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

Standards and datasets for reporting cancers

Dataset for the histopathological reporting of anal cancer

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Produced by	Dr Morgan Moorghen and Dr Newton Wong are consultant histopathologists actively engaged in the diagnosis and multidisciplinary care of patients with anal cancer and in the professional associations that promote research and guideline development on their diagnosis and treatment.
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Comments	This edition supersedes the 1st edition of the *Dataset for histopathological reporting of anal cancer*, published in 2018. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for an abridged consultation from 7 November to 21 November 2023. Responses and authors' comments are available to view on publication of the final document. **Dr Brian Rous** **Clinical Lead for Guideline Review**

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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.

Pathologists should be able to justify any variation from the recommended practice.

Each dataset contains core data items (see Appendices C–F) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) 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 sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in Appendix I.

The following stakeholders were consulted for this document:

- Association for Coloproctology of Great Britain and Ireland
- British Society of Gastroenterology, Pathology Section.

The evidence base has been obtained by consultation of the electronic databases PubMed and Scopus between March 2018 to July 2023 using the MeSH terms ‘anal cancer’ and ‘anal carcinoma’. Publications which referred to clinical guidelines were also included. For most items included the evidence was evaluated using modified SIGN guidance (see Appendix I). The dataset conforms to the criteria for grading and staging as set out in the

WHO *Classification of digestive tumours (5th edition)* and the *TNM Classification of malignant tumours (8th edition)* from the Union for International Cancer Control (UICC). Consensus of evidence in the guideline was achieved by expert review. No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset. Gaps in the evidence were identified by College members via feedback received during consultation.

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty adviser 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 exceptions are 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 2 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 Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group. It was placed on the College website for consultation with the membership from 7 November to 21 November 2023. All comments received from the Working Group and membership were addressed by the author 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 Professional Guidelines team and are available on request. The authors have declared no conflicts of interest.

1 Introduction

This document is the second edition of the *Dataset for histopathological reporting of anal cancer*, first published in 2018.[1] This dataset provides guidance for histopathologists so

that they may provide accurate, standardised, evidence-based data on the diagnosis of anal cancer and precursor lesions. This is important because:

- an accurate diagnosis is necessary for guiding optimal clinical treatment
- prognosis and likely response to therapy are determined by histopathological data
- the provision of standardised data allows for the development of databases in cancer registries and the stratification of patients in clinical trials.

Malignant tumours that are not of epithelial origin (e.g. melanomas) are out of the scope of this document; however, in this revised dataset, pre-cancerous lesions of anal canal are considered. This change is felt to be necessary because of informal feedback received since the first version of this dataset was issued and also because these lesions are often dealt with alongside anal cancers by the same clinical team and are discussed at the same anal cancer multidisciplinary team meeting (MDTM).

1.1 Target users and health benefits of this guideline

It is envisaged that the main users of the dataset will be consultant histopathologists and trainee histopathologists and, on their behalf, the suppliers of IT products to laboratories. Secondary users will include surgeons, specialist nurses, oncologists, gastroenterologists and radiologists. They will also be of use to cancer registries.

1.2 Changes from previous version

The specific changes to this dataset from the first edition are:

- the addition of anal intraepithelial neoplasia/squamous intraepithelial lesion (AIN/SIL)
- verrucous carcinoma of the canal and giant condyloma of Buschke–Lowenstein are now separate entities
- for neuroendocrine neoplasms, readers are requested to refer to the RCPath *Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract*[2]
- immunohistochemistry for p16 in squamous cell carcinoma is included as a non-core data item.

1.3 Anatomy of the anal canal[3]

The anal canal is the caudal part of the large intestine (Figure 1). It measures between 3–5 cm in length and is entirely extra-peritoneal in location. The anal canal extends from the

anorectal ring to the anal verge (i.e. the anus or anal orifice). The anorectal ring is a palpable structure which lies at the level of the puborectalis. This landmark is not readily identifiable in resection specimens and is lined by columnar mucosa resembling rectal mucosa. The anal verge marks the junction between anal canal and perianal skin. This, therefore, corresponds to the transition between non-keratinising squamous epithelium without skin appendages and keratinising squamous epithelium with underlying skin appendages. The dentate line, named because of its irregular tooth-like appearance, represents the point of embryological transition between endodermal and ectodermal tissue. The dentate line is, therefore, located at the level of the anal valves, which corresponds to the distal limits or bases of the anal columns. The dentate line is located between 1–2 cm distal to the level of the anorectal junction. Note: this does not correspond to the squamocolumnar junction, which is often erroneously considered to represent the dentate line; in fact, there is usually no direct transition from proximal columnar epithelium to distal squamous epithelium in the anal canal. Instead, separating both epithelial types, there is often a stretch of transitional-type epithelium (of 4 to 10 cells thick and resembling urothelium) known as the anal transition zone (ATZ). The length of the ATZ varies between individuals and some anal canals may not contain any ATZ. The relationship of the ATZ to the dentate line also varies between individuals.

Based on the above definitions, it is important to note that the anal canal is lined from proximal to distal by columnar epithelium, a varying amount of transitional type epithelium and, finally, non-keratinising squamous epithelium. The zone lined by transitional type epithelium represents an area of squamous metaplasia of columnar epithelium that is particularly prone to human papilloma virus (HPV) infection.

Tumours arising at the anal margin and in perianal skin within 5 cm of the anus are considered as anal cancer for staging and treatment purposes. Those situated beyond 5 cm of the anus are regarded as perineal skin cancers. This definition is used by the WHO classification and the American Joint Committee for Cancer (AJCC).[3,4]

