronic versions of the dataset are still not available in all pathology departments and there remain some laboratories that have to dictate or type the dataset into the pathology report.

1.1 Changes made to the third version of the dataset

- Comments added on the assessment of specimens following neoadjuvant therapy.
- Comments expanded on cancer specimens with intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasm (MCN).
- A section added on pancreatic biopsy reporting.
- Updated to WHO 2010 classification of tumours and included TNM 8.

The following specific changes have been made to the dataset proformas:

- 'Date of surgery' has been added to the proformas to allow mapping to College key performance indicators relating to turnaround times (www.rcpath.org/profession/quality-improvement/kpis-for-laboratory-services.html)
- specimen types have been listed
- response to neoadjuvant therapy has been added
- potential margins are now listed in table format
- TNM 8 has been added.

The number of resections for pancreatic, ampullary or bile duct cancers continues to increase.[3] This has led to the identification of new pathological entities and investigation of numerous potential prognostic factors.

Pathological tumour characteristics that (in most studies) have significant prognostic value in resected pancreatic adenocarcinoma include tumour size, tumour differentiation, lymph node involvement and resection margin status.[4–9]

Histopathological tumour characteristics that have significant prognostic value in resected ampullary adenocarcinoma include pancreatobiliary differentiation, tumour stage and lymph node involvement.[10,11]

[Level of evidence – C.]

The most important pathological prognostic factors identified to date for resected common bile duct adenocarcinoma are tumour stage, tumour grade and lymph node status.[12–16]

[Level of evidence – D.]

1.2 Developments since the second edition

Since the second edition of this dataset was published in 2010, there have been further requests for guidance particularly on dissection of the pancreatoduodenectomy specimen, identification of resection margins, definition of a positive resection margin and assessment of resection specimens following neoadjuvant therapy. Many of these requests were sought following the publication of the British Society of Gastroenterology survey of 'Pathologists' approach to pancreatectomies for ampullary, pancreatic and bile duct cancer' in 2013.[17] These requests have been addressed, but it is emphasised that the dataset is for guidance and is not prescriptive. There is no single internationally recognised, standardised method for dissecting and sampling pancreatic cancer resection specimens. Moreover, there are still many areas of controversy in reporting pancreatic cancer resection specimens, highlighting the need for international agreement and standardisation.[18]

The reporting proformas and guidance are based on the current WHO classifications of tumours of the exocrine pancreas, ampulla of Vater and extrahepatic bile duct[19] (Appendices C and D) and the 8th edition of the UICC TNM staging system[20] (Appendix A). The UICC TNM staging system has the advantage of being widely accepted and familiar, and is adhered to throughout this document.

These guidelines mainly apply to the reporting of pancreatic exocrine carcinomas, 90% of which are ductal adenocarcinomas, but similar principles may be applied to the reporting of carcinomas arising in the ampulla of Vater or common bile duct. The reporting of endocrine tumours is addressed in the College's separate *Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract.*[21]

1.3 Target users and health benefits of this dataset

The primary users of the dataset are cellular pathology trainees and consultants and, on their behalf, the suppliers of IT products to laboratories. Secondary users are surgeons, radiologists, oncologists, cancer registries and the National Cancer Registration and Analysis Service (NCRAS). MDT working and standardisation of cancer reporting reduce the risk of histological misdiagnosis and help ensure clinicians have all the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer-specific data also provides information for healthcare providers and epidemiologists, and facilitates national/international benchmarking and research.

2 Clinical information required on the specimen request form

Patients often proceed to pancreatic surgery on the basis of imaging and/or cytology. It is therefore desirable for the pathologist to be aware of the specimen type, the presumed site and type of the tumour and whether or not preoperative therapy has been given. The nature of the resection is usually obvious to the pathologist, but it is good practice to confirm this using the specimen request form. A diagram of the surgical procedure or a good clinical description can be very valuable in complex specimens. If there is doubt about the nature of the specimen or the procedure, advice or clarification should be sought from the surgeon.

[Level of evidence – GPP.]

3 Preparation of specimens before dissection

Resection specimens should, preferably, be opened and partially sectioned by the pathologist immediately after resection to aid fixation. The resection specimen should be received fresh in the laboratory if fresh tissue sampling is required for a biobank or other reasons. The stomach is opened along the greater curve. The duodenum is opened along the anti-mesenteric border, on the opposite aspect to the pancreas, being careful to avoid cutting through a duodenal or ampullary tumour.

The margins of the pancreas (see section 5.2.4) should be painted with an agreed colour code before blocks are taken, either when the specimen is fresh or when fixed, according to the preference of the examining pathologist. The presence of a stent or a named vessel (e.g. portal vein, superior mesenteric vein) should be noted. Identification of a resected vessel, particularly if small in size, may be facilitated by painting it with an extra colour. One or two slices may be made into the fresh pancreas to allow tissue sampling for biobanking, for example, and/or to aid fixation. The specimen may then be pinned to a cork board, but should always be placed in a large volume of formalin and allowed to fix for 24–48 hours.

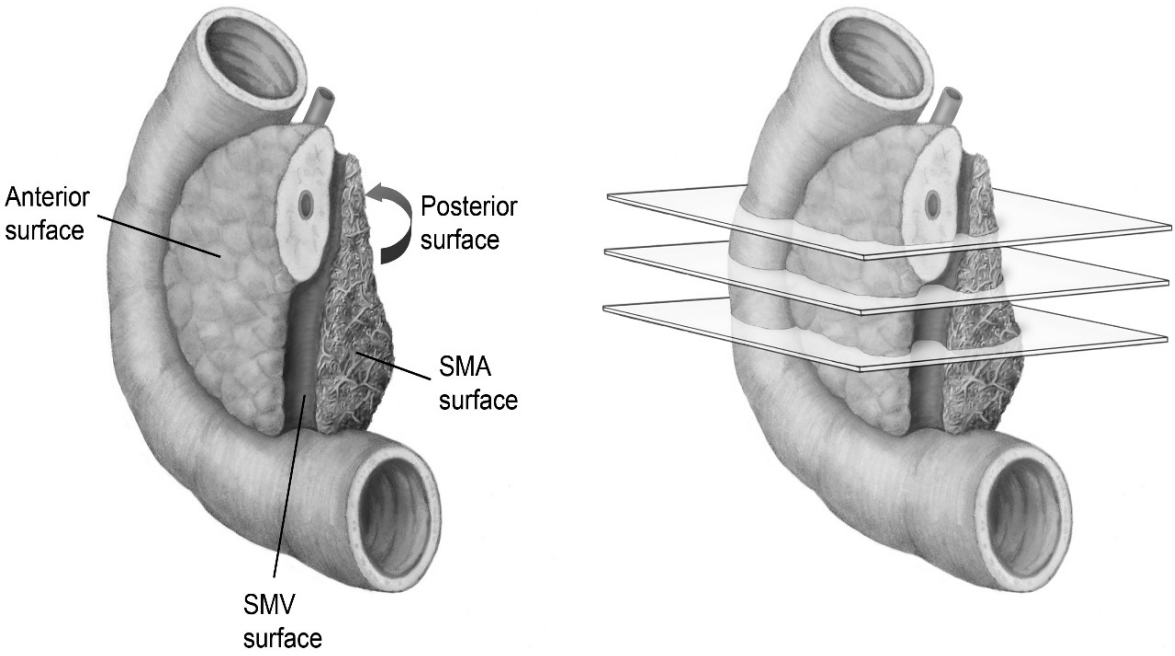
[Level of evidence – GPP.]

4 Specimen handling and block selection

Several different techniques are used for dissecting pancreatoduodenectomy specimens.[22,23] A detailed dissection protocol is beyond the scope of this document. However, a brief discussion of the axial dissection method is included because this technique has several advantages. After orientation of the specimen (Figure 1a), axial dissection (Figure 1b) serially slices the pancreatic head in an axial plane, i.e. perpendicular to the long axis of the duodenum. It is easy to perform, does not include longitudinal opening of the common bile duct or pancreatic duct and allows key anatomical structures (e.g. ampulla, common bile duct, main pancreatic duct) to be seen in the same slices. This dissection technique usually results in eight to ten slices, allowing thorough examination of the tumour and its relationship to the key anatomical structures and margins.[23]

[Level of evidence – GPP.]

Figure 1: (a) Head of the pancreas and (b) axial dissection, i.e. slicing perpendicular to the long axis of the duodenum.



SMA: superior mesenteric artery; SMV: superior mesenteric vein.
With acknowledgement to Paul Brown, St James's University Hospital, Leeds.

For distal pancreatectomy specimens, in which the splenic artery and vein run along the superior (cranial) aspect, the anterior and posterior surfaces may be painted. Painting the superior (cranial) and/or inferior (caudal) aspects may also help with orientation. The entire specimen can then be serially sliced in the sagittal plane. For total pancreatectomy specimens, a combined approach of axial slicing of the pancreatic head followed by serial slicing of the body and tail in the sagittal plane is recommended.

Overview photographs of the lined-up specimen slices and close-up images of individual slices may be helpful for reporting (e.g. to identify the tumour origin), for multidisciplinary case discussion and for review of the gross findings if required (e.g. for audit or clinical trials).

4.1 Specimen measurements

Record the lengths of the duodenum, stomach (lesser curve and greater curve), gall bladder, cystic duct and extrapancreatic bile duct, and the maximum dimensions of the pancreas (craniocaudally, mediolaterally and anteroposteriorly). The diameters of the common bile duct and main pancreatic duct can indicate the location of an obstruction and are useful for correlation with radiology. Record the dimensions of any attached vessels (e.g. segment of superior mesenteric vein or portal vein), spleen or other structures (e.g. colon).

4.2 Minimum samples recommended

If not already submitted as separate samples for frozen section assessment, the transection margins of the pancreatic neck, common bile duct and duodenum/distal stomach are sampled (usually *en face*) before specimen dissection. Tissue blocks should include the tumour where it approaches or involves anatomical structures relevant to (UICC TNM) T staging, e.g. duodenum, ampulla, common bile duct or peripancreatic tissue. Similarly, blocks should be taken from the tumour and the adjacent resection margin(s). It is often difficult to identify the invasive tumour front macroscopically, therefore extensive sampling of the tumour and the adjacent margins is recommended.[24] The importance of extensive sampling from the margins is supported by molecular studies.[25,26] If available, sampling with one or more wholemount blocks may be helpful for assessing the relationship of the tumour to anatomical structures and to margins, as well as allowing accurate measurement of tumour dimensions.

[Level of evidence – D.]

Following neoadjuvant therapy, large parts of a tumour may be replaced by fibrosis. Macroscopic distinction between tumour, fibrotic areas of tumour regression, and fibrosis of obstructing pancreatitis (that is present in nearly all pancreatic cancer resection specimens) may be difficult or impossible.[27] Extensive sampling is needed for accurate evaluation of the extent of viable tumour and its relationship to the margins. Extensive sampling is also necessary for a reliable diagnosis of complete response to neoadjuvant therapy, and sampling of the entire pancreas is recommended in this setting.[28]

[Level of evidence – GPP.]

Macroscopic examination plays an important role in determining the presence of an MCN or an IPMN in association with a cancer. Macroscopic papillary areas and solid areas in an MCN are most likely to show invasive carcinoma and should always be sampled. Similarly, solid nodules and mucoid areas in the wall of an IPMN should always be sampled as they likely represent invasive carcinoma. However, invasive carcinoma in an MCN or IPMN may not be apparent macroscopically, and may also be multifocal in IPMN. In the absence of macroscopic invasive carcinoma, embedding the entire MCN or IPMN is recommended, particularly if microscopic examination reveals high-grade dysplasia but no invasion.[29]

[Level of evidence – GPP.]

It is worth noting that an invasive adenocarcinoma and an IPMN may be present in the same pancreas, but the adenocarcinoma may not have arisen from the IPMN (i.e. the adenocarcinoma is a concomitant pancreatic ductal adenocarcinoma [PDAC]).[30] In this circumstance, the concomitant adenocarcinoma will not show transition from an IPMN to an invasive adenocarcinoma. For IPMNs, the resection specimen should also be assessed to determine whether the IPMN is of main duct type, branch duct type or mixed/combined duct type, as this has prognostic significance.[31] Placing a probe in the main pancreatic duct can help in this assessment.

When a segmental resection of the portal vein or superior mesenteric vein is removed *en bloc* with the pancreatoduodenectomy, then the proximal and distal ends of this vessel should be examined as additional transection margins. If a lateral sleeve resection of the vein is included in the specimen, then the entire edge of the vessel should be examined *en bloc* with the adjacent pancreas in the serial axial slices of the pancreas.

[Level of evidence – GPP.]

All lymph nodes (see Figure 2 and section 5.4.6) should be sampled in their entirety, because lymph node status is an important prognostic factor. Once lymph nodes have been identified and sampled individually, submission of the entire remaining peripancreatic fat and connective tissue may be considered to ensure that all lymph nodes are examined microscopically.

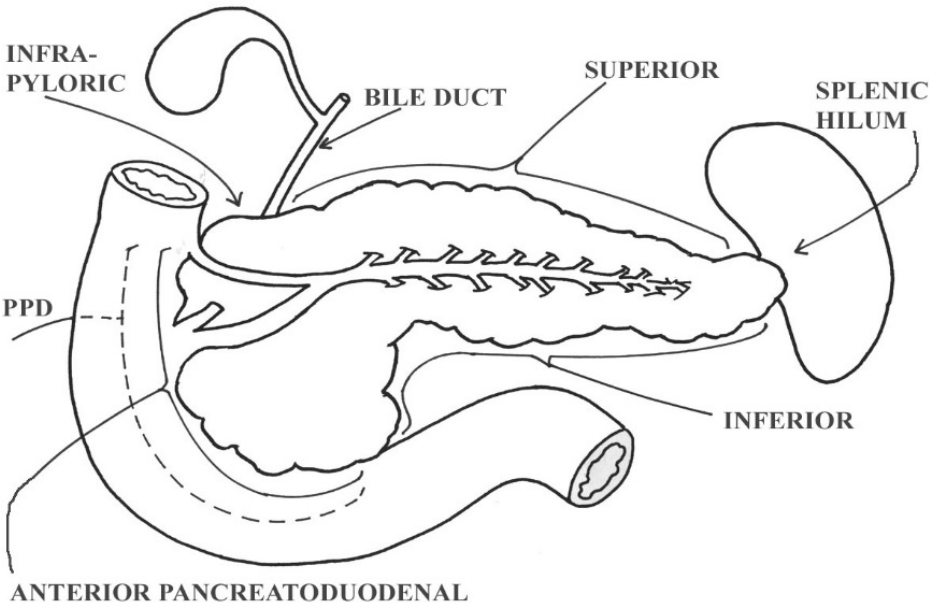
[Level of evidence – GPP.]

