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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of anal cancer

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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. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special 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 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 90% 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 stakeholders consulted for this document were:

- British Society of Gastroenterology.

The evidence base has been obtained by consultation of electronic databases using PubMed, review articles, original articles, and other guidelines and reporting protocols. This dataset conforms to the criteria for grading and staging as set out in the *WHO Classification of Digestive Tumours (4th edition, 2010)*[1] and the *TNM Classification of Malignant Tumours (8th edition)*[2] from the Union for International Cancer Control (UICC). For most of the items to be included, the strength of the supportive evidence has been reviewed according to SIGN guidelines (see Appendix H). Consensus was reached between the authors taking into account feedback received during the consultation process.

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

A formal revision cycle for all cancer datasets takes place on a three-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 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 short notice of change 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, Working Group on Cancer Services and Lay Governance Group and placed on the College website for consultation

with the membership from 25 October to 22 November 2017. 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 Director of Publishing and Engagement.

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 have declared no conflicts of interest.

1 Introduction

The National Institute for Health and Care Excellence (NICE) recommends that patients with anal cancer are treated by a specialist team. This dataset is developed in order to assist pathologists in providing useful and accurate information for the purpose of managing patients with cancer of the anal canal in an multidisciplinary team (MDT) meeting.

Malignant tumours that are not of epithelial origin (e.g. gastrointestinal stromal tumours, melanomas, etc.) are not dealt with in this dataset. For the pathological staging and grading of anal cancer, the *TNM Classification of Malignant Tumours (8th edition)*[2] from the UICC and the *WHO Classification of Digestive Tumours (4th edition, 2010)*[1] are used.

1.1 Target users and health benefits of this guideline

It is envisaged that the main users of the datasets 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, endocrinologists and radiologists. They will also be of use to cancer registries.

1.2 Anatomy of anal canal

The anal canal is the caudal part of the large intestine. This extends from the proximal end of the anorectal ring to the anal verge and measures between 3 cm and 5 cm. The anorectal ring represents an anatomical landmark that is palpable by digital examination and overlies the site where the outer longitudinal muscle layer of the rectal muscularis propria starts to blend with striated muscle fibres of puborectalis and levator ani muscle. This landmark is not readily identifiable in resection specimens and is lined by columnar mucosa resembling rectal mucosa. The anal verge is the junction between anal canal and perianal skin, and therefore corresponds to the transition between non-keratinising squamous epithelium without skin appendages and keratinising squamous epithelium with underlying skin appendages.

The dentate line, so-called 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. This is not the same as a definition that is often erroneously used for the dentate line corresponding to the level of the squamocolumnar junction. 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 four to ten 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 therefore not contain an ATZ. The relation 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 mucosa, a varying amount of transitional type epithelium and finally non-keratinising squamous epithelium. It is also important not to confuse the ATZ with the so-called 'transformation zone', which may occur proximal to the ATZ and represents a zone of metaplastic squamous mucosa of variable length. This 'transformation zone' is particularly prone to HPV infection and is associated with the development of anal squamous cell carcinoma.[1,3]

In the pre-treatment clinical assessment of tumours arising in the anal region, tumours located within 5 cm of the anus and seen completely when gentle traction is applied to the buttocks are considered to be perianal and those that cannot be seen entirely when gentle traction is applied on the buttocks are considered to be of anal origin. This definition is used by the WHO classification and is useful in the clinical management of these tumours.[1–3] Under TNM 8, cancers arising in perianal skin (within 5 cm of anal margin) are now classified with anal canal carcinomas.[2]

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 and NHS/CHI 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. HIV infection or other immunosuppression; genital warts, associated or previous anal intraepithelial neoplasia [AIN]; vulval/vaginal/cervical neoplasia)
- indication whether this is a diagnostic procedure, curative resection or palliative procedure
- anatomical location (see above under section 1.2 'Anatomy of anal canal')
- information about any suture markers in the specimen
- clinical diagnosis (e.g. squamous cell carcinoma)
- previous treatment (e.g. chemoradiotherapy)
- sites of any lymph nodes submitted separately (if applicable).