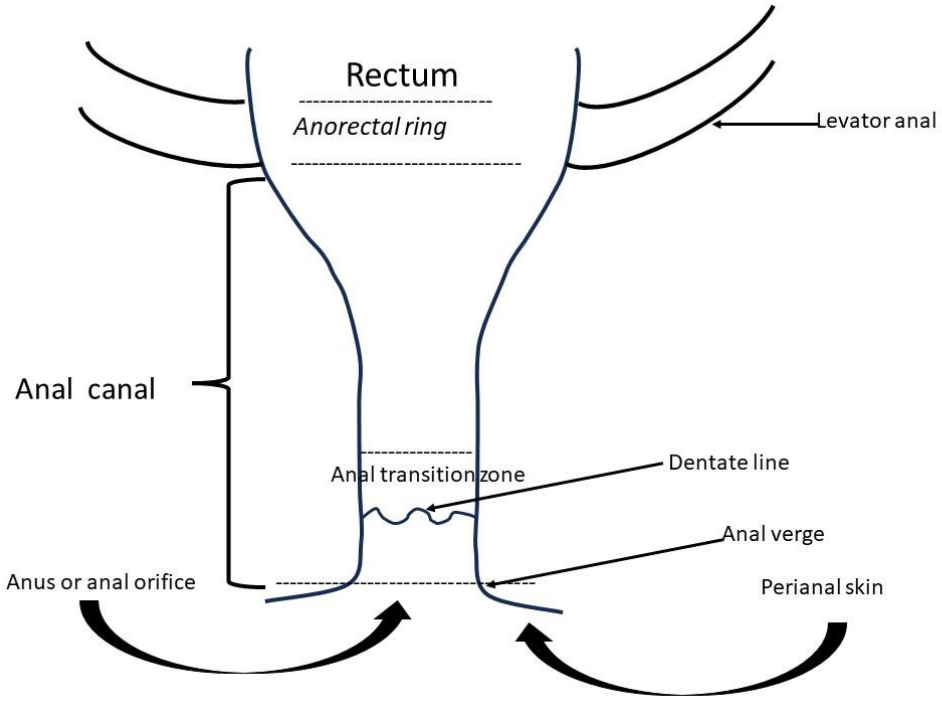

Figure 1. Anatomy of the anal canal.

2 Clinical information required on the request form

Information on the request form should include the patient's name, date of birth, sex, hospital number, NHS number and the name of the clinician to whom the report should be sent, as well as the date of the procedure. The following clinical data should also be provided:

- relevant history (e.g. human immunodeficiency virus (HIV) infection or other immunosuppression, genital warts, AIN, vulval/vaginal/cervical neoplasia)
- clinical diagnosis (e.g. squamous cell carcinoma)
- previous treatment (e.g. chemoradiotherapy)
- indication of whether this is a diagnostic procedure, curative resection or palliative procedure
- anatomical location of tumour (see above under section 1.3 'Anatomy of the anal canal')
- information about any suture markers in the specimen
- sites of any lymph nodes submitted separately (if applicable).

3 Preparation of specimen before dissection

All specimens should be fixed in formalin according to standard laboratory protocol. Excision specimens should be orientated according to the clinical information provided and the relevant margins inked. The specimens should be pinned before fixation in order to minimise tissue distortion and allow for adequate orientation. Abdominoperineal (AP) resection specimens should be handled as for rectal adenocarcinomas (see the RCPath *Dataset for colorectal cancer histopathology reports)*.[5]

4 Specimen handling and block dissection

4.1 Incisional biopsies

These are commonly performed for the purpose of diagnosing anal cancer and associated lesions (i.e. AIN/SIL and condylomas). The method of handling should be similar to that used for skin biopsies.[6] These biopsy specimens should be measured in 3 dimensions and embedded entirely on edge. Biopsies measuring more than 5 mm in diameter may be bisected**.** More than 1 level is recommended since this allows for a wider area to be visualised microscopically thus improving diagnostic accuracy.

4.2 Excision specimens

The purpose of the examination is to determine the type and grade of tumour and any precursor lesions if present, the tumour stage and completeness of excision.
The specimen should be measured in 3 dimensions and any macroscopically visible lesion should be described. Macroscopic measurement of the lesion/s is unnecessary when this is included as part of microscopic data (see section 5.2).

4.2.1 Number of blocks

There is no evidence base for the optimal number of blocks required. However, it is recommended that tumours measuring up to 1 cm in diameter should be serially sliced at 2–3 mm intervals to allow for the examination of sufficient material for a reliable assessment of tumour type and grade. We chose a thickness of 2–3 mm based on what we regard as reasonable, taking into account the optimal tissue thickness for adequate laboratory processing. The number of blocks should also allow for the assessment of the inked resection margins and assessment of mucosa adjacent to the invasive lesion for the presence of AIN/LSIL/HSIL, for example. Where a lymphadenectomy has been performed

as part of the main resection or separately (e.g. inguinal nodes) there should be an attempt to sample all lymph nodes for histological examination.

4.2.2 Block selection

Distinct from blocks demonstrating key morphological findings, where appropriate, at least 1 representative 'molecular block' should be identified, suitable for any required ancillary molecular testing. It is recognised that it is often not possible to retain a specific molecular block because of the limited amount of material in local excision and biopsy specimens.

This block should be selected as having high overall cellularity, low tumour necrosis and a high proportion of carcinoma cellularity, compared to inflammatory cells or other non-carcinomatous tissues.

An estimate of the carcinoma cellularity content (number of tumour cells/total number of nucleated cells) of the entire block should be provided, to the nearest 10%. As such blocks may be used for multiple purposes, including clinical trials, and therefore may be removed from the tissue archive, it is recommended to indicate more than 1 such representative molecular block. For similar reasons, it is recommended to avoid choosing any particularly clinically important blocks, for example blocks with key tumour features that are not evident in other blocks.

4.3 Large resection specimens

Abdominoperineal resections and wider exenterations are sometimes carried out for recurrent disease and/or following failure of chemoradiotherapy. These are handled as for rectal adenocarcinomas (see the RCPath *Dataset for colorectal cancer histopathology reports)*;[5] the specimen should be opened, cleaned, pinned and fixed in formalin before dissection.

[Level of evidence C – The evidence base for macroscopic examination and block selection is extrapolated from the need to provide microscopic confirmation and/or evaluation of prognostic and predictive factors.]

5 Core data items

5.1 Clinical data

Please see section 2 above.

5.2 Pathological data

The items to be included form the core data required for the accurate histological classification of the tumour[3] or pre-invasive lesion and pathological staging where required. The list provided below applies to incisional biopsies and local excision specimens of anal cancers and anal pre-invasive lesions. It is sometimes necessary for the surgeons to carry out more radical procedures for either palliative reasons or as definitive treatment in cases not responding fully to chemoradiotherapy. For AP resections and more extensive exenterations, the protocol employed is similar to that employed for colorectal cancer.