Samples of the ampulla of Vater, common bile duct and background pancreas should be taken.

A block code should be recorded using an easily accessible method (e.g. in the final report, in the IT system or on a scanned bench worksheet). This will aid identification of block origin at later review (e.g. for MDT meetings or clinical trials).

[Level of evidence – GPP.]

Figure 2: Lymph nodes.



Inferior includes lymph nodes around superior mesenteric vessels. PPD: posterior pancreatoduodenal.

5 Core data items

5.1 Macroscopic core data items

The following are core data items:

- type of specimen
- site of tumour
- maximum tumour dimension (measurement confirmed microscopically)
- resection margins (confirmed microscopically)
- named vessel present
- background pathology (e.g. IPMN, MCN, adenoma of the ampulla).

5.2 Notes on macroscopic assessment

Measurements made on the gross specimen are recorded in millimetres. They are confirmed or amended, where appropriate, by microscopy.

5.2.1 Type of specimen

The type of specimen should be recorded, e.g. a standard Kausch-Whipple's pancreato-duodenectomy (PD), a pylorus-preserving PD, a total PD, a subtotal pancreatectomy or a left (distal) pancreatectomy. The standard Kausch-Whipple's PD includes the head of pancreas, duodenum, common bile duct, gall bladder and two thirds of the stomach. Modifications of this procedure include pylorus-preserving PD (stomach not included), total PD (also includes the body and tail of pancreas with or without the spleen and/or stomach) and subtotal pancreatectomy (includes the body of the pancreas with or without the stomach). A left (or distal) pancreatectomy consists of the body and tail of pancreas only, with or without the spleen.

The type of operation will depend on the site and size of the tumour. Clinical trials, single-centre studies and a Cochrane Database Systematic Review have not shown any difference in patient survival between standard PD versus pylorus-preserving PD,[32–34] PD with or without vascular resection,[35] and PD with or without extended lymphadenectomy.[36,37]

5.2.2 Site of tumour (Appendix B)

State, when possible, whether the tumour appears to arise in the ampulla of Vater, in the intrapancreatic or extrapancreatic bile duct, or in the head, body or tail of the pancreas. Ampullary tumours are centred around the level of the ampulla and may involve the posterior or anterior pancreatoduodenal crevices. Common bile duct tumours arise along the route of the common bile duct, in the posterior-cranial aspect of the pancreatic head, above or at the level of the ampulla, and often involve the posterior pancreatic margin. Pancreatic tumours can occur in any part of the pancreatic head, body or tail.[1] The precise origin of a tumour in the head of the pancreas may be difficult to determine, particularly when the tumour is large and involves more than one potential site of origin. The tumour origin may then be determined by the location of the epicentre of the tumour.

[Level of evidence – GPP.]

Microscopic confirmation of the site of origin of the tumour should be sought. In some cases, the presence of microscopic precursor lesions may be helpful (adenoma or flat dysplasia in the ampulla for ampullary carcinoma, dysplasia in the bile duct for distal bile duct cancer). However, note that pancreatic intraepithelial neoplasia (PanIN) is a frequent finding and can be found in the background pancreas of specimens with ampullary or bile duct cancer, as well as pancreatic cancer.[38,39] Moreover, cancerisation of background structures can mimic

dysplasia.[40] An abrupt transition from highly atypical (cancer) epithelium to normal epithelium is helpful in recognising cancerisation. Although immunohistochemistry may help distinguish intestinal-type carcinomas (CK20+, CDX2+, MUC2+) from pancreatobiliary-type carcinomas (CDX2-, MUC1+, MUC2-) arising in the ampulla of Vater,[41] there are no immunohistochemical markers that distinguish between pancreatobiliary-type carcinomas of the ampulla and PDAC or bile duct carcinoma.

Anatomically, the head is that part of the pancreas to the right of the left border of the superior mesenteric vein, and the uncinate process is considered part of the head. The body lies between the left border of the superior mesenteric vein and the left border of the aorta, and the tail lies between the left border of the aorta and the hilum of the spleen. Carcinomas of the body or tail are usually more advanced than those of the head at the time of diagnosis, owing to the lack of obstructive symptoms and because they usually spread into extrapancreatic tissue and metastasise before detection. They are therefore seldom resected. Note that pancreatic carcinomas may be multicentric (please complete a separate proforma for each carcinoma).

A recent study has subclassified ampullary carcinomas into four subtypes based on their location (intra-ampullary, ampullary-ductal, periampullary-duodenal and ampullary-not otherwise specified) and has shown that the four clinicopathological subtypes are prognostically distinct.[42] It remains to be seen whether or not this site subclassification is adopted by the WHO and/or the UICC.

Following a good response to neoadjuvant therapy, it may be difficult or impossible to determine the site or origin of the cancer.[28] This should be stated in the report.

5.2.3 Tumour size

Tumour size is an independent prognostic factor for pancreatic carcinoma. [5–7]

[Level of evidence – C.]

Optimally, three dimensions should be measured but, for staging purposes, at least the maximum dimension of the tumour should be measured. The tumour size is based on macroscopic assessment that is confirmed or amended on the basis of microscopy. This is often necessary for assessing tumour size in pancreatic cancer (which has a highly infiltrative growth pattern) and particularly following successful neoadjuvant therapy, when it can be very difficult to identify residual tumour macroscopically.[28] Use of wholemount blocks facilitates the measurement of tumour size.

In IPMNs, the size of the invasive component should be measured as accurately as possible. For unifocal invasive carcinomas, the largest dimension of the invasive focus should be measured. For multifocal invasive carcinomas in IPMNs, it is recommended that both the maximum dimension of the largest invasive tumour and the overall estimated size of all invasive foci in aggregate should be provided.[43] It is not yet clear which of these reflects the tumour burden more accurately.

5.2.4 Distance from tumour to nearest margin

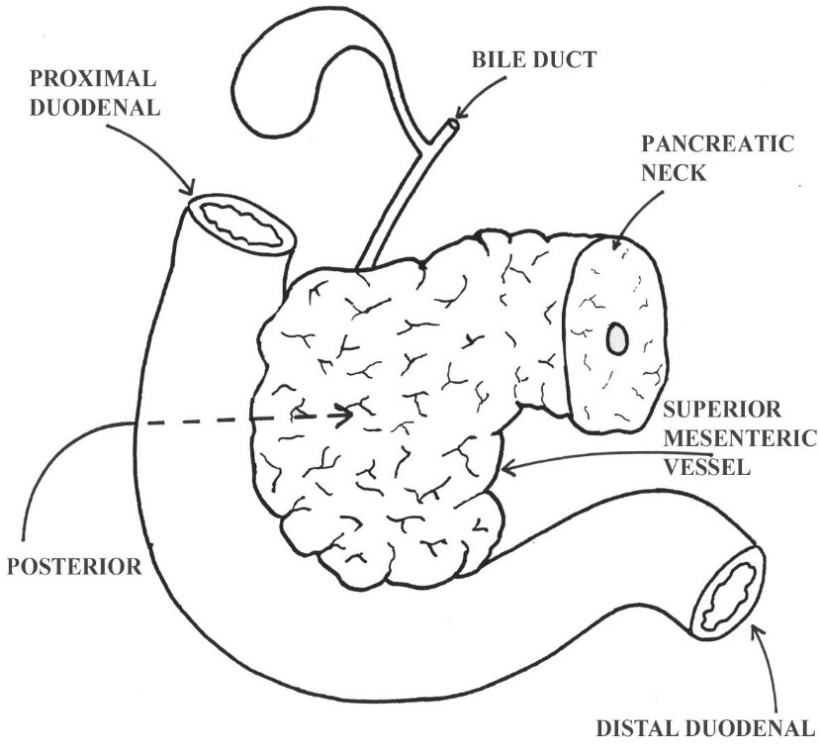
Completeness of excision should be assessed macroscopically and confirmed by microscopic examination. The transection margins are those of the pancreatic neck, common bile duct, superior mesenteric artery, jejunum and stomach/duodenum. The dissection or mobilisation margins are the superior mesenteric vein margin and the posterior margin (Figure 1a and Figure 3). The superior mesenteric vessel margin includes the superior mesenteric vein margin (defined as the smooth groove-like surface facing the superior mesenteric vein) and the superior mesenteric artery margin (defined as the rough area to the left of the superior mesenteric vein margin and facing the superior mesenteric artery; Figure 1a). The superior mesenteric artery margin is also referred to as the medial or uncinate margin. The resected

segment of superior mesenteric vein or portal vein will be found attached towards the cranial end of the mesenteric vein groove. The posterior margin is defined as the fibrous but smooth surface of the pancreatic head overlying the aorto-caval groove, which extends from the superior mesenteric artery margin to the posterior pancreatoduodenal groove.

The anterior surface of the pancreas (which extends from the superior mesenteric vein groove to the anterior pancreatoduodenal groove) is not a surgical margin but invasion of this surface has been shown to be associated with local recurrence and decreased survival time.[44,45]

The distance from the tumour to the nearest margins and surfaces should be recorded macroscopically, and refined by histological examination.

Figure 3: Resection margins for the head of the pancreas.



5.3 Microscopic core data items

The following are core data items:

- histological type of tumour
- tumour grade/histological differentiation
- size and maximum extent of local invasion
- perineural invasion
- named vessel involvement
- lymph node status (number present, number involved)
- resection margin status
- regression following neoadjuvant therapy
- histologically confirmed distant metastatic disease

- background abnormalities
- UICC TNM stage (8th edition)
- completeness of excision (R category)
- SNOMED codes.

5.4 Notes on microscopic assessment

5.4.1 Tumour type

The histological classification is based on the WHO typing of tumours of the exocrine pancreas, ampulla of Vater and extrahepatic bile duct[19] (Appendices C and D). Ductal adenocarcinoma, including its variants, accounts for 90% of pancreatic tumours. Recognition of the variants of PDAC is important because they can differ in clinical behaviour, e.g. colloid carcinoma has a significantly better prognosis than conventional PDAC.[46]

[Level of evidence – D.]

Unusual growth patterns of PDAC include clear cell,[47] foamy gland,[48] intestinal type,[49] large duct pattern and cystic papillary pattern,[50,51] but none of these is currently included as a variant of PDAC in the WHO classification.[19]

It is important to recognise and state whether an adenocarcinoma has arisen from an MCN (when the invasive tumour is typically a ductal type carcinoma) or from an IPMN (when the invasive carcinoma may be ductal type, colloid type or oncocytic type).[30,31] The five-year survival rate for resected invasive carcinoma arising in an MCN is 50–60%, which is much better than for non-MCN-related PDAC.[30,31] IPMNs with an associated invasive carcinoma may also have a better outcome than conventional PDAC, but this depends on the subtype of the invasive carcinoma. The prognosis for IPMNs associated with a colloid carcinoma or an oncocytic carcinoma (five-year survival rates of 60–90%) is significantly better than for IPMNs with associated PDAC. IPMNs with associated PDAC have a prognosis equivalent to that of conventional PDAC (five-year survival rate of 37% versus 16%).[52–54]

[Level of evidence – C.]

Adenocarcinomas originating in the ampulla of Vater have intestinal-type and/or pancreatobiliary-type differentiation, and this should be stated in the report. Immunohistochemistry may be helpful in making the distinction since intestinal-type carcinoma is CK20+, CDX2+ and MUC2+ while pancreatobiliary-type carcinoma is CDX2-, MUC1+ and MUC2-.[41] Pancreatobiliary-type adenocarcinoma of the ampulla has a poorer prognosis.[11]

5.4.2 Tumour grade

Histological grading of PDAC, moderately and poorly differentiated, according to the criteria of Klöppel *et al*[55] (Table 1), also has prognostic significance in most studies[2,56,57] and gives predictive values similar to those of the TNM grading system.[58]

[Level of evidence – C.]

The criteria used for grading PDAC are detailed in Table 1. The tumour is graded according to the least differentiated area, regardless of prevalence. Duct structures and nuclei are usually the most informative criteria. There is no published guidance on whether this system can be used for grading bile duct carcinoma and pancreatobiliary-type carcinoma of the ampulla.

Table 1: Histological grading of PDAC.[19,55]

Tumour grade/ differentiation	Duct structures	Nuclei	Mitotic figures per 10 high power fields*	Mucin production
Grade 1, well differentiated	Well-formed duct-like structures and tubular glands	Little polymorphism, polar arrangement	≤5	Intensive
Grade 2, moderately differentiated	Some well-formed duct-like structures and tubular glands	Moderate polymorphism	6–10	Irregular
Grade 3, poorly differentiated	Abortive mucoepidermoid and pleomorphic structures	Marked polymorphism and increased size	>10	Abortive

*High power field of Klöppel *et al*[55] measured 1,356 μm^2

5.4.3 Local invasion (pT stage)

UICC TNM staging for pancreatic carcinoma requires assessment of the maximum size of the tumour, which should be assessed by a combination of macroscopic and microscopic examination (see section 5.2.3). The UICC pT stage correlates well with prognosis.[59]

[Level of evidence – C.]

Since very small invasive carcinomas can be detected in MCNs and IPMNs, it was recently proposed that such small tumours are subdivided into pT1a for those that are ≤0.5 cm, pT1b for those that are >0.5 cm but ≤1 cm, and pT1c for those that are 1–2 cm.[31,43] This proposal has been adopted by the AJCC/UICC TNM 8th edition.[20]

T4 pancreatic tumours are locally advanced (involving the coeliac axis, superior mesenteric artery and/or common hepatic artery) and in the UK are considered to be unresectable.