3 Preparation of specimens before dissection

All specimens should be fixed in formalin according to standard laboratory protocol. Excision specimens should be orientated according to the information provided and the relevant margins should be inked. The specimens should be pinned prior to fixation in order to minimise tissue distortion and allow for adequate orientation. Abdominoperineal (AP) resection specimens should be handled as for rectal adenocarcinomas (see RCPath *Dataset for colorectal cancer histopathology reports)*;[4] the specimen should be opened, cleaned, pinned and fixed in formalin prior to dissection.

4 Specimen handling and block selection

Only resection specimens of anal cancer are considered in this document. Anal squamous cell carcinomas are treated primarily by non-surgical means. Therefore, large resection specimens (e.g. abdominoperineal resection) are seen infrequently; these are usually

performed for recurrent disease and/or following failure of chemoradiotherapy. A more common form of resection specimen is the local excision of a small cancer, hereafter referred to as an excisional biopsy specimen.

4.1 Resection specimen types

These specimens can vary from a small segment of the anal canal to the entire anorectum to include the mesorectum and lymph nodes or extensive exenterations which include adjacent organs such as the coccyx. The purpose of the examination is to determine the type and grade of the tumour, the stage of the tumour and completeness of excision. It may therefore be required to serially slice the tumour and take representative blocks taking care to maintain orientation and allow for accurate assessment of all margins, which are to be inked as appropriate.

4.2 Number of blocks

There is no evidence-based protocol for tumour sampling in respect of the minimum number of blocks required. However, it is recommended that tumours measuring up to 1 cm in diameter should be blocked entirely in order to allow for the examination of sufficient material for a reliable assessment of tumour type and grade. The number of blocks should also allow for the assessment of inked margins and assessment of mucosa adjacent to the invasive lesion for the assessment of, for example, AIN. 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.

[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[1] and pathological staging[2] where required. The list provided below applies to all resection specimens of anal cancers. 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

Items include:

- specimen dimensions
- site of tumour
- tumour appearance (e.g. ulcerated nodule) and size
- distance of tumour to peripheral and deep margins (for excisional biopsies)

- any lymph nodes received (if applicable).

5.2.2 Microscopic data

Items include:

- type of background epithelium (e.g. keratinising/non-keratinising squamous epithelium)
- histological type of tumour (see histological classification below)
- tumour differentiation
- maximum size of tumour
- depth of invasion
- involvement of margins (deep and peripheral)
- distance to deep margin and nearest peripheral margin
- number of lymph nodes and number of involved lymph nodes (if applicable)
- adjacent abnormality (e.g. AIN).

5.3 Specific information about anal cancers

5.3.1 Histological classification of anal cancers (WHO 2010)[1]

- Squamous cell carcinoma.
- Verrucous carcinoma.
- Adenocarcinoma.
- Mucinous adenocarcinoma.
- Neuroendocrine carcinoma.
- Undifferentiated carcinoma.

Squamous cell carcinoma

This tumour is frequently associated with HPV infection and comprises the majority of anal cancers.[5] The histological appearances are variable and include large cell non-keratinising, large cell keratinising, basaloid tumours and squamous cell carcinomas with focal ductal differentiation and often more than one subtype coexists within any particular tumour. It is recommended[1,6] 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. 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

The WHO and AJCC (American Joint Committee on Cancer) recommend the grading of squamous cell carcinoma using a three-tier grading system (well differentiated, moderately differentiated and poorly differentiated).[1,7] Poor differentiation is a probable marker of adverse prognosis,[1,7,8] but there is no evidence for a difference in outcome between well differentiated and moderately differentiated carcinomas. Tumours showing no evidence of squamous differentiation in either H&E sections or following immunohistochemical staining should be categorised as undifferentiated carcinoma.[9] The grading of squamous cell carcinoma does not alter the management of anal carcinoma in most cases. However, for early (i.e. T1N0) cancers that are not poorly differentiated, a primary surgical approach may be favoured.[10] For this reason tumour grading should be included as a core item especially for excisional biopsy specimens.