5.2.1 Macroscopic data

For incisional biopsies (including punch biopsies), the size of the specimen in 3 dimensions should be recorded.

For excision specimens, the following should be recorded:

- specimen dimensions
- appearance of surface mucosa
- site of tumour
- distance of tumour/lesion to peripheral and deep margins (see microscopic data below)
- any lymph nodes received (if applicable).

[Level of evidence B – Size of tumour, site of tumour, completeness of excision and lymph node status are important for prognosis and staging.]

5.2.2 Microscopic data

- For incisional biopsies (including punch biopsies), type of epithelium, i.e.:
  - keratinising squamous
  - non-keratinising squamous
  - columnar anal mucosal epithelium
  - transitional zone epithelium
  - cutaneous appendages, if present
- For excision specimens, type of background epithelium, i.e.:

  - keratinising squamous
  - non-keratinising squamous
  - columnar anal mucosal epithelium
  - transitional zone epithelium
  - cutaneous appendages, if present
- histological type of tumour (see histological classification below)
- tumour differentiation
- maximum size of tumour (see macroscopic data above)
- depth of invasion (plane of bowel wall)
- involvement of margins (deep and peripheral)
- distance to deep margin and nearest peripheral margin (this should not be duplicated with and should override any macroscopic measurements)
- number of lymph nodes and number of involved lymph nodes (if applicable)
- adjacent abnormality (e.g. AIN/HSIL/LSIL).

[Level of evidence B – Histological type, size, grade of differentiation, depth of invasion, completeness of excision and lymph node status are important determinants of prognosis in anal neoplasia.]

5.3 Specific information about anal cancers

5.3.1 Histological classification of anal tumours (WHO 2019)[3]

Benign

- Squamous intraepithelial neoplasia, low grade (Condyloma and AIN 1).
- Squamous intraepithelial neoplasia, high grade (AIN 2 and AIN3).

Malignant

- Squamous cell carcinoma.
- Verrucous carcinoma.
- Adenocarcinoma NOS.
- Neuroendocrine tumour, neuroendocrine carcinoma, mixed neuroendocrine – non-neuroendocrine neoplasm.

Anal condyloma

Anal condylomas are caused by HPV of low oncogenicity (mainly HPV 6 and 11). In these lesions, HPV infection is in a productive phase which is characterised by epithelial hyperplasia, alteration in squamous differentiation and the development of koilocytosis. These cellular alterations are not pre-malignant, per se, but because of the inherent subjectivity involved in the assessment of these lesions and also because of concomitant infection with HPV of high oncogenicity, condylomas are managed as low risk lesions along with AIN1. The giant condyloma (or Buschke–Lowenstein lesion) is also associated with HPV of low oncogenic risk. This may present as a locally destructive lesion and can be difficult to separate from squamous cell carcinoma (see verrucous carcinoma below).[7]

Anal squamous dysplasia (AIN, HSIL/LSIL)

The terminology used to describe pre-neoplastic lesions in the anogenital tract has undergone a number of changes since the first descriptions dated from the 19th century. The now commonly used term ‘cervical intraepithelial neoplasia’ was first introduced in 1967 by Richart;[8] soon after, a 3-tier grading system was proposed, which has gradually become part of accepted practice in the UK.[9] A similar grading system was later introduced for equivalent lesions in the anal canal and the term ‘anal intraepithelial neoplasia’ (AIN1, 2 and 3) came into use.[10]

An alternative 2-tier grading system (HSIL and LSIL) was also developed, first as part of the Bethesda protocol for the reporting of cervical cytology,[11] which was later applied to histology. This 2-tier system is widely accepted in the USA, whereas the 3-tier system conforms to UK practice; this is largely a consequence of differences in clinical management in different health systems.

It is generally recognised that a common unified terminology should be applied to anogenital lesions since they share a common aetiology via HPV infection.[12] It follows from this that a 3-tier grading system for AIN should be adopted, with the further qualifications of LSIL and HSIL in parentheses (i.e. LSIL/condyloma and AIN1; HSIL/AIN2 and AIN3), in order to maintain uniformity with cervical and vulval neoplasia. This would also be consistent with WHO recommendations and the Lower Anogenital Squamous Terminology (LAST) project.[12]

Squamous cell carcinoma

The histological appearances are variable and include

- large cell non-keratinising tumours

- large cell keratinising tumours which may resemble urothelial carcinomas
- basaloid carcinomas.

Basaloid carcinoma which was formerly referred to as cloacogenic carcinoma, can sometimes have an adenoid cystic appearance with stromal hyalinisation.

Foci of mucinous differentiation are sometimes present, giving rise to appearances that, in other sites, would be designated as mucoepidermoid carcinoma.

The recommendation is that all these histological variants be classified under the single heading of squamous cell carcinoma with an additional statement to include the presence and extent of any particular histological subtype.[3] This recommendation is justified on grounds of poor diagnostic interobserver reproducibility, tumour heterogeneity and a general lack of significant prognostic differences among the different subtypes.

Grading of squamous cell carcinoma

In anal squamous cell carcinoma, prognosis and treatment are determined largely by tumour stage. Tumour grade is less important, although this may become relevant in the discussion of complex cases in the MDTM. A 3-tier grading system (well differentiated, moderately differentiated, poorly differentiated) is recommended in line with WHO, UICC and AJCC.[3,4,13] The overall grade is based on the worst area.

Tumour size and depth of invasion

The stage of the tumour is dependent on size, which relates directly to prognosis. Although the anatomical depth of invasion has no direct bearing upon the T stage, it is correlated with size and is also a prognostic factor following salvage surgery in patients treated primarily with chemoradiotherapy.[13–15]

Post-treatment tumour regression

Surgery is no longer the primary treatment modality for anal squamous cell carcinoma. However, surgery may be required for recurrent disease or residual disease following radiotherapy and chemotherapy. Thus, in the assessment of resection specimens, the effects of treatment in respect of tumour regression need to be documented. There are several tumour regression scores applicable in various organ sites. It is recommended to employ the scheme proposed by Ryan *et al.*[16] as supported by the AJCC (Appendix G). This has the advantage of simplicity and relatively good interobserver reproducibility. The grade of tumour regression is a marker of sensitivity to radiation and chemotherapy but there is no evidence that this regression score is related to overall prognosis.