If more than one invasive pancreatic cancer is present in the specimen, the specimen should be classified by the tumour with the highest T category, and the number of tumours should be indicated in parentheses after the T category (e.g. pT3[2]).

The UICC TNM staging systems for carcinomas of the distal extrahepatic bile duct and of the ampulla of Vater are different from that for pancreatic carcinoma (Appendix A).[20] Controversies about staging ampullary carcinomas are discussed in the review by Adsay *et al*,[60] and have also been addressed in the UICC TNM 8th edition.[20]

5.4.4 Perineural invasion

Perineural invasion is a histological characteristic of pancreatic carcinoma. There is a significant correlation between intrapancreatic neural invasion and extrapancreatic plexus invasion,[61] which is a major cause of local recurrence. Although the frequency of perineural invasion differs between studies, it remains a significant prognostic factor.[62–64]

[Level of evidence – C.]

5.4.5 Vascular invasion

Large named vessel involvement is a factor determining survival.[65] Radiological evidence of tumour extension into the coeliac axis (i.e. T4 tumour, Appendix A) is a contraindication for surgery. Resection of pancreatic carcinoma infiltrating the superior mesenteric artery or

hepatic artery is technically possible and performed in some European and North American centres.[35] However, it is currently a contraindication for surgery in the UK. Named venous involvement (i.e. portal vein or superior mesenteric vein) is not a contraindication to surgery, provided venous reconstruction is possible. Involvement is diagnosed histologically when there is a segment of vein wall attached to the resection specimen (in the superior mesenteric vein groove) that is clearly infiltrated by tumour (i.e. tumour invades into the media, with or without invasion of the intima). In a significant proportion of cases, however, there is no histological evidence of tumour invasion of the resected vessel wall, and the tethering of the vessel is caused by fibro-inflammatory changes. Controversy exists as to whether the presence or absence of microscopic tumour infiltration of the vessel wall influences survival.[35,64–66] Prognosis appears to be related to the depth of invasion of the vein wall; invasion of the media or intima (but not just the adventitia) is associated with a poor prognosis.[67]

5.4.6 Lymph node spread

The regional lymph nodes (Figure 2) for the pancreas and ampulla of Vater (according to UICC TNM) can be grouped into anterior pancreatoduodenal, posterior pancreatoduodenal, inferior (including the lymph nodes around the superior mesenteric vessels), common bile duct, infrapyloric (for tumours of head of pancreas or ampulla) and superior.[20] Coeliac lymph nodes (sent separately) are regional lymph nodes for tumours of the head of the pancreas only. Lymph nodes in the hilum of the spleen and tail of the pancreas are regional lymph nodes for tumours of the body and tail only.

The regional lymph nodes for the distal extrahepatic bile duct (according to UICC TNM) are along the common bile duct, common hepatic artery, back towards the coeliac trunk, posterior and anterior pancreaticoduodenal nodes, and nodes along the superior mesenteric vein and the right lateral wall of the superior mesenteric artery.[20]

In the Japan Pancreas Society (JPS) classification of lymph node stations[68] numbers are given to these groups of lymph nodes (Table 2). Lymph nodes 8 (around the common hepatic artery) and 16 (para-aortic) may be sent separately with pancreatoduodenectomy specimens.

Table 2: JPS classification of lymph node stations.[68]

JPS node stations	Equivalent UICC node stations
6	Infrapyloric
8	Common hepatic artery
9	Coeliac
10	Splenic hilum
11	Superior/along splenic artery
12	Hepatoduodenal ligament (portal/bile duct)
13	Posterior pancreatoduodenal
14	Superior mesenteric vessel
16	Para-aortic
17	Anterior pancreatoduodenal
18	Inferior

Lymph nodes around the common hepatic artery are considered to be regional lymph nodes in AJCC TNM and JPS systems, and in UICC TNM 8.[20] Para-aortic lymph nodes are not regional nodes, and metastases to these nodes are considered distant metastases (i.e. pM1).

The number of examined lymph nodes has been shown to influence survival; inadequate lymph node sampling results in understaging.[69,70] All of the lymph nodes in the specimen should be examined histologically. A Whipple's resection should usually yield a minimum of 15 lymph nodes from the main specimen.[5,70–72]

Direct invasion of a lymph node by the primary tumour may occur in the absence of non-contiguous nodal metastasis in up to 20% of resections. It has been suggested by some authors that direct invasion does not represent a true lymph node metastasis (i.e. via lymphatic spread) and that it is equivalent to pN0 prognostically.[73] Others have shown that direct invasion is associated with an outcome equivalent to that of a 'true' pN1 resection.[74,75] Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis in this dataset, and in UICC TNM 8.[20]

There is conflicting evidence on whether extracapsular lymph node spread in pancreatic cancer or ampullary cancer is a prognostic factor.[74,76] A very recent meta-analysis suggests that extracapsular spread is associated with a poorer prognosis, but the authors acknowledge that a standard definition is needed and that lymph nodes will need to be sampled with their entire surrounding fat to allow such assessment.[77] This assessment is not currently recommended for routine practice.

Multivariate analysis has shown lymph node involvement is a negative prognostic indicator in pancreatic carcinoma.[6, 78–80]

[Level of evidence – B.]

The lymph node ratio (the ratio of the number of lymph nodes with metastatic cancer to the total number of lymph nodes examined) is considered a more powerful prognostic marker than the overall nodal status in resected pancreatic cancer, with a lymph node ratio >20% significantly correlating with a poorer survival.[71,81,82]

[Level of evidence – C.]

The total number of positive lymph nodes also influences survival significantly.[75] Two studies of pancreatic carcinoma have shown that, with high numbers of examined lymph nodes, the number of positive lymph nodes is superior to the lymph node ratio in predicting survival[83,84] and can distinguish N categories (N0, N1, N2, N3 proposed by Strobel *et al*;[83] N0, N1, N2 proposed by Basturk *et al*[84]) that improve prognostic accuracy. UICC TNM 8 has now modified the N classification for pancreatic cancer to include pN1, metastases in one to three regional lymph nodes, and pN2, metastases in four or more regional lymph nodes.[20]

Two other studies have found that patients with pancreatic cancer and positive para-aortic lymph nodes (lymph node group 16) have significantly worse survival than cancer patients with negative para-aortic nodes.[85,86] This has led to the suggestion that detection of a positive para-aortic lymph node at frozen section should be a contraindication to pancreatoduodenectomy, but this has not yet been adopted into clinical practice.

In ampullary carcinoma, lymph node involvement and lymph node ratio are independent prognosticators.[87,88] The number of positive lymph nodes in ampullary cancer also influences survival, leading to a proposed nodal classification of N0, N1 (for one to three positive lymph nodes) and N2 (for four or more positive lymph nodes).[89,90] In extrahepatic bile duct carcinoma, increasing numbers of lymph node metastases are also associated with poorer survival.[91,92]

UICC TNM 8 has modified the N classifications for ampullary cancer and bile duct cancer to include pN1 and pN2 categories (Appendix A).[20] Although lymph node involvement in ampullary carcinoma is associated with a poorer prognosis, survival figures are still better than for node-positive pancreatic adenocarcinoma.

Lymph node micrometastases, detected by immunohistochemistry, are an adverse prognostic factor in many, but not all, studies.[85,93] The use of immunohistochemistry, however, is not currently recommended for routine practice.

5.4.7 Margins

The rates of microscopic margin involvement (R1) vary markedly between studies.[94] Although resection margin status is believed to be a key prognostic factor, the rates of margin involvement and local tumour recurrence are often incongruous.[5,7,8,71,95] The disparities in R1 rate and its prognostic value may be due to differences in opinion on what constitutes a resection margin, controversy over the definition of microscopic margin involvement and lack of standardisation of the histopathology examination of pancreatoduodenectomy specimens.[22] When a fully standardised, detailed pathology examination protocol is used, microscopic margin involvement is a common finding in pancreatic carcinoma (>75%) and correlates strongly with survival.[9,24,96,97]

[Level of evidence – B.]

Compared with pancreatic carcinoma, the rate of margin involvement is similar in common bile duct carcinoma and lower in ampullary carcinoma.[97–102] Microscopic margin involvement is more frequent in extrapancreatic bile duct carcinoma than in intrapancreatic bile duct carcinoma, and more frequently affects the periductal margin.[102] In pancreatic carcinoma, the posterior and superior mesenteric vessel margins are involved the most frequently.[9,24,96,97]

Currently, there is controversy over the adequate minimum clearance for pancreatic, common bile duct and ampullary carcinoma. While some pathologists define margin involvement when carcinoma is present at the margin (i.e. 0 mm clearance), others use the 1 mm rule adopted from margin assessment in rectal carcinoma. The growth pattern of pancreatobiliary-type cancer is infiltrative and discontinuous, unlike colorectal cancer, and there is growing evidence that a cut-off point of 0 mm to distinguish between adequate and inadequate resection is inappropriate for pancreatic cancer.[103] Studies have shown no significant difference in survival for patients with pancreatic carcinoma less than 1 mm from a margin compared with those with direct tumour involvement of a margin.[96,104] Other studies have shown that patients with a margin clearance of less than 1.5 mm have a long-term survival equivalent to those with directly involved resection margins (i.e. 0 mm clearance).[105,106] Moreover, involvement of transection margins (requiring lymphovascular division) is associated with a significantly shorter median survival than involvement of mobilisation margins.[107] Sampling is important, and there is a significant correlation between the number of tissue blocks taken and the likelihood of an R1 classification.[24]

In this dataset, carcinomas less than 1 mm from any resection margin are considered to be incompletely excised, while further studies are awaited.

[Level of evidence – D.]

Since the anterior surface of the pancreatic head is an anatomical surface, rather than a surgical margin, the rule of less than 1 mm does not apply, and this surface has to be breached by the tumour to be considered involved.

[Level of evidence – GPP.]

When there is no direct margin involvement by tumour, it is unclear whether those rare cases in which tumour cells are found within lymph nodes, lymphovascular channels or perineural clefts at, or less than 1 mm from, a resection margin should be classed as R1 resections.[9] In the UICC TNM classification, when tumour cells are found in the lumen of a lymphovascular channel at the resection margin, without contact with the endothelium, the classification is R0.[108] When the tumour is attached to the lumen of the vessel wall or invades the vessel wall

at the resection margin, a classification of R1 is appropriate.[108] Owing to the absence of evidence about lymph node or perineural involvement at a resection margin, it is recommended that such margin involvement be considered as incomplete excision if it is the only reason to report a case as a R1 resection. However, this should be clearly stated in the report.

[Level of evidence – GPP.]

5.4.8 Regression following neoadjuvant therapy

Neoadjuvant therapy is now increasingly used as an alternative to the 'surgery-first' approach in the treatment of patients with potentially resectable pancreatic cancer, especially for patients with borderline resectable disease. Neoadjuvant therapy potentially treats early micrometastatic disease and reduces tumour volume, increasing the likelihood of a complete resection. Pathologists have an important role in assessing the degree of tumour regression and completeness of excision in the resection specimen.

Several different schemes for assessing the degree of tumour regression have been proposed, based on assessment of either the amount of tumour destruction or the amount of residual tumour.[109–113] The histological grading of extent of residual tumour has been shown to be an independent prognostic factor for overall survival in multivariate analysis.[114]

[Level of evidence – C.]

The most widely used tumour regression grading systems for pancreatic cancer are those proposed by Evans *et al* and the College of American Pathologists (CAP).[110,113] The system proposed by Evans *et al* (reproduced in Table 3) assesses the percentage of tumour cell destruction.[110] This requires the pathologist to be able to recognise the presumed area of initial (pre-therapy) tumour and assess the proportion now occupied by viable neoplastic cells. The Evans *et al* system does include the option to record abundant mucin pools. Acellular mucin pools are not considered residual tumour, but their presence should prompt the pathologist to search carefully for viable tumour cells.

Table 3: The tumour regression grading system of Evans *et al*.[110]

Grade	Extent of tumour cell destruction/residual tumour
I	Little (<10%) or no tumour destruction
2a	Destruction of 10–50% of tumour cells
2b	Destruction of 51–90% of tumour cells
3/3M*	Few (<10%) viable-appearing tumour cells
4/4M*	No viable tumour cells

*Addition of the M suffix indicates abundant residual mucin pools.

CAP (2016) proposes a four-tiered system (reproduced in Table 4) and originally applied to rectal cancer.[113] It is based on the amount of residual tumour, but there is no specific reference to acellular mucin pools.

Table 4: The CAP tumour regression grading system.[113]

Grade	Proportion of residual viable tumour
0	No viable cancer cells (complete histological response)
1	Single cells or rare small groups of cancer cells (near complete response)

2	Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response)
3	Extensive residual cancer with no evident tumour regression (poor or no response)

Patients with a complete response (CAP grade 0, Evans grade 4) or minimal residual disease (CAP grade 1, Evans grade 3) have better disease-free and overall survival than patients with moderate or no response. There is no difference in disease-free survival or overall survival between CAP grades 2 and 3. This has led Chatterjee *et al* to propose a modified (three-tiered) CAP grading system (Table 5),[114] which they suggest is simpler to use and more likely to improve inter-observer agreement.[115]

Table 5: The tumour regression grading system of Chatterjee *et al*.[114]

Grade	Proportion of residual viable tumour
0	No residual cancer
1	Minimal residual cancer (single cells or small groups of cancer cells, <5% residual cancer)
2	5% or more residual cancer

The CAP system is recommended for this dataset since it is used for other organs and is simple to use. Furthermore, it is easier to recognise and assess residual tumour than to estimate what tumour has been destroyed.

[Level of evidence – GPP.]

Extensive sampling of resection specimens following neoadjuvant therapy is essential. After inadequate sampling, complete tumour regression rates as high as 10–33% have been reported, but these fall to <3% with thorough sampling.[28,114,116]

Since neoadjuvant therapy can influence tumour morphology, the grade of tumour differentiation of residual cancer is not reported.