Verrucous carcinoma

This variant of squamous cell carcinoma should be recorded separately on account of its more favourable prognosis. This is a low-grade tumour characterised by an endophytic growth pattern with marked hyperkeratosis. The invasive component has a deceptively benign appearance and consists of well differentiated, broad, bulbous formations with no evidence of single cell infiltration. This should not be confused with the condylomatous Buschke–Lowenstein tumour, which is characterised by koilocytosis, an exophytic growth pattern and only mild hyperkeratosis. In both lesions, an accompanying invasive conventional-type squamous cell carcinoma may be present, in which case the grade and stage of this component overrides that of the verrucous carcinoma.[3]

Adenocarcinoma

Adenocarcinoma of the anal canal arises from either the columnar mucosal lining of the anal canal, which is in continuity with rectal mucosa or extraluminal columnar epithelium present in anal glands, an anal fistula or a developmental remnant/cyst. The exact location of the tumour mass in either a predominantly mucosal or extramucosal site, taken together with the clinical history and imaging features (e.g. fistulating Crohn's disease), is helpful in determining the likely origin of the tumour. Immunohistochemical profiling with CDX2, CK7 and CK20 may also help to determine this origin.[3,21] For both mucosal and extramucosal adenocarcinomas, the same grading and staging criteria apply irrespective of site of origin within the anal canal. Where a rectal origin is established, it is recommended that the full guidance in the *Dataset for the histopathological reporting of colorectal cancer*[5] be followed, which would include considerations of tumour budding and molecular testing.

Neuroendocrine neoplasms

Neuroendocrine neoplasms (NEN) are tumours of epithelial cell lineage showing neuroendocrine differentiation. This is discussed in the section relating to rectal/hindgut neuroendocrine neoplasms in the RCPath *Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract*.[2]

Undifferentiated carcinoma

This term is not included in the WHO *2019 Classification of anal tumours* but is included in the CAP AJCC classification). This term should be reserved for the rare poorly differentiated epithelial neoplasm showing no evidence of either squamous, neuroendocrine or glandular differentiation by standard H&E staining or immunohistochemistry.[18]

Adjacent dysplasia

Where AIN is present adjacent to an invasive squamous cell carcinoma, this needs to be documented. Any margin involvement should be reported as this impacts on further management and follow-up.

[Level of evidence B – Histological type and grade are important determinants of prognosis and management in anal neoplasia.]

5.3.2 Excision margin

In the surgical management of recurrent and residual anal cancer, completeness of excision (R0) is an important prognostic factor.[15] R1 represents residual microscopic disease and R2 represents residual macroscopic disease. For tumours reaching close to the deep plane of excision (within 1 mm), there are no data that would allow these to be allocated to further prognostic subgroups. Therefore, there is no current evidence that a clearance of <1 mm qualifies for a R1 resection for anal cancer. In the absence of such evidence, this dataset uses the default definition of a R1 resection as the presence of tumour at the resection margin. However, if the clearance is <1 mm this should be explicitly stated.

[Level of evidence B – Completeness of excision is an important determinant of prognosis in surgically treated anal cancer.]

5.3.3 Lymph nodes

Tumours located above the dentate line drain towards the mesorectal, inferior mesenteric and internal iliac systems, whereas tumours below the dentate line drain towards the inguinal nodes. It is suggested that inguinal node involvement occurs at a later stage for tumours in the lower part of the large bowel via retrograde spread as the proximal lymphatic channels of the lower rectum become obliterated by tumour cells.[19] Therefore, both the lymph node group and the number of involved lymph nodes inform the pN stage.[13] Where lymph nodes are included with the resection specimen, it is recommended that all lymph nodes are evaluated histologically.

[Level of evidence B – The extent of tumour spread provides important prognostic information.]

6 Non-core data items

6.1 Angiolymphatic and perineural invasion

Neither angiolymphatic invasion nor perineural invasion constitute a mandatory staging item in the UICC TNM (version 8) classification of anal cancer.[3] There is insufficient data in the literature relating to the relevance of these items regarding prognosis and treatment of anal squamous cell carcinoma. However, depending on specific clinical circumstances (for example anal adenocarcinoma), it may be useful to include these items in the report for discussion at the MDTM.

6.2 Immunohistochemistry

6.2.1 AIN and condylomas

In AIN and condylomas, the diagnosis is primarily based on the examination of H&E-stained sections for the presence of dysplasia in the former and koilocytosis in the latter. The expression of p16 by immunohistochemistry is a surrogate marker of HPV infection and is positive in up to 90% of AIN and squamous cell carcinoma. The presence of p16 expression is useful in separating AIN from condylomas (usually negative) and normal squamous mucosa but immunohistochemistry with either p16 or proliferation markers is not particularly helpful in the grading of dysplasia.[20]

6.2.2 Immunohistochemistry as biomarker of prognosis and response to treatment

HPV

In oropharyngeal squamous cell carcinomas where there is also a strong association with HPV infection, the determination of HPV-status is a mandatory requirement in TNM staging.[2,3] In the anogenital tract the clinical relevance of HPV status is lessened by the fact that most squamous cell carcinomas are HPV+. There is, nevertheless, good evidence that HPV+ tumours as detected by p16 immunohistochemistry carry a better prognosis and respond more favourably to radiochemotherapy.[21] For at least some patients, HPV status may, therefore, become an important point of discussion at the MDTM and this, therefore, should be considered at least as a non-core data item in the histopathology report.

HPV status can be determined by PCR-based assay, in situ hybridisation or immunohistochemistry (with p16 antibody). There is insufficient data that allow for comparison of these methodologies in relation to anal cancer but p16 immunohistochemistry is reliable. It is recommended that immunohistochemical

interpretation of p16 is carried out using the same criteria as proposed for other HPV-associated lesions of the anogenital tract. Thus, patchy mild staining may be seen in normal non-neoplastic cells, whereas block-positivity in nuclear and cytoplasmic distributions represents abnormal over-expression of p16.[20]

PDL1

HPV-associated cancers are prime candidates for immunotherapy with PD-L1/PD1 inhibitors. There is evidence to support a role for nivolumab and pembrolizumab in advanced palliative disease.[14] Although this is not yet in universal practice, it is likely that this will gain increasing acceptance in the near future.[14] Response to therapy will depend on PDL1 expression as determined by immunohistochemistry. There are different assays available and individual laboratories will be required to perform their own validation studies in line with quality assurance arrangements.

Mismatch repair

Mismatch repair/microsatellite instability (MMR/MSI) analysis is indicated in rectal adenocarcinomas as part of screening for Lynch syndrome and also to give an indication in regard to potential response to chemotherapy. With anal squamous cell carcinoma, MMR/MSI analysis is not indicated because it does not form part of Lynch syndrome; MMR/MSI status of these tumours has no bearing on prognosis or treatment response. Adenocarcinomas of the anal canal are often managed oncologically as rectal adenocarcinomas and, therefore, should be subjected to MMR/MSI analysis.

6.3 Predisposing lesions

In resected specimens for squamous cell carcinoma, precursor lesions may be present. These include HPV-associated condylomata and AIN. With adenocarcinomas, evidence of association with Crohn's disease or an origin in an anal gland may be present. While these associated findings do not influence TNM staging and are, therefore, not included as core data, they may have implications for future management. Consideration should, therefore, be given for their inclusion in the free text of the report.

7 Diagnostic coding and staging

The UICC TNM 8 stage[13] is used (see Appendix A) for anal squamous cell carcinomas. The T stage is dependent on size (T1<2 cm; T2 2–5 cm; T3 >5 cm; T4 invasion of an adjacent organ) but often management is based on clinical staging rather pathological

staging, since the primary treatment is not surgical excision in most cases. For adenocarcinomas, it is often difficult to be certain of the exact site of origin in the anorectal region and management of these tumours is similar to that of rectal adenocarcinoma. However, anal adenocarcinoma is staged as for anal squamous cell carcinoma in line with UICC and AJCC.

The site and histological diagnosis should be coded using SNOMED-CT (Appendix B).

8 Frozen sections

Intraoperative frozen sections are not routinely required in the management of anal cancers. Occasionally, however, frozen section diagnoses may be required for the assessment of margins with respect to involvement by either carcinoma or dysplasia.

9 Specific aspects of individual tumours not covered elsewhere

9.1 Superficially invasive squamous cell carcinoma

In the development of anal neoplasia, there is a continuum of dysplastic changes involving the lower 1-third, the lower 2-thirds and near full-thickness squamous epithelium leading to AIN1, AIN2 and AIN3, respectively. Squamous cell carcinoma arises when neoplastic cells breach the basement membrane. The maximum dimension of the invasive component determines the T stage of the anal cancer. In the LAST project,[12] the term superficially invasive carcinoma is used for early tumours of the anogenital tract with an invasive depth of <3 mm and a horizontal dimension of <7 mm when completely excised. In the cervix, such lesions would be sub-classified as corresponding stage T1 and carry specific prognostic and treatment implications. In the anal canal, there is no evidence base to support the further subclassification of T1 tumours; therefore the term ‘superficially invasive squamous cell carcinoma’ is not encouraged. However, it is recognised that it is sometimes difficult to separate early invasion from high grade AIN/HSIL; these lesions require careful consideration at the MDTM in regard to optimal management.

9.2 Paget’s disease

This represents intraepithelial infiltration by neoplastic cells that often contain mucin. In approximately 50% of cases, these cells originate from an invasive adenocarcinoma

arising in either the large bowel, including anal glands, or more rarely in the urogenital tract. In the remaining cases of so-called primary Paget's disease, the tumour most probably originates from the stem cell region of perianal skin in the infundibulo-sebaceous unit. Paget cells may sometimes be seen infiltrating the epithelium of the anal canal, which should be documented in the main text of the histology report. Immunohistochemistry is useful in determining the likely site of origin (refer to page 208 of the WHO *Classification of digestive system tumours, 5th edition*, 2019).[3]

9.3 Perianal cancers

This dataset deals only with tumours that are classified as anal neoplasms according to the WHO 2019 *Classification of tumours* and UICC TNM *Classification of malignant tumours, version 8*. All squamous cell carcinomas arising within 5 cm of the anal margin are staged as carcinoma of the anal canal and are treated according to the same management protocol. Primary adnexal cutaneous tumours including basal cell carcinomas arising in the perianal region are not discussed here. The relevant histological features and grading of these tumours are discussed in the RCPath dataset on primary cutaneous tumours.[6]

10 Criteria for audit

The following are recommended by the College as key assurance indicators (see Key assurance indicators for pathology services, November 2019) and key performance indicators (see Key Performance Indicators – Proposals for implementation, July 2013):

- cancer resections must be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer datasets. English trusts are required to implement the structured recording of core pathology data in the COSD
  - standard: 95% of reports must contain structured data.
- cellular pathology reporting turnaround times: this informs CPA standard G1 and ISO15189:2012 standards 4.4.1 and 4.14.1. The proportion of all final reports on diagnostic cytology and histopathology cases that are reported, confirmed and authorised within 7 and 10 calendar days of the procedure shall be published and recorded.

– standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.

11 References

1. Moorghen M, Wong NACS. *Standards and datasets for reporting cancers: Dataset for histopathological reporting of anal cancer*. London, UK: Royal College of Pathologists, 2018. Available at: www.rcpath.org/resourceLibrary/g165-dataset-for-histopathological-reporting-of-anal-cancer.html

2. Luong TV, Watkins J, Chakrabarty B, Wang LM. *Standards and datasets for reporting cancers: Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract*. London, UK: Royal College of Pathologists, 2019. Available at: www.rcpath.org/uploads/assets/f5fb75c6-77c7-4305-9b406a617f81391e/g081_dataset_for_histopathological_reporting_of_neuroendocrine_neoplasms_of_the_gastrointestinal_tract.pdf

3. World Health Organization. *WHO Classification of tumours: Digestive system tumours (5th edition)*. Lyon, France: International Agency for Research on Cancer, 2019.

4. Amin MB, Edge SB, Greene LF, Byrd RD, Gershenwald EJ, Compton CC *et al*. *AJCC Cancer Staging Manual (8th edition)*. Chambersburg, Pennsylvania: Springer, 2017.