Assessing resection margin status post-neoadjuvant therapy is difficult, and reported R1 rates range from 0 to 100%.[28,117] Following a response to neoadjuvant therapy, the number of tumour cells is reduced, and the distances between remaining tumour cells increases. Therefore, the improved outcome of tumours greater than 1 mm from a given resection margin, compared with those less than 1 mm away, in the non-neoadjuvant therapy setting, may not be applicable in this circumstance.[28] The appropriate distance for a clear margin following neoadjuvant therapy is yet to be determined, but 5 mm has been proposed by Liu *et al*.[118] The prognostic significance of acellular mucin pools at resection margins is also unknown. However, their presence does suggest that, before neoadjuvant therapy, the tumour is likely to have extended beyond the surgical resection field. This has led to the proposal in colorectal cancer management that the presence of mucin at the margin of a neoadjuvant resection is an indicator for further surgery (whenever possible) if detected at frozen section.[119] It seems prudent to adopt this approach for post-neoadjuvant therapy pancreatic resection margin assessment at frozen section. When assessing margins in the resection specimen following neoadjuvant therapy, it is suggested that the distance between tumour cells and the nearest resection margin is recorded in the final report. When acellular mucin pools are present at, or close to, the margin(s), this should also be noted in the report.

[Level of evidence – GPP.]

For tumour staging following preoperative therapy, only the presence of tumour cells in the resection specimen is used to determine the stage. Fibrosis, haemorrhage, necrosis, inflammation and acellular mucin are ignored. Cases with complete regression are therefore recorded as ypT0 ypN0.

5.4.9 Histologically confirmed distant metastatic disease

The presence of histologically confirmed distant metastases (pM1) and their site should be recorded.

Metastases to the liver, peritoneum, omentum or extra-abdominal sites are contraindications for resection in PDAC.[120]

5.4.10 Background abnormalities

As stated in section 5.2.2, the presence of microscopic precursor lesions (e.g. ampullary adenoma, flat dysplasia) may be helpful in determining the primary origin of a tumour.

PanIN[38] is the most common precursor to PDAC but is a frequent finding in all pancreatic resections, including those for non-neoplastic disease.[38,39] The presence of an underlying IPMN or MCN should always be recorded.[43,121]

[Level of evidence – C.]

6 Non-core data items

6.1 Macroscopic

The following are non-core data items:

- specimen measurements for each organ
- recording whether or not there is a stent in place.

6.2 Microscopic

Small vessel invasion is common in resections for pancreatic cancer and is considered by some to be an adverse prognostic factor.[122] Detection may be influenced by the number of tumour blocks sampled and the use of additional stains, such as elastic van Gieson. Microvascular invasion may also be mistaken for PanIN when invasive tumour cells replace the endothelial cells, such that the vascular lumen is surrounded by neoplastic cells. The presence of smooth muscle around such a structure will confirm that it is vascular invasion.[123]

6.3 Other markers

A number of molecular markers, such as K-ras, SMAD4, S100A6 and cyclin E, have prognostic value following resection, but use of such molecular or immunohistochemical studies in routine practice is currently not justified.[25,26,124–127]

7 Diagnostic coding

Tumours should be coded according to the SNOMED system (see Appendices B and C).

8 Pathological staging

Multivariate analysis shows that tumour stage is the most significant factor in predicting long-term survival in pancreatic carcinoma.[59] The UICC TNM classification obtained from the histopathological data can be converted to a stage grouping,[20] but full clinical data will need to be taken into account before the final stage can be determined.

9 Reporting of diagnostic biopsy specimens

Preoperative diagnosis is usually made on the basis of cytology (including fine needle biopsy) in combination with imaging. Ampullary biopsies may be taken at upper endoscopy. Liver biopsies may be taken for exclusion of metastatic disease, and intraoperative pancreas biopsies may be taken to establish or confirm the diagnosis. Distinction between metastasis and benign biliary lesions in the liver, and distinction between pancreatic adenocarcinoma and chronic pancreatitis, are discussed in section 10.

10 Reporting of frozen sections

The most common indications for intraoperative frozen section diagnosis are as follows:[128,129]

- histological confirmation of the primary diagnosis
- assessment of the presence or absence of carcinoma or IPMN at the pancreatic transection margin
- the presence of carcinoma at the bile duct margin
- histological confirmation of a potentially metastatic nodule in the liver, the peritoneum or a lymph node.

Distinction between a liver metastasis and a bile duct hamartoma or bile duct adenoma (peribiliary gland hamartoma) may be problematic. The presence of necrosis, desmoplastic stroma, irregularity of ducts, apoptosis, cellular atypia or mitoses in ducts all favour a diagnosis of malignancy,[129] as does extension of atypical glands into the adjacent liver or along portal tracts.

[Level of evidence – GPP.]

The distinction between pancreatitis and adenocarcinoma in the pancreas may also be difficult on frozen section because of cautery or freezing artefacts, or the distortion and reactive nuclear atypia in small residual ductules in chronic pancreatitis. Often a low-power microscopic view is most useful for identifying the lack of a lobular distribution of the ducts and the irregularity of duct outline in adenocarcinoma. In chronic pancreatitis, the lobular architecture is preserved, the intralobular stroma is paler than the dense collagen that surrounds the lobules and there is no cellular desmoplastic stroma. In the normal pancreas, ducts do not run alongside muscular blood vessels. Therefore, the presence of an atypical duct adjacent to a muscular blood vessel should be considered suspicious for adenocarcinoma.

[Level of evidence – GPP.]

The distinction between adenocarcinoma and chronic pancreatitis on the basis of ductular architecture and cytological atypia can be difficult. The major and minor criteria established by Hyland *et al*[130] for distinguishing neoplastic from non-neoplastic ducts on frozen section are equally applicable to formalin-fixed, paraffin-embedded tissue.[129,130]

Assessment of the pancreatic transection (neck) margin or the bile duct margin for invasive carcinoma should include microscopic examination of the peripancreatic or periductal connective tissue (as well as the pancreas and bile duct), since this may be the only site of tumour infiltration.

It has been shown that PanIN-3 at the transection margin (in the absence of invasive carcinoma) does not influence outcome in patients with PDAC.[131] This reflects the fact that survival after resection for pancreatic carcinoma is generally too short for PanIN to become prognostically significant.[129] However, in patients with a small invasive carcinoma without evidence of lymph node metastases, or in those undergoing resection for benign disease, the presence of PanIN-3 at the transection margin may justify consideration of further resection, and this should be mentioned in the intraoperative report.

Frozen section of the transection margin may be used to determine whether an IPMN (with or without associated invasive carcinoma) is completely excised and to check if duct dilatation is due to tumour involvement or is secondary to obstruction.[129,132] Frozen section in IPMN, however, does have limitations, particularly because there may be erosion of the duct epithelium, duct inflammation and reactive epithelial atypia. The duct epithelium may be denuded, in which case deeper levels should be cut from the tissue block and/or further tissue samples should be requested from the surgeon. In the absence of any duct epithelium for assessment, the pathologist cannot state whether (non-invasive) neoplasm is present at the margin or not.[129]

11 Criteria for audit of the dataset

It is recommended that MDTs and/or pathology departments audit their pathology reports at regular intervals (perhaps yearly) to ensure the completeness of data within the reports. Considering the standard of pathology, there is currently little evidence on the frequencies with which important adverse prognostic features are found by individual pathologists. It has been reported that the mean harvest of lymph nodes from a Whipple's resection should be at least 15 nodes[5,69,71] and that the number of retrieved lymph nodes does influence survival.[69,70,88] Therefore, to evaluate the standard of pathology dissection, it is recommended that in a series of Whipple's resections for carcinoma, the mean number of lymph nodes examined should be 15. As more evidence accumulates, it may be possible to adjust this level and to introduce other outcome measures for pathology.

12 References

1. Verbeke CS, Gladhaug IP. Resection margin involvement and tumour origin in pancreatic head cancer. *Br J Surg* 2012;99:1036–1049.

2. Cross SS, Feeley KM, Angel CA. The effect of four interventions on the informational content of histopathology reports of resected colorectal carcinomas. *J Clin Pathol* 1998;51:481–482.

3. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 2015;220:530–536.

4. Cleary SP, Gryfe R, Guindi M, Greig P, Smith L, Mackenzie R *et al*. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5 year survivors. *J Am Coll Surg* 2004;198:722–731.

5. Han SS, Jang JY, Kim SW, Kim WH, Lee KU, Park YH. Analysis of long-term survivors after surgical resection for pancreatic cancer. *Pancreas* 2006;32:271–275.

6. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J *et al.* 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006;10:1199–1210.

7. Moon HJ, An JY, Heo JS, Choi SH, Joh JW, Kim YI. Predicting survival after surgical resection for pancreatic ductal adenocarcinoma. *Pancreas* 2006;32:37–43.

8. Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH *et al.* Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg* 2007;246:52–60.

9. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H *et al.* Most pancreatic cancer resections are R1 resections. *Ann Surg Oncol* 2008;15:1651–1660.

10. Fisher WE, Bakey ME. Differences between ampullary, periampullary and pancreatic cancer. *World J Surg* 2007;31:144–146.

11. Robert PE, Leux C, Ouaissi M, Miguet M, Paye F, Merdrignac A *et al.* Predictors of long-term survival following resection for ampullary carcinoma: a large retrospective French multicentric study. *Pancreas* 2014;43:692–697.

12. Hong SM, Cho H, Lee O, Ro JY. The number of metastatic lymph nodes in extrahepatic bile duct carcinoma as a prognostic factor. *Am J Surg Pathol* 2005;29:1177–1183.

13. Jang JY, Kim SW, Park DJ, Ahn YJ, Yoon YS, Choi MG *et al.* Actual long-term outcome of extrahepatic bile duct cancer after surgical resection. *Ann Surg* 2005;241:77–84.

14. Nomura T, Tsuchiya Y, Nashimotos A, Yabusaki H, Takii Y, Nagagawa S *et al.* Prognostic factors for radical resection of middle and distal bile duct cancer. *Hepatogastroenterology* 2009;56:294–298.

15. Kwon HJ, Kim SG, Chun JM, Lee WK, Hwang YJ. Prognostic factors in patients with middle and distal bile duct cancers. *World J Gastroenterol* 2014;20:6658–6665.

16. Andrianello S, Paiella S, Allegrini V, Ramera M, Pulvirenti A, Malleo G *et al.* Pancreaticoduodenectomy for distal cholangiocarcinoma: surgical results, prognostic factors, and long-term follow-up. *Langenbecks Arch Surg* 2015;400:623–628.

17. Feakins R, Campbell F, Verbeke CS. Survey of UK histopathologists' approach to the reporting of resection specimens for carcinomas of the pancreatic head. *J Clin Pathol* 2013;66:715–717.

18. Rau BM, Moritz K, Schuschan S, Alsfasser G, Prall F, Klar E. R1 resection in pancreatic cancer has significant impact on long-term outcome in standardized pathology modified for routine use. *Surgery* 2012;152:S103–111.

19. IARC, Bosman FT, Carneiro F, Hruban RH, Tniese ND. *WHO Classification of Tumors of the Digestive System (4th edition).* Lyon, France: IARC Press, 2010.

20. Brierley JD, Gospodarowicz MK, Wittekind C (eds). *TNM Classification of Malignant Tumours (8th edition)*. Oxford, UK: Wiley-Blackwell, 2017.

21. Luong TV, Watkins J, Chakrabarty B, Wang LM. *Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract*. London, UK: The Royal College of Pathologists (In preparation).

22. Verbeke CS. Resection margins and R1 rates in pancreatic cancer – are we there yet? *Histopathology* 2008;52:787–796.

23. Campbell F, Verbeke CS. Specimen Dissection and Sampling. *In:* Campbell F, Verbeke CS (eds). *Pathology of the pancreas – a practical approach*. London, UK: Springer-Verlag, 2013.

24. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. *Br J Surg* 2006;93:1232–1237.

25. Ohigashi H, Ishikawa O, Sasaki Y, Yamada T, Furukawa H, Imaoka S *et al.* K-ras point mutation in the nerve plexuses around the superior mesenteric artery in resectable adenocarcinoma of the pancreatic head: distribution pattern and related factors. *Arch Surg* 2000;135:1450–1455.

26. Kim J, Reber HA, Dry SM, Elashoff D, Chen SL, Umetani N *et al.* Unfavourable prognosis associated with K-ras gene mutation in pancreatic cancer surgical margins. *Gut* 2006; 55:1598–1605.

27. Chatterjee D, Katz MH, Rashid A, Estrella JS, Wang H, Varadhachary GR *et al.* Pancreatic intraepithelial neoplasia and histological changes in non-neoplastic pancreas associated with neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma. *Histopathology* 2013;63:841–851.

28. Verbeke C, Lohr M, Karlsson JS, Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. *Cancer Treatment Rev* 2015; 41:17–26.

29. Del Chiaro M, Verbeke C, Salvia R, Kloppel G, Werner J, McKay C *et al.* European experts consensus statement on cystic tumours of the pancreas. *Dig Liver Dis* 2013;45:703–711.

30. Campbell F, Verbeke CS. Intraductal Papillary Neoplasm. *In:* Campbell F, Verbeke CS (eds). *Pathology of the pancreas – a practical approach*. London, UK: Springer-Verlag, 2013.

31. Tanaka M, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY *et al.* International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012;12:183–197.

32. Diener MK, Heukäufer C, Schwarzer G, Seiler CM, Antes G, Buchler M *et al.* Pancreaticoduodenectomy (classic Whipple) versus pylorus-preserving pancreaticoduodenectomy (pp Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database Syst Rev* 2008; 6:CD006053.

33. Seiler CA, Wagner M, Bachmann T, Redaelli CA, Schmied B, Uhl W *et al.* Randomized clinical trial of pylorus-preserving duodenopancreatectomy versus classical Whipple resection – long term results. *Br J Surg* 2005;92:547–556.

34. Tran KT, Smeenk HG, van Eijck CH, Kazemier G, Hop WC, Greve JW *et al.* Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective randomized, multicenter analysis of 170 patients with pancreatic or periampullary tumors. *Ann Surg* 2004;240:738–745.

35. Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK *et al.* En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. *Ann Surg* 2008; 247:300–309.

36. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK *et al.* Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. *Ann Surg* 2002;236:355–368.

37. Farnell MB, Aranha GV, Nimura Y, Michelassi F. The role of extended lymphadenectomy for adenocarcinoma of the head of the pancreas: strength of the evidence*. J Gastrointest Surg* 2008;12:651–656.

38. Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN *et al.* Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001;25:579–586.

39. Agoff SN, Crispin DA, Bronner MP, Dail DH, Hawes SE, Haggitt RC. Neoplasms of the ampulla of Vater with concurrent pancreatic intraductal neoplasia: a histological and molecular study. *Mod Pathol* 2001;14:139–146.

40. Campbell F, Verbeke CS. *Pathology of the pancreas – a practical approach*. London, UK: Springer-Verlag, 2013.

41. Ang DC, Shia J, Tang LH, Katabi N, Klimstra DS. The utility of immunohistochemistry in subtyping adenocarcinoma of the ampulla of Vater. *Am J Surg Pathol* 2014;38:1371–1379.

42. Adsay V, Ohike N, Tajiri T, Kim GE, Krasinskas A, Balci S *et al.* Ampullary region carcinomas. Definition and site specific classification with delineation of four clinicopathologically and prognostically distinct subtypes in an analysis of 249 cases. *Am J Surg Pathol* 2012;36:1592–1608.

43. Adsay V, Mino-Kenudson M, Furukawa T, Basturk O, Zamboni G, Marchegiani G *et al.* Pathologic evaluation and reporting of intraductal papillary mucinous neoplasms of the pancreas and other tumoral intraepithelial neoplasms of pancreatobiliary tract. *Ann Surg* 2015;263:162–177.

44. Nagakawa T, Nagamori M, Futakami F, Tsukioka Y, Kayahara M, Ohta T *et al.* Results of extensive surgery for pancreatic carcinoma. *Cancer* 1996;77:640–645.

45. Nagakawa T, Sanada H, Inagaki M, Sugama J, Ueno K, Konishi I *et al*. Long-term survivors after resection of the head of the pancreas: significance of histologically curative resection. *J Hepatobiliary Pancreat Surg* 2004;11:402–408.

46. Adsay NV, Pierson C, Sarkar F, Abrams J, Weaver D, Conlon KC *et al*. Colloid (mucinous non-cystic) carcinoma of the pancreas. *Am J Surg Pathol* 2001;25:26–42.

47. Ray S, Lu Z, Rajendiran S. Clear cell ductal adenocarcinoma of pancreas: a case report and review of the literature. *Arch Pathol Lab Med* 2004;128:693–696.

48. Adsay V, Logani S, Sarkar F, Crissman J, Vaitkevicius V. Foamy gland pattern of pancreatic ductal adenocarcinoma: a deceptively benign-appearing variant. *Am J Surg Pathol* 2000; 24:493–504.

49. Albores-Saavedra J, Simpson K, Dancer YJ, Hruban R. Intestinal type adenocarcinoma: a previously unrecognized histologic variant of ductal carcinoma of the pancreas. *Ann Diagn Pathol* 2007;11:3–9.

50. Bagci P, Andea AA, Basturk O, Jang KT, Erbarut I, Adsay V. Large duct type invasive adenocarcinoma of the pancreas with microcystic and papillary patterns: a potential microscopic mimic of non-invasive ductal neoplasia. *Mod Pathol* 2012;25:439–448.

51. Kelly PJ, Shinagare S, Sainani N, Hong X, Ferrone C, Yilmaz O *et al.* Cystic papillary pattern in pancreatic ductal adenocarcinoma: a heretofore undescribed morphological pattern that mimics intraductal papillary mucinous carcinoma. *Am J Surg Pathol* 2012;36:696–701.

52. Mino-Kenudson M, Fernandez-del Castillo C, Baba Y, Valsangkar NP, Liss AS, Hsu M *et al.* Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. *Gut* 2011;60:1712–1720.

53. Nakata K, Ohuchida K, Aishima S, Sadakari Y, Kayashima T, Miyasaka Y *et al.* Invasive carcinoma derived from intestinal-type intraductal papillary mucinous neoplasm is associated with minimal invasion, colloid carcinoma, and less invasive behaviour, leading to a better prognosis. *Pancreas* 2001;40:58–1587.

54. Yopp AC, Katabi N, Janakos M, Klimstra DS, D'Angelica MI, DeMatteo RP *et al.* Invasive carcinoma arising in intraductal papillary mucinous neoplasm of the pancreas: a matched control study with conventional pancreatic ductal adenocarcinoma. *Ann Surg* 2011;253:968–974.

55. Klöppel G, Lingenthal G, von Bülow M, Kern HF. Histological and fine structural features of pancreatic ductal adenocarcinomas in relation to growth and prognosis: studies in xenografted tumours and clinico-pathological correlation in a series of 75 cases. *Histopathology* 1985;9:841–856.

56. Kuhlmann KF, de Castro SM, Wesseling JG, ten Kate FJ, Offerhaus GJ, Busch OR *et al.* Surgical treatment of pancreatic adenocarcinoma; actual survival and prognostic factors in 343 patients. *Eur J Cancer* 2004;40:549–558.

57. Shoup M, Conlon KC, Klimstra D, Brennan MF. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? *J Gastrointest Surg* 2003;7:946–952.

58. Giulianotti PC, Boggi U, Fornaciari G, Bruno J, Rossi G, Giardino D *et al.* Prognostic value of histological grading in ductal adenocarcinoma of the pancreas: Kloppel vs TNM grading. *Int J Pancreatol* 1995;17:279–288.

59. Isaji S, Kawarada Y, Uemoto S. Classification of pancreatic cancer: comparison of Japanese and UICC classifications. *Pancreas* 2004;28:231–234.

60. Adsay NV, Bagci P, Tajiri T, Oliva I, Ohike N, Balci S *et al.* Pathologic staging of pancreatic, ampullary, biliary, and gallbladder cancers: pitfalls and practical limitations of the current AJCC/UICC TNM staging system and opportunities for improvement. *Sem Diagn Pathol* 2012;29:127–141.

61. Kayahara M, Nagakawa T, Konishi I, Ueno K, Ohta T, Miyazaki I. Clinicopathological study of pancreatic carcinoma with particular reference to the invasion of the extrapancreatic neural plexus. *Int J Pancreatol* 1991;10:105–111.

62. Ozaki H, Hiraoka T, Mizumoto R, Matsuno S, Matsumoto Y, Nakayama T *et al.* The prognostic significance of lymph node metastasis and intrapancreatic perineural invasion in pancreatic cancer after curative resection. *Surg Today* 1999;29:16–22.

63. Shimada K, Sakamoto Y, Sano T, Kosuge T, Hiraoka N. Reappraisal of the clinical significance of tumor size in patients with pancreatic ductal carcinoma. *Pancreas* 2006;33:233–239.

64. van Roest MH, Gouw AS, Peeters PM, Porte RJ, Slooff MJ, Fidler V *et al.* Results of pancreaticoduodenectomy in patients with periampullary adenocarcinoma: perineural growth more important prognostic factor than tumor localization. *Ann Surg* 2008;248:97–103.

65. Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S. Survival benefits of portal vein resection for pancreatic cancer. *Am J Surg* 2003;186:149–153.

66. Tseng JF, Tamm EP, Lee JE, Pisters PW, Evans DB. Venous resection in pancreatic cancer surgery. *Best Prac Res Clin Gastroenterol* 2006;20:349–364.

67. Fukuda S, Oussoultzoglou E, Bachellier P, Rosso E, Nakano H, Audet M *et al.* Significance of the depth of portal vein wall invasion after curative resection for pancreatic adenocarcinoma. *Arch Surg* 2007;142:172–179.

68. Kondo S. Japanese Pancreas Society staging systems for pancreatic cancer. *In:* Neoptolemos JP, Urrutia R, Abbruzzese J, Buchler MW (eds). *Pancreatic cancer*. New York, USA: Springer Science + Business Media, LLC, 2010.

69. Tomlinson JS, Jain S, Bentrem DJ, Sekeris EG, Maggard MA, Hines OJ *et al.* Accuracy of staging node-negative pancreas cancer: a potential quality measure. *Arch Surg* 2007;142: 767–774.

70. Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. *Ann Surg Oncol* 2006;13:1189–1200.

71. Sierzega M, Popiela T, Kulig J, Nowak K. The ratio of metastatic/resected lymph nodes is an independent prognostic factor in patients with node-positive pancreatic head cancer. *Pancreas* 2006;33:240–245.

72. Valsangkar NP, Bush DM, Michaelson JS, Ferrone CR, Wargo JA, Lillemoe KD *et al.* N0/N1, PNL or LNR? The effect of lymph node number on accurate survival prediction in pancreatic ductal adenocarcinoma. *J Gastroint Surg* 2013;17:257–266.

73. Pai RK, Beck AH, Mitchem J, Linehan DC, Chang DT, Norton JA *et al.* Pattern of lymph node involvement and prognosis in pancreatic adenocarcinoma: direct lymph node invasion has similar survival to node negative disease. *Am J Surg Pathol* 2011;35:228–234.

74. Buc E, Couvelard A, Kwiatkowski F, Dokmak S, Ruszniewski P, Hammel P *et al.* Adenocarcinoma of the pancreas: does prognosis depend on mode of lymph node invasion? *Eur J Surg Oncol* 2014;40:1578–1585.

75. Konstantinidis IT, Deshpande V, Zheng H, Wargo JA, Fernandez-del Castillo C, Thaver SP *et al. Does* the mechanism of lymph node invasion affect survival in patients with pancreatic ductal adenocarcinoma? *J Gastroint Surg* 2010;4:261–267.

76. Prenzel KL, Holscher AH, Drebber U, Bollschweiler E, Gutschow CA, Stipple DL *et al.* Extracapsular lymph node spread as a negative prognostic factor of adenocarcinoma of the pancreas and cancer of the papilla of Vater. *Pancreas* 2014;43:64–68.

77. Luchini C, Veronese N, Pea A, Sergi G, Manzato E, Nottegar A *et al*. Extranodal extension in N1-adenocarcinoma of the pancreas and papilla of Vater: a systematic review and meta-analysis of its prognostic significance. *Eur J Gastroenterol Hepatol* 2016;28:205–209.

78. Shimada K, Sakamoto Y, Sano T, Kosuge T. Prognostic factors after distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail. *Surgery* 2006;139:288–295.

79. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-del Castillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. *J Clin Oncol* 2006;24:2897–2902.

80. Schnelldorfer T, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R *et al.* Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? *Ann Surg* 2008; 247:456–462.

81. Berger AC, Watson JC, Ross EA, Hoffman JP. The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg* 2004;70:235–240.

82. Pawlik TM, Gleisner AL, Cameron JL, Winter JM, Assumpcao L, Lillemoe KD *et al.* Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. *Surgery* 2007;141:610–618.

83. Strobel O, Hinz U, Gluth A, Hank T, Hackert T, Bergmann F *et al.* Pancreatic adenocarcinoma: number of positive nodes allows to distinguish several N categories. *Ann Surg* 2015;261:961–969.

84. Basturk O, Saka B, Balci S, Postlewait LM, Knight J, Goodman M *et al.* Substaging of Lymph Node Status in Resected Pancreatic Ductal Adenocarcinoma Has Strong Prognostic Correlations: Proposal for a Revised N Classification for TNM Staging. *Ann Surg Oncol* 2015;22:S1187–1195.

85. Schwarz L, Lupinacci RM, Svrcek M, Lesurtel M, Bubenheim M, Vuarnesson H *et al.* Para-aortic lymph node sampling in pancreatic head adenocarcinoma. *Br J Surg* 2014;101:530–538.

86. Paiella S, Malleo G, Maggino L, Bassi C, Salvia R, Butturini G. Pancreatectomy with para-aortic lymph node dissection for pancreatic head adenocarcinoma: Pattern of nodal metastasis spread and analysis of prognostic factors. *J Gastrointest Surg* 2015;19:1610–1620.

87. Brown KM, Tompkins AJ, Yong S, Aranha GV, Shoup M. Pancreaticoduodenectomy is curative in the majority of patients with node-negative ampullary cancer. *Arch Surg* 2005;140:529–533.

88. Falconi M, Crippa S, Dominguez I, Barugola G, Capelli P, Marcucci S *et al.* Prognostic relevance of lymph node ratio and number of resected nodes after curative resection of ampulla of Vater carcinoma. *Ann Surg Oncol* 2008;15:3178–3186.

89. Kang HJ, Eo SH, Kim SC, Park KM, Lee YJ, Lee SK *et al.* Increased number of metastatic lymph nodes in adenocarcinoma of the ampulla of Vater as a prognostic factor: a proposal of new nodal classification. *Surgery* 2014;155:74–84.

90. Balci S, Basturk O, Saka B, Bagci P, Postlewait LM, Tajiri T *et al.* Substaging Nodal Status in Ampullary carcinomas has significant prognostic value: Proposed revised staging based on an analysis of 313 well-characterized cases. *Ann Surg Oncol* 2015;22;4392–4401.

91. Hong SM, Cho H, Lee OJ, Ro JY. The number of metastatic lymph nodes in extrahepatic bile duct carcinoma as a prognostic factor. *Am J Surg Pathol* 2005;29:1177–1183.

92. Kim BH, Kim K, Chie EK, Kwon J, Jang JY, Kim SW *et al.* The prognostic importance of the number of metastatic lymph nodes for patients undergoing curative resection followed by adjuvant chemoradiotherapy for extrahepatic bile duct cancer. *Gastrointest Surg* 2015;19: 1833–1841.

93. Bogoevski D, Yekebas EF, Schurr P, Kaifi JT, Kutup A, Erbersdobler A *et al*. Mode of spread in the early phase of lymphatic metastasis in pancreatic ductal adenocarcinoma: prognostic significance of nodal microinvolvement. *Ann Surg* 2004;240:993–1001.

94. Chandrasegaram MD, Goldstein D, Simes J, Gebski V, Kench JG, Gill AJ *et al.* Meta-analysis of radical resection rates and margin assessment in pancreatic cancer. *Br J Surg* 2015;102:1459–1472.