5. Loughrey MB, Quirke P, Shepherd NA. *Standards and datasets for reporting cancers: Dataset for histopathological reporting of colorectal cancer*. London, UK: Royal College of Pathologists, 2018. Available at: www.rcpath.org/static/c8b61ba0-ae3f-43f1-85ffd3ab9f17cfe6/G049-Dataset-for-histopathological-reporting-of-colorectal-cancer.pdf

6. Slater D, Barrett P. *Standards and datasets for reporting cancers: Dataset for histopathological reporting of primary invasive cutaneous squamous cell carcinoma and regional lymph nodes*. London, UK: Royal College of Pathologists, 2019. Available at: www.rcpath.org/uploads/assets/9c1d8f71-5d3b-4508-8e6200f11e1f4a39/Dataset-for-histopathological-reporting-of-primary-invasive-cutaneous-squamous-cell-carcinoma-and-regional-lymph-nodes.pdf

7. Zidar N, Langner C, Odar K, Hošnjak L, Kamaradova K, Poljak M *et al*. Anal verrucous carcinoma is not related to infection with human papillomaviruses and should be distinguished from giant condyloma (Buschke–Lowenstein tumour). *Histopathology* 2017;70: 938–945.

8. Richart RM. Natural history of cervical intraepithelial neoplasia. *Clin Obstet Gynecol* 1967;10:748–84.

9. Buckley CH, Butler EB, Fox H. Cervical intraepithelial neoplasia. *J Clin Pathol* 1982;35-13.

10. Fenger C, Nielsen VT. Intraepithelial neoplasia in the anal canal. The appearance and relation to genital neoplasia. *Acta Pathol Microbiol Scand A* 1986;94:343–349.

11. Solomon D. The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. *Acta Cytol* 1989;33:567–574.

12. Darragh TM, Colgan TJ, Cox TJ, Heller SD, Henry MR, Luff RD *et al*. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Int J Gynecol Pathol* 2013;32:76–115.

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

14. National Comprehensive Cancer Network. *NCCN Clinical practice guidelines in oncology. Anal carcinoma version 1*. 2022. Accessed October 2022. Available at: www.NCCN.org

15. Rao S, Guren MG, Khan K, Brown G, Renehan AG, Steigen ES *et al*. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol* 2021;32:1087–1100.

16. Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE *et al*. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 2005;47:141–146.

17. Meriden Z, Montgomery EA. Anal duct carcinoma: a report of 5 cases. *Hum Pathol* 2012;43:216–220.

18. Balachandra B, Marcus V, Jass JR. Poorly differentiated tumours of the anal canal: a diagnostic strategy for the surgical pathologist. *Histopathology* 2007;50:163–174.

19. Morson BC. The pathology and results of treatment of squamous cell carcinoma of the anal canal and anal margin. *Proc R Soc Med* 1960;53:416–420.

20. The British Association of Gynaecological Pathologists. *Interpretation of p16 immunohistochemistry in lower anogenital tract neoplasia*. Accessed October 2022.

Available at: www.thebagp.org/download/bagp-ukneqas-c1qc-project-interpretation-guide-2018

21. Urbute A, Rasmussen CL, Belmonte F, Obermueller T, Prigge SE, Arbyn M *et al*. Prognostic significance of HPV DNA and p16INK4a in anal cancer: A systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2020;29:703–710.

Appendix A Anal cancer staging (UICC TNM 8)[13]

Primary tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ. Bowen's disease, high-grade squamous intraepithelial lesion (HSIL) and intraepithelial neoplasia II–III (AINII and III)

T1 Tumour 2 cm or less in greatest dimension

T2 Tumour >2 cm but </= 5 cm in greatest dimension

T3 Tumour >5 cm in greatest dimension

T4 Tumour of any size invades adjacent organ(s), e.g. vagina, urethra, bladder. (Direct invasion of the rectal wall, perianal skin, subcutaneous tissue or the sphincter muscle(s) alone is not classified as T4.)

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in regional lymph node(s)

- N1a Metastases in inguinal, mesorectal and/or internal iliac nodes
- N1b Metastases in external iliac nodes
- N1c Metastases in external iliac and in inguinal, mesorectal and/or internal iliac nodes

Distant metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

TNM descriptors

'm' suffix, i.e. pT(m), indicates multiple tumours.

‘y’ prefix indicates neoadjuvant chemotherapy, radiation therapy or both chemotherapy and radiotherapy.

‘r’ prefix indicates recurrent tumour.

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T1, T2	N1	M0
Stage IIIB	T4	N0	M0
Stage IIIC	T3, T4	N1	M0
Stage IV	Any T	Any N	M1

Appendix B SNOMED codes for anal tumours

Topographical codes are used in SNOMED to indicate the organ/site of lesions and morphological codes (M) are used for indicate the morphological diagnosis.

Topographical codes	**SNOMED**	**SNOMED-CT terminology**	**SNOMED-CT code**
Anus	T69000 (SNOMED 2) T59910 (SNOMED 3)	Anal canal structure (body structure)	34381000

Morphological codes	**SNOMED 2 or 3**	**SNOMED-CT terminology**	**SNOMED-CT code**
Squamous cell carcinoma	M80703	Squamous cell carcinoma, no ICD-O subtype (morphologic abnormality)	28899001
Dysplasia	M74000	Dysplasia (morphologic abnormality)	25723000
Dysplasia high grade	M74003	Severe dysplasia (morphologic abnormality)	28558000
Carcinoma	M80103	Carcinoma, no subtype (morphologic abnormality)	68453008
Verrucous carcinoma	M80513	Verrucous carcinoma (morphologic abnormality)	89906000
Adenocarcinoma	M81403	Adenocarcinoma, no subtype (morphologic abnormality)	59367005
Mucinous adenocarcinoma	M81403	Mucinous adenocarcinoma (morphologic abnormality)	72495009
Undifferentiated carcinoma	M80203	Carcinoma, undifferentiated (morphologic abnormality)	3854900

Procedure codes (P) Local P codes should be recorded. At present, P codes vary according to the SNOMED system used in different institutions.

Appendix C Reporting proforma for anal cancer: excisional specimen biopsy

Surname: ……Forenames:……Date of Birth: ……Sex:……

Hospital…….…… Hospital No: ……..……NHS No:……..