95. Jarufe NP, Coldham C, Mayer AD, Mirza DF, Buckels JA, Bramhall SR. Favourable prognostic factors in a large UK experience of adenocarcinoma of the head of the pancreas and periampullary region. *Dig Surg* 2004;21:202–209.

96. Campbell F, Smith RA, Whelan P, Sutton R, Raraty M, Neoptolemos JP *et al.* Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. *Histopathology* 2009;55:277–283.

97. Menon KV, Gomez D, Smith AM, Anthoney A, Verbeke CS. Impact of margin status on survival following pancreatoduodenectomy for cancer: the Leeds Pathology Protocol (LEEPP*). HPB (Oxford)* 2009;11:18–24.

98. van Geenen RC, van Gulik TM, Offerhaus GJ, de Wit LT, Busch OR, Obertop H *et al.* Survival after pancreaticoduodenectomy for periampullary adenocarcinoma: an update. *Eur J Surg Oncol* 2001;27:549–557.

99. de Castro SM, van Heek NT, Kuhlmann KF, Busch OR, Offerhaus GJ, van Gulik TM *et al.* Surgical management of neoplasms of the ampulla of Vater: local resection or pancreatoduodenectomy and prognostic factors for survival. *Surgery* 2004;136:994–1002.

100. Katz MH, Bouvet M, Al-Refaie W, Gilpin EA, Moossa AR. Non-pancreatic periampullary adenocarcinomas: an explanation for favorable prognosis. *Hepatogastroenterology* 2004;51:842–846.

101. Schmidt CM, Powell ES, Yiannoutsos CT, Howard TJ, Wiebke EA, Wiesenauer CA *et al.* Pancreaticoduodenectomy: a 20-year experience in 516 patients. *Arch Surg* 2004;139:718–727.

102. Kamposioras K, Anthoney A, Fernandez Moro C, Cairns A, Smith AM, Liaskos C *et al.* Impact of intrapancreatic or extrapancreatic bile duct involvement on survival following pancreatoduodenectomy for common bile duct cancer. *Br J Surg* 2014;101:89–99.

103. Verbeke CS, Knapp J, Gladhaug IP. Tumour growth is more dispersed in pancreatic head cancers than in rectal cancer: implications for resection margin assessment. *Histopathology* 2011;59:1111–1121.

104. Van den Broeck A, Sergeant G, Ectors N, Van Steenbergen W, Aerts R, Topal B. Patterns of recurrence after curative resection of pancreatic ductal adenocarcinoma. *Eur J Surg Oncol* 2009;35:600–604.

105. Chang DK, Johns AL, Merrett ND, Gill AJ, Colvin EK, Scarlett CJ *et al.* Margin clearance and outcome in resected pancreatic cancer. *J Clin Oncol* 2009;27:2855–2862.

106. Jamieson NB, Chan NI, Foulis AK, Dickson EJ, McKay CJ, Carter CR. The prognostic influence of resection margin clearance following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. *J Gastrointest Surg* 2013;17:511–521.

107. Jamieson NB, Foulis AK, Oien KA, Going JJ, Glen P, Dickson EJ *et al.* Positive mobilization margins alone do not influence survival following pancreatico-duodenectomy for pancreatic ductal adenocarcinoma. *Ann Surg* 2010;251:1003–1010.

108. Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumour classification revisited. *Cancer* 2002;94:2511–2516.

109. Ishikawa O, Ohhigashi H, Teshima T, Chatani M, Inoue T, Tanaka S *et al.* Clinical and histopathological appraisal of preoperative irradiation for adenocarcinoma of the pancreatoduodenal region. *J Surg Oncol* 1989;40:143–151.

110. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B *et al.* Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 1992;127:1335–1339.

111. Breslin TM, Hess KR, Harbison DB, Jean ME, Cleary KR, Dackiw AP *et al.* Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. *Ann Surg Oncol* 2001;8:123–132.

112. White RR, Xie HB, Gottfried MR, Czito BG, Hurwitz HI, Morse MA *et al.* Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer. *Ann Surg Oncol* 2005;12:214–221.

113. Washington K, Berlin J, Branton P, Burgart LJ, Carter DK, Compton CC *et al. Protocol for the Examination of Specimens from Patients with Carcinoma of the Exocrine Pancreas*. Northfield, IL, USA: College of American Pathologists, 2016.

114. Chatterjee D, Katz MH, Rashid A, Varadhachary GR, Wolff RA, Wang H *et al.* Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. *Cancer* 2012;118:3182–3190.

115. Lindebjerg J, Hansborg N, Ploen J, Rafaelsen S, Jorgensen JC, Jakobsen A. Factors influencing reproducibility of tumour regression grading after high-dose chemoradiation of locally advanced rectal cancer. *Histopathology* 2011;59:18–21.

116. Zhao Q, Rashid A, Gong Y, Katz MH, Lee JE, Wolf R *et al.* Pathologic complete response to neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma is associated with a better prognosis. *Ann Diagn Pathol* 2012;16:29–37.

117. Winner M, Goff SL, Chabot JA. Neoadjuvant therapy for non-metastatic pancreatic ductal adenocarcinoma. *Semin Oncol* 2015;42:86–97.

118. Liu L, Katz MH, Lee SM, Fischer LK, Prakash L, Parker N *et al*. Superior mesenteric artery margin of posttherapy pancreaticoduodenectomy and prognosis in patients with pancreatic ductal adenocarcinoma. *Am J Surg Pathol* 2015;39:1395–1403.

119. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorect Dis* 1997;12:19–23.

120. Doi R, Kami K, Ito D, Fujimoto K, Kawaguchi Y, Wada M *et al.* Prognostic implication of para-aortic lymph node metastasis in resectable pancreatic cancer. *World J Surg* 2007;31: 147–154.

121. Basturk O, Hong SM, Wood LD, Adsay NV, Albores-Saavedra J, Biankin AV *et al.* A revised classification system and recommendations from the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas. *Am J Surg Pathol* 2015;39:1730–1741.

122. Garcea G, Dennison AR, Ong SL, Pattenden CJ, Neal CP, Sutton CD *et al.* Tumor characteristics predictive of survival following resection for ductal adenocarcinoma of the head of pancreas. *Eur J Surg Oncol* 2007;33:892–897.

123. Hong SM, Goggins M, Wolfgang CL, Schulick RD, Edil BH, Cameron JL *et al.* Vascular invasion in infiltrating ductal adenocarcinoma of the pancreas can mimic pancreatic intraepithelial neoplasia: a histopathologic study of 209 cases. *Am J Surg Pathol* 2012;36: 235–241.

124. Kawesha A, Ghaneh P, Andrén-Sandberg A, Ograed D, Skar R, Dawiskiba Set *et al*. K-ras oncogene subtype mutations are associated with survival but not expression of p53, p16(INK4A), p21(WAF-1), cyclin D1, erbB-2 and erbB-3 in resected pancreatic ductal adenocarcinoma. *Int J Cancer* 2000;89:469–474.

125. Tascilar M, Skinner HG, Rosty C, Sohn T, Wilentz RE, Offerhaus GJ *et al.* The SMAD4 protein and prognosis of pancreatic ductal adenocarcinoma. *Clin Cancer Res* 2001;7: 4115–4121.

126. Vimalachandran D, Greenhalf W, Thompson C, Lüttges J, Prime W, Campbell F *et al*. High nuclear S100A6 (Calcyclin) is significantly associated with poor survival in pancreatic cancer patients. *Cancer Res* 2005;65:3218–3225.

127. Skalicky DA, Kench JG, Segara D, Coleman MJ, Sutherland RL, Henshall SM *et al.* Cyclin E expression and outcome in pancreatic ductal adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 2006;15:1941–1947.

128. Cioc AM, Ellison EC, Proca DM, Lucas JG, Frankel WL. Frozen section diagnosis of pancreatic lesions. *Arch Pathol Lab Med* 2002;126:1169–1173.

129. Campbell F, Verbeke CS. The Role of Frozen Section. *In:* Campbell F, Verbeke CS (eds). *Pathology of the pancreas – a practical approach*. London, UK: Springer-Verlag, 2013.

130. Hyland C, Kheir SM, Kashlan MB. Frozen section diagnosis of pancreatic carcinoma. A prospective study of 64 cases. *Am J Surg Pathol* 1981;5:179–191.

131. Matthaei H, Hong SM, Mayo SC, dal Molin M, Olino K, Venkat R *et al.* Presence of pancreatic intraepithelial neoplasia in the pancreatic transection margin does not influence outcome in patients with R0 resected pancreatic cancer. *Ann Surg Oncol* 2011;18: 3493–3499.

132. Sauvanet A, Couvelard A, Belghiti J. Role of frozen section assessment for intraductal papillary and mucinous tumour of the pancreas. *World J Gastrointest Surg* 2010;2:352–358.

Appendix A UICC TNM 8 histopathological classification[20]

General

TX	Primary tumour cannot be assessed histologically
T0	No histological evidence of primary tumour
Tis	Carcinoma in situ
NX	Regional lymph nodes cannot be assessed histologically
N0	No regional lymph node metastasis histologically
M1	Distant metastasis microscopically confirmed

Pancreas

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 but 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
N1	Metastases in 1 to 3 regional lymph nodes histologically*
N2	Metastases in 4 or more regional lymph nodes histologically*

Ampulla of Vater

T1a	Tumour limited to ampulla of Vater or sphincter of Oddi
T1b	Tumour invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa
T2	Tumour invades the muscularis propria of the duodenum
T3	Tumour invades pancreas or peripancreatic tissue
T3a	Tumour invades 0.5 cm or less into the pancreas
T3b	Tumour invades more than 0.5 cm into the pancreas or extends into peripancreatic tissue or duodenal serosa but without involvement of the coeliac axis or superior mesenteric artery
T4	Tumour with vascular involvement of the superior mesenteric artery, coeliac axis or common hepatic artery
N1	Metastasis in 1 to 3 regional lymph nodes histologically*
N2	Metastasis in 4 or more regional lymph nodes histologically*

Distal extrahepatic bile duct

T1 Tumour invades bile duct wall to a depth less than 5 mm
T2 Tumour invades bile duct wall to a depth of 5 mm up to 12 mm
T3 Tumour invades bile duct wall to a depth of more than 12 mm
T4 Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery

N1 Metastases in 1 to 3 regional lymph nodes histologically*
N2 Metastases in 4 or more regional lymph nodes histologically*

*For regional lymph nodes, see section 5.4.6.

Appendix B ICD-10 and SNOMED 'T' coding for tumour site

Tumour site	ICD-10	SNOMED code (version 2/ version 3.5)	SNOMED CT terminology	SNOMED CT code
Head of pancreas	C25.0	T-59100/T-65100	Structure of head of pancreas (body structure)	64163001
Body of pancreas	C25.1	T-59200/T-65200	Structure of body of pancreas (body structure)	40133006
Tail of pancreas	C25.2	T-59300/T-65300	Structure of tail of pancreas (body structure)	73239005
Whole pancreas	C25.8	T-59000/T-65000	Pancreatic structure (body structure)	15776009
Extrahepatic bile ducts	C24.0	T-58000/T-64000	Extrahepatic duct structure (body structure)	16014003
Ampulla of Vater	C24.1	T-58700/T-64700	Structure of ampulla of Vater (body structure)	67109009

Appendix C WHO classification of malignant exocrine pancreatic tumours[19] and SNOMED 'M' codes

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Ductal adenocarcinoma	M8500/3	Infiltrating duct carcinoma (morphologic abnormality)	82711006
Adenosquamous carcinoma	M8560/3	Adenosquamous carcinoma (morphologic abnormality)	59367005
Colloid carcinoma (mucinous non-cystic carcinoma)	M8480/3	Mucinous adenocarcinoma (morphologic abnormality)	72495009
Hepatoid carcinoma	M8576/3	Hepatoid adenocarcinoma (morphologic abnormality)	128706007
Medullary carcinoma	M8510/3	Medullary carcinoma (morphologic abnormality)	32913002
Signet ring cell carcinoma	M8490/3	Signet ring cell carcinoma (morphologic abnormality)	87737001
Undifferentiated (anaplastic or sarcomatoid) carcinoma	M8020/3	Carcinoma, undifferentiated (morphologic abnormality)	38549000
Undifferentiated carcinoma with osteoclast-like giant cells	M8035/3	Carcinoma with osteoclast-like giant cells (morphologic abnormality)	128631001
Acinar cell carcinoma	M8550/3	Acinar cell carcinoma (morphologic abnormality)	45410002
Acinar cell cystadenocarcinoma	M8551/3	Acinar cell cystadenocarcinoma (morphologic abnormality)	128703004
Intraductal papillary mucinous neoplasm with an associated invasive carcinoma	M8453/3	Intraductal papillary mucinous carcinoma, invasive (morphologic abnormality)	128692006
Mixed acinar-ductal carcinoma	M8552/3	Mixed acinar-ductal carcinoma (morphologic abnormality)	450897002
Mixed acinar-neuroendocrine carcinoma	M8154/3	Mixed islet cell and exocrine adenocarcinoma (morphologic abnormality)	999000

Morphological codes (continued)	SNOMED code	SNOMED CT terminology	SNOMED CT code
Mucinous cystic neoplasm with an associated invasive carcinoma	M8470/3	Mucinous cystadenocarcinoma (morphologic abnormality)	79143006
Pancreatoblastoma	M8971/3	Pancreatoblastoma (morphologic abnormality)	53618008
Serous cystadenocarcinoma	M8441/3	Serous cystadenocarcinoma (morphologic abnormality)	90725004
Solid-pseudopapillary neoplasm	M8452/3	Solid-pseudopapillary carcinoma (morphologic abnormality)	116061001

Procedure codes (P)

These are used in SNOMED 2 and SNOMED 3 to distinguish biopsies, partial resections and radical resections to indicate the nature of the procedure.

Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

Appendix D WHO classification of carcinomas of the ampulla of Vater and extrahepatic bile ducts[19] and SNOMED 'M' codes

WHO classification of carcinomas of the ampulla of Vater[19]

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Adenocarcinoma	M8140/3	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Invasive intestinal type	M8144/3	Adenocarcinoma, intestinal type (morphologic abnormality)	25190001
Pancreatobiliary type	M8163/3	Pancreatobiliary-type carcinoma (morphologic abnormality)	450894009
Adenosquamous carcinoma	M8560/3	Adenosquamous carcinoma (morphologic abnormality)	59367005
Clear cell adenocarcinoma	M8310/3	Clear cell adenocarcinoma (morphologic abnormality)	30546008
Hepatoid adenocarcinoma	M8576/3	Hepatoid adenocarcinoma (morphologic abnormality)	128706007
Invasive papillary adenocarcinoma	M8260/3	Papillary adenocarcinoma (morphologic abnormality)	4797003
Mucinous adenocarcinoma	M8480/3	Mucinous adenocarcinoma (morphologic abnormality)	72495009
Signet ring cell carcinoma	M8490/3	Signet ring cell carcinoma (morphologic abnormality)	87737001
Squamous cell carcinoma	M8070/3	Squamous cell carcinoma, no International Classification of Diseases for Oncology subtype (morphologic abnormality)	28899001
Undifferentiated carcinoma	M8020/3	Carcinoma, undifferentiated (morphologic abnormality)	38549000
Undifferentiated carcinoma with osteoclast-like giant cells	M8035/3	Carcinoma with osteoclast-like giant cells (morphologic abnormality)	128631001

WHO classification of carcinomas of the extrahepatic bile ducts[19]

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
Adenocarcinoma	M8140/3	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Adenocarcinoma, biliary type	M8140/3	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Adenocarcinoma, gastric foveolar type	M8140/3	Well differentiated adenocarcinoma, gastric foveolar type (morphologic abnormality)	388676006
Adenocarcinoma, intestinal type	M8144/3	Adenocarcinoma, intestinal type (morphologic abnormality)	25190001
Clear cell carcinoma	M8310/3	Clear cell adenocarcinoma (morphologic abnormality)	30546008
Mucinous carcinoma	M8480/3	Mucinous adenocarcinoma (morphologic abnormality)	72495009
Signet ring cell carcinoma	M8490/3	Signet ring cell carcinoma (morphologic abnormality)	87737001
Adenosquamous carcinoma	M8560/3	Adenosquamous carcinoma (morphologic abnormality)	59367005
Intraductal (bile duct) papillary neoplasm with an associated invasive carcinoma	M8503/3	Intraductal papillary adenocarcinoma with invasion (morphologic abnormality)	64524002
Squamous cell carcinoma	M8070/3	Squamous cell carcinoma, no International Classification of Diseases for Oncology subtype (morphologic abnormality)	28899001
Undifferentiated carcinoma	M8020/3	Carcinoma, undifferentiated (morphologic abnormality)	38549000

Appendix E Reporting proforma for pancreatic carcinoma

Surname: ..... Forename(s): ..... Date of birth: ....…..... Sex:……

Hospital: .....…… Hospital no: .....…….. NHS no: .....……..….....

Date of surgery: ……..... Date of report authorisation:…….... Report number: ....……..…….....

Date of receipt: …… Pathologist: …… Surgeon:..……..……...

Specimen type†

Kausch-Whipple's pancreatoduodenectomy (PD) □ Pylorus-preserving PD □

Total pancreatectomy □ Subtotal PD □ Left pancreatectomy □

Other □ (specify) …….

Gross description

Site of tumour ……..…… Maximum tumour diameter†……..…… mm

Macroscopic margin involvement: None □ Yes (R2) □ (which margin(s))……..

Identifiable named vessel(s) None □ Yes □ (which vessel)…….…….…

Background pathology None □ Yes □ (specify)……..…

Microscopic description

Histological type of tumour†**:** Ductal adenocarcinoma □ Other □ (specify)……..……..

Variant of PDAC (specify): ……..……..

Differentiation†: Not applicable *(post-neoadjuvant therapy)* □

Well (Grade 1) □ Moderate (Grade 2) □ Poor (Grade 3) □

Assessment of size†**:** macroscopic appearances confirmed □
measured histologically □ …… mm

Maximum extent of invasion (pT)†**:**

pT0: No residual tumour □

pTis: Carcinoma in situ □

pT1a: Tumour 5 mm or less in greatest dimension □

pT1b: Tumour greater than 5 mm but no more than 10 mm in greatest dimension □

pT1c: Tumour greater than 10 mm but no more than 20 mm in greatest dimension □

pT2: Tumour more than 20 mm but no more than 40 mm in greatest dimension □

pT3: Tumour more than 40 mm in greatest dimension □

pT4: Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery □

Response to neoadjuvant therapy†**:** Not applicable □

CAP Grade 0 (No residual tumour) □ CAP Grade 1 (Moderate/marked response) □

CAP Grade 2 (Minimal response) □ CAP Grade 3 (Poor/no response) □

Margin status†	**Involved**	**Not involved**	**Not sampled**	**Not applicable**	**Clearance***
Gastric transection margin:	□	□	□	□	……. mm
Duodenal transection margin:	□	□	□	□	……. mm
Pancreatic transection margin:	□	□	□	□	……. mm
Bile duct transection margin:	□	□	□	□	……. mm
SMV/SMA dissection margin:	□	□	□	□	……. mm
Posterior dissection margin:	□	□	□	□	……. mm
Anterior pancreatic surface:	□	□	□	□	……. mm

**Specify clearance of closest margin(s)*

Named vessel status: □ □ □ □

If named vessel involved, specify ……..

Perineural invasion: Present □ Not identified □

Regional lymph node status (pN)

Total number of nodes† ……

Number of involved nodes† ……

N stage†: pN0 (Regional lymph nodes not involved) □

pN1 (Metastases in 1 to 3 regional lymph nodes) □

pN2 (Metastases in 4 or more regional lymph nodes) □

Distant metastasis (pM)†

Distant metastasis confirmed No □ Yes (pM1) □ specify site(s)……

Background pathology: Intraductal papillary mucinous neoplasm (IPMN) □

Mucinous cystic neoplasm (MCN) □ Other □ (specify)…… None □

Comments

Pathological staging: (y)pT…. (y)pN…. (y)pM….. UICC version 8

Resection status†**:** Complete at all margins (R0) □ Incomplete microscopic (R1) □
Incomplete macroscopic (R2) □

Signature:…… Date:…… SNOMED codes: T…… / M…….

†Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) version 8/9.

Appendix F Reporting proforma for ampulla of Vater carcinoma

Surname: ..... Forename(s): ..... Date of birth: ...…..... Sex:……

Hospital: .....……. Hospital no: .....…….…... NHS no: .....……..….....

Date of surgery: ……..... Date of report authorisation:……..... Report number: ...……..…….....

Date of receipt: …… Pathologist: ……..…… Surgeon:..……..……...

Specimen type†

Kausch-Whipple's pancreatoduodenectomy (PD) □ Pylorus-preserving PD □

Other □ (specify)

Gross description

Maximum tumour diameter†……..…… mm

Macroscopic margin involvement: None □ Yes (R2)□ (which margin(s))……

Identifiable named vessel(s) None □ Yes □ (which vessel)……

Background pathology None □ Yes □ (specify)……..…..

Microscopic description

Type of tumour†**:** Adenocarcinoma □ Other □ (specify) ……..……..

Phenotype†**:** Pancreaticobiliary □ Intestinal □

Other □ (specify) ……

Differentiation:† Not applicable *(e.g. post-neoadjuvant therapy)* □

Well (Grade 1) □ Moderate (Grade 2) □ Poor (Grade 3) □

Maximum extent of invasion (pT)†**:**

pT0: No residual tumour □

pTis: Carcinoma in situ □

pT1a: Tumour limited to ampulla of Vater or sphincter of Oddi □

pT1b: Tumour invades beyond the sphincter of Oddi and/or into the duodenal submucosa □

pT2: Tumour invades the muscularis propria of the duodenum □

pT3a: Tumour invades 5 mm or less into the pancreas □

pT3b: Tumour invades more than 5 mm into the pancreas or extends into peripancreatic tissue or duodenal serosa but without involvement of the coeliac axis or the superior mesenteric artery □

pT4: Tumour with vascular involvement of the superior mesenteric artery, coeliac axis, or common hepatic artery □

Response to neoadjuvant therapy†: Not applicable □

CAP Grade 0 (No residual tumour) □ CAP Grade 1 (Moderate/marked response) □

CAP Grade 2 (Minimal response) □ CAP Grade 3 (Poor/no response) □

Margin status†	**Involved**	**Not involved**	**Not sampled**	**Not applicable**	**Clearance***
Gastric transection margin:	□	□	□	□	……. mm
Duodenal transection margin:	□	□	□	□	……. mm
Pancreatic transection margin:	□	□	□	□	……. mm
Bile duct transection margin:	□	□	□	□	……. mm
SMV/SMA dissection margin:	□	□	□	□	……. mm
Posterior dissection margin:	□	□	□	□	……. mm
Anterior pancreatic surface:	□	□	□	□	……. mm

**Specify clearance of closest margin(s)*

Named vessel status: □ □ □ □

If named vessel involved, specify ……..

Perineural invasion: Present □ Not identified □

Regional lymph node status (pN)

Total number of nodes† ……

Number of involved nodes† ……

N stage†: pN0 (Regional lymph nodes not involved) □

pN1 (Metastases in 1 to 3 regional lymph nodes) □

pN2 (Metastases in 4 or more regional lymph nodes) □

Distant metastasis (pM)

Distant metastasis confirmed† No □ Yes (pM1) □ specify site(s)……

Background pathology: Ampullary adenoma □ Other (specify)…… None □

Comments

Pathological staging: (y)pT…. (y)pN…. (y)pM….. UICC version 8

Resection status†: Complete at all margins (R0) □ Incomplete microscopic (R1) □
Incomplete macroscopic (R2) □

Signature:…… Date:…… SNOMED codes: T…… / M……..

†Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) version 8/9.

Appendix G Reporting proforma for common bile duct carcinoma

Surname: ..... Forename(s): ..... Date of birth: ...…..... Sex:……

Hospital: .....…… Hospital no: .....…….…... NHS no: .....……..….....

Date of surgery: ……..... Date of report authorisation:…….... Report number: ...……..…….....

Date of receipt: …… Pathologist: …… Surgeon:..……..……...

Specimen type†

Kausch-Whipple's pancreatoduodenectomy (PD) □ Pylorus-preserving PD □

Other □ (specify) **……**

Gross description

Site of tumour ……..…… Maximum tumour diameter † …… mm

Macroscopic margin involvement: None □ Yes (R2) □ (which margin(s))……..

Identifiable named vessel(s) None □ Yes □ (which vessel)……..…

Background pathology None □ Yes □ (specify)……

Microscopic description

Type of tumour†**:** Adenocarcinoma □ Other □ (specify) ……..……...

Differentiation†**:** Not applicable *(e.g. post-neoadjuvant therapy)* □

Well (Grade 1) □ Moderate (Grade 2) □ Poor (Grade 3) □

Maximum extent of invasion (pT) †**:**

T0: No residual tumour □

Tis: Carcinoma in situ □

T1: Tumour invades bile duct wall to a depth less than 5 mm □

T2: Tumour invades bile duct wall to a depth of 5 mm up to 12 mm □

T3: Tumour invades bile duct wall to a depth of more than 12 mm □

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

Response to neoadjuvant therapy†**:** Not applicable □

CAP Grade 0 (No residual tumour) □ CAP Grade 1 (Moderate/marked response) □

CAP Grade 2 (Minimal response) □ CAP Grade 3 (Poor/no response) □

Margin status†	**Involved**	**Not involved**	**Not sampled**	**Not applicable**	**Clearance***
Gastric transection margin:	□	□	□	□	……. mm
Duodenal transection margin:	□	□	□	□	……. mm
Pancreatic transection margin:	□	□	□	□	……. mm
Bile duct transection margin:	□	□	□	□	……. mm
SMV/SMA dissection margin:	□	□	□	□	……. mm
Posterior dissection margin:	□	□	□	□	……. mm
Anterior pancreatic surface:	□	□	□	□	……. mm

**Specify clearance of closest margin(s)*

Named vessel status: □ □ □ □

If named vessel involved, specify ……..

Perineural invasion: Present □ Not identified □

Regional lymph node status (pN)

Total number of nodes† ……

Number of involved nodes† ……

N stage†: pN0 (Regional lymph nodes not involved) □

pN1 (Metastases in 1 to 3 regional lymph nodes) □

pN2 (Metastases in 4 or more regional lymph nodes) □

Distant metastasis (pM)

Distant metastasis confirmed† No □ Yes (pM1) □ Specify site(s)……

Background pathology: Biliary IPMN □ Bil-IN □ Other (specify) …….. None □

Comments

Pathological staging: (y)pT…. (y)pN…. (y)pM….. UICC version 8

Resection status†: Complete at all margins (R0) □ Incomplete microscopic (R1) □
Incomplete macroscopic (R2) □

Signature:…… Date:…… SNOMED codes: T…… / M……..

†Data items that are currently part of the Cancer Outcomes and Services Dataset (COSD) version 8/9.

Appendix H Reporting proforma for pancreatic carcinoma in list format

Element name	Values	Implementation notes
Specimen type	Single selection value list: • Kausch-Whipple's pancreatoduodenectomy (PD) • Pylorus-preserving PD • Total pancreatectomy • Subtotal PD • Left pancreatectomy • Other	
Specimen type, specify	Free text	Only applicable if 'Specimen type, Other' is selected.
Site of tumour	Free text	
Maximum tumour diameter	Size in mm	
Macroscopic margin involvement	Single selection value list: • None • Yes (R2)	
Macroscopic margin involvement, which margin	Free text	Only applicable if 'Macroscopic margin involvement, Yes' is selected.
Identifiable named vessel(s)	Single selection value list: • None • Yes	
Identifiable named vessel(s), which vessel	Free text	Only applicable if 'Identifiable named vessel(s), Yes' is selected.
Background pathology	Single selection value list: • None • Yes	
Background pathology, specify	Free text	Only applicable if 'Background pathology, Yes' is selected.
Histological type of tumour	Single selection value list: • Ductal adenocarcinoma • Other	
Histological type of tumour, Other, specify	Free text	Only applicable if 'Histological type of tumour, Other' is selected.
Variant of PDAC	Free text	

Element name	Values	Implementation notes
Differentiation	Single selection value list: • Not applicable (post-neoadjuvant therapy) • Well (Grade 1) • Moderate (Grade 2) • Poor (Grade 3)	
Assessment of size	Single selection value list: • Macroscopic appearances confirmed • Measured histologically	
Assessment of size measured histologically	Free text	Only applicable if 'Assessment of size, Measured histologically' is selected.
Maximum extent of invasion	Single selection value list: • pT0 • pTis • pT1a • pT1b • pT1c • pT2 • pT3 • pT4	
Response to neoadjuvant therapy	Single selection value list: • Not applicable • CAP Grade 0 (No residual tumour) • CAP Grade 1 (Moderate/marked response) • CAP Grade 2 (Minimal response) • CAP Grade 3 (Poor/no response)	
Margin status, Gastric transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Gastric transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Gastric transection margin, Not involved' is selected.

Element name	Values	Implementation notes
Margin status, Duodenal transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Duodenal transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Duodenal transection margin, Not involved' is selected.
Margin status, Pancreatic transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Pancreatic transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Pancreatic transection margin, Not involved' is selected.
Margin status, Bile duct transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Bile duct transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Bile duct transection margin, Not involved' is selected.
Margin status, SMV/SMA dissection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, SMV/SMA dissection margin, Clearance	Distance in mm	Only applicable if 'Margin status, SMV/SMA dissection margin, Not involved' is selected.
Margin status, Posterior dissection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	

Element name	Values	Implementation notes
Margin status, Posterior dissection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Posterior dissection margin, Not involved' is selected.
Margin status, Anterior pancreatic surface	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Anterior pancreatic surface, Clearance	Distance in mm	Only applicable if 'Margin status, Anterior pancreatic surface, Not involved' is selected.
Named vessel status	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Named vessel, specify	Free text	Only applicable if 'Named vessel status, Involved' is selected.
Perineural invasion	Single selection value list: • Present • Not identified	
Total number of nodes	Integer	
Number of involved nodes	Integer	
N stage	Single selection value list: • pN0 • pN1 • pN2	
Distant metastasis confirmed	Single selection value list: • No • Yes	
Distant metastasis confirmed, specify site	Free text	Only applicable if 'Distant metastasis confirmed, Yes' is selected.
Background pathology	Single selection value list: • Intraductal papillary mucinous neoplasm (IPMN) • Mucinous cystic neoplasm (MCN) • Other • None	

Element name	Values	Implementation notes
Background pathology, Other, specify	Free text	Only applicable if 'Background pathology, Other' is selected.
Comments	Free text	
T stage	Single selection value list: • pT0 • pTis • pT1a • pT1b • pT1c • pT2 • pT3 • pT4 • ypT0 • ypTis • ypT1a • ypT1b • ypT1c • ypT2 • ypT3 • ypT4	
N stage	Single selection value list: • pNX • pN0 • pN1 • pN2 • ypNX • ypN0 • ypN1 • ypN2	
M stage	Single selection value list: • Not applicable • pM1 • ypM1	
UICC version	Single selection value list: • 8	
Resection status	Single selection value list: • Complete at all margins (R0) • Incomplete microscopic (R1) • Incomplete macroscopic (R2)	
SNOMED T code	May have multiple codes. Look up from SNOMED tables.	

Element name	Values	Implementation notes
SNOMED M code	May have multiple codes. Look up from SNOMED tables.	

Appendix I Reporting proforma for ampulla of Vater carcinoma in list format

Element name	Values	Implementation notes
Specimen type	Single selection value list: • Kausch-Whipple's pancreatoduodenectomy (PD) • Pylorus-preserving PD • Other	
Specimen type, specify	Free text	Only applicable if 'Specimen type, Other' is selected.
Maximum tumour diameter	Size in mm	
Macroscopic margin involvement	Single selection value list: • None • Yes (R2)	
Macroscopic margin involvement, which margin	Free text	Only applicable if 'Macroscopic margin involvement, Yes' is selected.
Identifiable named vessel(s)	Single selection value list: • None • Yes	
Identifiable named vessel(s), which vessel	Free text	Only applicable if 'Identifiable named vessel(s), Yes' is selected.
Background pathology	Single selection value list: • None • Yes	
Background pathology, specify	Free text	Only applicable if 'Background pathology, Yes' is selected.
Histological type of tumour	Single selection value list: • Adenocarcinoma • Other	
Histological type of tumour, Other, specify	Free text	Only applicable if 'Histological type of tumour, Other' is selected.
Phenotype	Single selection value list: • Pancreatobiliary • Intestinal • Other	Only applicable if 'Histological type of tumour, Adenocarcinoma' is selected.
Phenotype, Other, specify	Free text	Only applicable if 'Phenotype, Other' is selected.

Element name	Values	Implementation notes
Differentiation	Single selection value list: • Not applicable (post-neoadjuvant therapy) • Well (Grade 1) • Moderate (Grade 2) • Poor (Grade 3)	
Maximum extent of invasion	Single selection value list: • pT0 • pTis • pT1a • pT1b • pT2 • pT3a • pT3b • pT4	
Response to neoadjuvant therapy	Single selection value list: • Not applicable • CAP Grade 0 (No residual tumour) • CAP Grade 1 (Moderate/marked response) • CAP Grade 2 (Minimal response) • CAP Grade 3 (Poor/no response)	
Margin status, Gastric transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Gastric transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Gastric transection margin, Not involved' is selected.
Margin status, Duodenal transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Duodenal transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Duodenal transection margin, Not involved' is selected.

Element name	Values	Implementation notes
Margin status, Pancreatic transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Pancreatic transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Pancreatic transection margin, Not involved' is selected.
Margin status, Bile duct transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Bile duct transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Bile duct transection margin, Not involved' is selected.
Margin status, SMV/SMA dissection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, SMV/SMA dissection margin, Clearance	Distance in mm	Only applicable if 'Margin status, SMV/ SMA dissection margin, Not involved' is selected.
Margin status, Posterior dissection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Posterior dissection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Posterior dissection margin, Not involved' is selected.
Margin status, Anterior pancreatic surface	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	

Element name	Values	Implementation notes
Margin status, Anterior pancreatic surface, Clearance	Distance in mm	Only applicable if 'Margin status, Anterior pancreatic surface, Not involved' is selected.
Named vessel status	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Named vessel, specify	Free text	Only applicable if 'Named vessel status, Involved' is selected.
Perineural invasion	Single selection value list: • Present • Not identified	
Total number of nodes	Integer	
Number of involved nodes	Integer	
N stage	Single selection value list: • pN0 • pN1 • pN2	
Distant metastasis confirmed	Single selection value list: • No • Yes	
Distant metastasis confirmed, specify site	Free text	Only applicable if 'Distant metastasis confirmed, Yes' is selected.
Background pathology	Single selection value list: • Ampullary adenoma • Other • None	
Background pathology, Other, specify	Free text	Only applicable if 'Background pathology, Other' is selected.
Comments	Free text	

Element name	Values	Implementation notes
T stage	Single selection value list: • pT0 • pTis • pT1a • pT1b • pT2 • pT3a • pT3b • pT4 • ypT0 • ypTis • ypT1a • ypT1b • ypT2 • ypT3a • ypT3b • ypT4	
N stage	Single selection value list: • pNX • pN0 • pN1 • pN2 • ypNX • ypN0 • ypN1 • ypN2	
M stage	Single selection value list: • Not applicable • pM1 • ypM1	
UICC version	Single selection value list: • 8	
Resection status	Single selection value list: • Complete at all margins (R0) • Incomplete microscopic (R1) • Incomplete macroscopic (R2)	
SNOMED T code	May have multiple codes. Look up from SNOMED tables.	
SNOMED M code	May have multiple codes. Look up from SNOMED tables.	

Appendix J Reporting proforma for common bile duct carcinoma in list format

Element name	Values	Implementation notes
Specimen type	Single selection value list: • Kausch-Whipple's pancreatoduodenectomy (PD) • Pylorus-preserving PD • Other	
Specimen type, specify	Free text	Only applicable if 'Specimen type, Other' is selected.
Site of tumour	Free text	
Maximum tumour diameter	Size in mm	
Macroscopic margin involvement	Single selection value list: • None • Yes (R2)	
Macroscopic margin involvement, which margin	Free text	Only applicable if 'Macroscopic margin involvement, Yes' is selected.
Identifiable named vessel(s)	Single selection value list: • None • Yes	
Identifiable named vessel(s), which vessel	Free text	Only applicable if 'Identifiable named vessel(s), Yes' is selected.
Background pathology	Single selection value list: • None • Yes	
Background pathology, specify	Free text	Only applicable if 'Background pathology, Yes' is selected.
Histological type of tumour	Single selection value list: • Adenocarcinoma • Other	
Histological type of tumour, Other, specify	Free text	Only applicable if 'Histological type of tumour, Other' is selected.
Differentiation	Single selection value list: • Not applicable (post-neoadjuvant therapy) • Well (Grade 1) • Moderate (Grade 2) • Poor (Grade 3)	

Element name	Values	Implementation notes
Maximum extent of invasion	Single selection value list: • pT0 • pTis • pT1 • pT2 • pT3 • pT4	
Response to neoadjuvant therapy	Single selection value list: • Not applicable • CAP Grade 0 (No residual tumour) • CAP Grade 1 (Moderate/marked response) • CAP Grade 2 (Minimal response) • CAP Grade 3 (Poor/no response)	
Margin status, Gastric transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Gastric transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Gastric transection margin, Not involved' is selected.
Margin status, Duodenal transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Duodenal transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Duodenal transection margin, Not involved' is selected.
Margin status, Pancreatic transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Pancreatic transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Pancreatic transection margin, Not involved' is selected.

Element name	Values	Implementation notes
Margin status, Bile duct transection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Bile duct transection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Bile duct transection margin, Not involved' is selected.
Margin status, SMV/SMA dissection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, SMV/SMA dissection margin, Clearance	Distance in mm	Only applicable if 'Margin status, SMV/SMA dissection margin, Not involved' is selected.
Margin status, Posterior dissection margin	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Posterior dissection margin, Clearance	Distance in mm	Only applicable if 'Margin status, Posterior dissection margin, Not involved' is selected.
Margin status, Anterior pancreatic surface	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Margin status, Anterior pancreatic surface, Clearance	Distance in mm	Only applicable if 'Margin status, Anterior pancreatic surface, Not involved' is selected.
Named vessel status	Single selection value list: • Involved • Not involved • Not sampled • Not applicable	
Named vessel, specify	Free text	Only applicable if 'Named vessel status, Involved' is selected.

Element name	Values	Implementation notes
Perineural invasion	Single selection value list: • Present • Not identified	
Total number of nodes	Integer	
Number of involved nodes	Integer	
N stage	Single selection value list: • pN0 • pN1 • pN2	
Distant metastasis confirmed	Single selection value list: • No • Yes	
Distant metastasis confirmed, specify site	Free text	Only applicable if 'Distant metastasis confirmed, Yes' is selected.
Background pathology	Single selection value list: • Biliary IPMN • Bil-IN • Other • None	
Background pathology, Other, specify	Free text	Only applicable if 'Background pathology, Other' is selected.
Comments	Free text	
T stage	Single selection value list: • pT0 • pTis • pT1 • pT2 • pT3 • pT4 • ypT0 • ypTis • ypT1 • ypT2 • ypT3 • ypT4	

Element name	Values	Implementation notes
N stage	Single selection value list: • pNX • pN0 • pN1 • pN2 • ypNX • ypN0 • ypN1 • yPN2	
M stage	Single selection value list: • Not applicable • pM1 • ypM1	
UICC version	Single selection value list: • 8	
Resection status	Single selection value list: • Complete at all margins (R0) • Incomplete microscopic (R1) • Incomplete macroscopic (R2)	
SNOMED T code	May have multiple codes. Look up from SNOMED tables.	
SNOMED M code	May have multiple codes. Look up from SNOMED tables.	

Appendix K Summary table – Explanation of levels of evidence

(modified from Palmer K *et al*. *BMJ* 2008;337:1832)

Grade (level of evidence)	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised control trials or a randomised control trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised control trials or randomised control trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is casual and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix L AGREE II compliance monitoring sheet

The cancer datasets of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines (www.agreecollaboration.org). The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard		Section of dataset
Scope and purpose		
1	The overall objective(s) of the guideline is (are) specifically described	Foreword
2	The clinical question(s) covered by the guideline is (are) specifically described	1
3	The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	1
Stakeholder involvement		
4	The guideline development group includes individuals from all the relevant professional groups	Foreword
5	The views and preferences of the target population (patients, public, etc.) have been sought	N/A
6	The target users of the guideline are clearly defined	1
Rigour of development		
7	Systematic methods were used to search for evidence	Foreword
8	The criteria for selecting the evidence are clearly described	Foreword
9	The strengths and limitations of the body of evidence are clearly described	Foreword
10	The methods for formulating the recommendations are clearly described	Foreword
11	The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword, 1
12	There is an explicit link between the recommendations and the supporting evidence	All
13	The guideline has been externally reviewed by experts prior to its publication	Foreword
14	A procedure for updating the guideline is provided	Foreword
Clarity of presentation		
15	The recommendations are specific and unambiguous	All
16	The different options for management of the condition or health issue are clearly presented	All
17	Key recommendations are easily identifiable	4–9, 11
Applicability		
18	The guideline describes facilitators and barriers to its application	Foreword
19	The guideline provides advice and/or tools on how the recommendations can be put into practice	Foreword
20	The potential resource implications of applying the recommendations have been considered	Foreword
21	The guideline presents monitoring and/or auditing criteria	11
Editorial independence		
22	The views of the funding body have not influenced the content of the guideline	Foreword
23	Competing interest of guideline development group members have been recorded and addressed	Foreword