Date of Surgery: …… Date of Report Authorisation: ……Report No:……

Date of Receipt:…… Pathologist:…….…… Clinician:……

Macroscopic description

Specimen type

Anal canal □ Perianal skin (within 5 mm of anal verge) □ Anal canal and perianal skin □ Anal canal and rectum □

Size of specimen: ….. mm x ….. mm x ….. mm

Maximum size of tumour: ….. mm

Histology

Tumour type

Squamous cell carcinoma □ Adenocarcinoma □
Adenocarcinoma (mucinous variant) □ Adenocarcinoma (signet ring cell variant) □
Undifferentiated carcinoma □ Verrucous carcinoma □

Differentiation

Well differentiated □ Moderately differentiated □ Poorly differentiated □ Undifferentiated □

Background epithelium

Non-keratinising squamous □ Keratinising squamous □ Columnar □

Adjacent surface squamous dysplasia: Not identified □ AIN1 (LSIL) □ AIN2/3 (HSIL) □

Margin/s involved by dysplasia

N/A □ Yes □ No □

Maximum microscopic size of tumour: ….. mm or □ N/A (more than 20 mm see macroscopic description)

Depth of invasion

Lamina propria □ Submucosa □ Muscularis propria □ Striated muscle □

Post-treatment tumour regression

Grade N/A □ 0 □ 1 □ 2 □ 3 □

Peripheral margins

Involved □ Not involved □

Distance to nearest peripheral margin: N/A □ ….. mm

Deep (CRM) margin

Involved □ Not involved □

Distance to deep margin: …..mm

Lymph nodes submitted separately

No □ Yes □

If yes: Peri-rectal lymph nodes: total no: …; no positive:…

Internal iliac/inguinal: total no: …; no positive:…

Stage (UICC TNM version 8)

pT category: pTx □ pT0 □ pTis □ pT1 □ pT2 □ pT3 □ pT4 □

pN category: pNx □ pN0□ pN1a □ pN1b □ pN1c □

Excision: pT0 □ pR0 □ pR1 □ pR2 □

Post-neoadjuvant therapy (y): Yes □ No □

Distant metastasis/es: N/A □ Yes □ No □

Representative molecular block(s):

Tumour percentage assessment (Number of tumour cells / total number of nucleated cells): ……%

Signature: **Date:** **SNOMED CODE:**

Appendix D Reporting proforma for anal cancer: abdominoperineal resection

Surname: ……Forenames:……Date of Birth: ……Sex:……

Hospital…… Hospital No: ……NHS No:……..

Date of Surgery: …… Date of Report Authorisation: ……Report No:……

Date of Receipt:…… Pathologist:…… Clinician:……

Macroscopic description

Length of specimen: .... mm

Length of perianal skin: .... mm

Surgical plane of excision: Extra-levator □ Sphincteric □ Intra-sphincteric □

Adjacent organs included: Bladder □ Coccyx □ Uterus □ Other □ (specify ……..)

Site of tumour: Anterior □ Posterior □ Right lateral □ Left lateral □

Maximum size of tumour: .... mm

Distance of tumour to perianal skin resection margin: .... mm

Distance of tumour to anal verge: .... mm

Distance of tumour to deep (CRM) margin: .... mm

Histology

Tumour type

Squamous cell carcinoma □ Adenocarcinoma □
Adenocarcinoma (mucinous variant) □ Adenocarcinoma (signet ring cell variant) □
Undifferentiated carcinoma □ Verrucous carcinoma □

Differentiation

Well differentiated □ Moderately differentiated □ Poorly differentiated □ Undifferentiated □

Adjacent surface squamous dysplasia: Not identified □ AIN1 (LSIL) □ AIN2/3 (HSIL) □□

Margin/s involved by dysplasia

N/A □ Yes □ No □

Maximum microscopic size of tumour: ….. mm or □ N/A (more than 20 mm see macroscopic description)

Depth of invasion

Lamina propria □ Submucosa □ Muscularis propria □ Smooth muscle □
Striated muscle□ Named adjacent organ (e.g. coccyx) □ (specify ……..)

Post-treatment tumour regression

Grade N/A □ 0 □ 1 □ 2 □ 3 □

Deep (CRM) margin

Involved □ Not involved □

Distance to deep margin: ….. mm

Lymph nodes with main specimen

Total no: No positive:

Lymph nodes submitted separately: No □ Yes □

If yes: Peri-rectal lymph nodes: total no: …; no positive:…

Internal iliac/inguinal: total no: …; no positive:…

Distant metastasis/es: N/A □ No □ Yes □

Stage (UICC TNM version 8)

pT category: pTx □ pT0 □ pTis □ pT1 □ pT2 □ pT3 □ pT4 □

pN category: pNx □ pN0 □ pN1a □ pN1b □ pN1c □

Excision: pT0 pR0 pR1 pR2

Post-neoadjuvant therapy (y): Yes □ No □

Distant metastasis/es: N/A □ Yes □ No □

Representative molecular block(s):

Tumour percentage assessment (Number of tumour cells / total number of nucleated cells): ……%

Signature: **Date:** **SNOMED CODE:**

Appendix E Reporting proforma for anal cancer: excisional specimen biopsy in list format

Element name	Values	COSD v9
Specimen type	Single selection value list: Anal canal Perianal skin (within 5 mm of anal verge) Anal canal and perianal skin Anal canal and rectum	
Size of specimen	Size in mm x mm x mm	
Maximum size of tumour	Size in mm	pCR0830
Tumour type	Single selection value list: Squamous cell carcinoma Adenocarcinoma (mucinous variant) Adenocarcinoma (signet ring cell variant) Undifferentiated carcinoma Verrucous carcinoma	
Differentiation	Single selection value list: Well differentiated Moderately differentiated Poorly differentiated Undifferentiated	pCR0860 G1 = Well differentiated G2 = Moderately differentiated G3 = Poorly differentiated G4 = Undifferentiated/anaplastic GX = Blank
Background epithelium	Multiple selection value list: Non-keratinising squamous Keratinising squamous Columnar	
Adjacent squamous dysplasia	Single selection value list: Not identified AIN1 (LSIL) AIN2/3 (HSIL)	
Margin/s involved by dysplasia	Single selection value list: N/A No Yes	

Maximum microscopic size of tumour	Size in mm or N/A	
Depth of invasion	Single selection value list: Lamina propria Submucosa Muscularis propria Smooth muscle Striated muscle	
Post-treatment tumour regression	Single selection value list: N/A 0 1 2 3	pCO5290 97 = N/A 08 = 0 09 = 1 10 = 2 11 = 3
Peripheral margins	Single selection value list: Involved Not involved	pCO5190 1 = Involved 0 = Not involved 9 = Blank
Distance to nearest peripheral margin	Distance in mm or N/A	
Deep (CRM) margin	Single selection value list: Involved Not involved	pCO5300 1 = Involved 0 = Not involved 9 = Blank
Distance to deep margin	Distance in mm	pCO5210
Lymph nodes submitted separately	Single selection value list: No Yes	
Total peri-rectal lymph nodes	Integer	
Positive peri-rectal lymph nodes	Integer	
Total internal iliac/inguinal lymph nodes	Integer	
Positive internal iliac/inguinal lymph nodes	Integer	
UICC TNM version 8 pT category	Single selection value list: pTX	pCR0910

	pT0 pTis pT1 pT2 pT3 pT4	
UICC TNM version 8 pN category	Single selection value list: pNX pN0 pN1a pN1b pN1c	pCR0920
Excision	Single selection value list: N/A pT0 R0 R1 R2	
Post-neoadjuvant therapy (y)	Single selection value list: Yes No	pCR1000
Distant metastasis/es	Single selection value list: N/A Yes (M1) No	
Representative molecular block(s)	Free text	
Tumour percentage assessment (number of tumour cells/total number of nucleated cells)	0–100 %	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	pCR6410
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	pCR6420

Appendix F Reporting proforma for anal cancer: abdominoperineal resection in list format

Element name	Values	Implementation notes	COSD v9
Length of specimen	Distance in mm		
Length of perianal skin	Distance in mm		
Surgical plane of excision	Single selection value list: • Extra-sphincteric • Inter-sphincteric • Intra-sphincteric		
Adjacent organs included	Multiple selection value list: • Bladder • Coccyx • Uterus • Other		
Adjacent organs included, other, specify	Free text	Only applicable if 'Adjacent organs included, Other' is selected.	
Site of tumour	Multiple selection value list: • Anterior • Posterior • Right lateral • Left lateral		
Maximum size of tumour	Size in mm		pCR0830
Distance of tumour to perianal skin resection margin	Distance in mm		
Distance of tumour to anal verge	Distance in mm		
Distance of tumour to deep margin, macroscopic	Distance in mm		pCO5210
Tumour type	Single selection value list:		

	• Squamous cell carcinoma • Adenocarcinoma Adenocarcinoma (mucinous variant) • Adenocarcinoma (signet ring cell variant) • Undifferentiated carcinoma • Verrucous carcinoma		
Differentiation	Single selection value list: • Well differentiated • Moderately differentiated • Poorly differentiated • Undifferentiated		pCR0860 G1 = Well differentiated G2 = Moderately differentiated G3 = Poorly differentiated G4 = Undifferentiated GX = Blank
Adjacent squamous dysplasia	Single selection value list: • Not identified • AIN1(LSIL) • AIN2/3 (HSIL)		
Adjacent squamous dysplasia, grade	Single selection value list: • 1 • 2 • 3	Only applicable if 'Adjacent squamous dysplasia, Present' is selected.	
Margin/s involved by dysplasia	Single selection value list: • N/A • No • Yes		
Maximum microscopic size of tumour	Size in mm or N/A		
Depth of invasion	Single selection value list: • Lamina propria • Submucosa		

	• Muscularis propria • Smooth muscle • Striated muscle • Named adjacent organ		
Depth of invasion, named adjacent organ, specify	Free text	Only applicable if 'Depth of invasion, Named adjacent organ' is selected.	
Post-treatment tumour regression	Single selection value list: • N/A • 0 • 1 • 2 • 3		
Deep (CRM) margin	Single selection value list: • Involved • Not involved		pCO5300 • Involved = 1 – Margin involved • Not involved = 0 – Margin not involved • Blank = 9 – Not known
Distance to deep margin	Distance in mm		pCO5210
Total lymph nodes with main specimen	Integer		pCR0890
Positive lymph nodes with main specimen	Integer		pCR0900
Lymph nodes submitted separately	Single selection value list: • No • Yes		
Total peri-rectal lymph nodes	Integer	Only applicable if 'Lymph nodes	

		submitted separately, Yes' is selected.	
Positive peri-rectal lymph nodes	Integer	Only applicable if 'Lymph nodes submitted separately, Yes' is selected.	
Total internal iliac/inguinal lymph nodes	Integer	Only applicable if 'Lymph nodes submitted separately, Yes' is selected.	
Positive internal iliac/inguinal lymph nodes	Integer	Only applicable if 'Lymph nodes submitted separately, Yes' is selected.	
UICC TNM version 8 pT category	Single selection value list: • pTX • pT0 • pTis • pT1 • pT2 • pT3 • pT4		pCR0910
Excision	Single selection value list: • N/A pT0 • R0 • R1 • R2		
Post-neoadjuvant therapy (y)	Single selection value list: • Yes • No		pCR1000
Distant metastasis/es	Single selection value list: • N/A • Yes • No		
Representative molecular block(s)	Free text		
Tumour percentage assessment (number of tumour	0–100 %		

cells/total number of nucleated cells)			
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.		pCR6410
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.		pCR6420

Appendix G Anal cancer tumour regression (post-neoadjuvant therapy)[4]

No viable cancer cells	Grade 0 (complete regression)
Single cells or small groups of cells	Grade 1 (moderate response)
Residual cancer outgrown by fibrosis	Grade 2 (minimal response)
Minimal or no regression	Grade 3 (poor response)

Appendix H Summary table – Explanation of grades of evidence

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

Grade (level) of evidence	Nature of evidence
Grade A	At least 1 high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled 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 causal and which are directly applicable to the target population 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 population 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 I AGREE II guideline monitoring sheet

The autopsy guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this autopsy guideline that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Foreword, 1
2 The health question(s) covered by the guideline is (are) specifically described	Foreword, 1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 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	Foreword
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	4, 5
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	2–9
16 The different options for management of the condition or health issue are clearly presented	2–9
17 Key recommendations are easily identifiable	2–9
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	Appendices A–G
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	10
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