Adjacent dysplasia

Where AIN is present adjacent to the invasive squamous cell carcinoma this needs to be documented and completeness of excision commented upon because this impacts upon further management regarding follow-up.

Tumour size and depth of invasion

The stage of the tumour is dependent upon size and this relates directly to prognosis. Although the 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.[7,8,11]

Effects of chemoradiotherapy

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.*[12] 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

Verrucous carcinoma is a variant that should be recorded separately from squamous cell carcinoma on account of its more favourable prognosis. This is a low-grade tumour characterised by an endophytic condylomatous growth pattern and is also referred to as a giant condyloma or a Bushke-Lowenstein tumour. These tumours typically invade locally and do not metastasise and are treated primarily by surgery. Sometimes the tumour includes focal areas of severe cytological atypia with stromal invasion; in this situation these features should lead to the designation of squamous cell carcinoma instead and graded appropriately. It may be difficult to establish the exact site of origin of verrucous carcinomas since these are typically large exophytic tumours forming cauliflower-like masses originating from a wide base. Where these are deemed to arise from the perianal skin rather than anal canal it is more appropriate to apply the TNM staging system for skin cancer instead.

Adenocarcinoma

Adenocarcinoma of the anal canal arises from the surface mucosa (columnar cuff), anal glands or the lining of fistula tracts; however, most adenocarcinomas within the anal canal represent downward spread from rectal lesions. Tumours are graded using the same criteria as colorectal adenocarcinomas.[1] Adenocarcinomas arising in anal glands sometimes show a mucinous phenotype and often these are composed of small tubular acini. The immunohistochemical staining profile is CK7+, CK20+/- and CDX2-. However, based solely on these histopathological criteria it may be impossible to separate these from rectal adenocarcinomas and the only clues then would be the absence of surface glandular dysplasia, the presence of background anal gland dysplasia and an origin centred in the wall of the anal canal.[13,14] Such cases should be carefully considered by the MDT specialist team who may take the pragmatic view that tumours should be classified as rectal if the epicentre is more than 2 cm proximal to the dentate line and anal cancer if the epicentre is at or less than 2 cm from the dentate line.

Adenocarcinomas arising in fistula tracts are often mucinous but again an exact point of origin is often difficult to determine. Indirect supportive evidence for such an origin may be sought from the clinical history (e.g. Crohn's disease), and demonstration of an anatomical relationship with a fistula tract if possible.

Mucinous adenocarcinoma

These are rare tumours, many of which arise from the rectum. The criteria for diagnosis are the same as for colorectal mucinous adenocarcinoma with more than 50% of the tumour comprising extracellular mucin.[1]

Neuroendocrine tumours

These are predominantly of rectal origin although some may originate in the ATZ.[13] The RCPath *Dataset for neuroendocrine tumours of the gastrointestinal tract including the pancreas*[15] should be completed for these tumours. Neuroendocrine tumours (NET) are graded as Grade 1 and Grade 2 according to proliferative activity (Grade 1: <2 mitoses per 10 high power fields [HPF] and/or <2% Ki67 index; Grade 2: 2–20 mitoses per 10 HPF and/or 3–20% Ki67 index) and correspond to 'carcinoid' tumours in old terminology. Evidence of neuroendocrine differentiation, usually by staining for synaptophysin and chromogranin, is required.[1] Neuroendocrine carcinomas are either of small cell type or large/non-small cell type and show high mitotic activity (>20 per 10 HPF and/or >20% Ki67 index); these tumours are graded as Grade 3. There is a further subgroup of mixed tumours (mixed adenoneuroendocrine carcinoma) where the second component comprises at least 30% of the tumour. In the anal canal the mixed tumour may include either a squamous or a glandular component. It follows, therefore, that focal neuroendocrine differentiation comprising less than 30% of the tumour precludes a designation of NET/carcinoma.

Undifferentiated carcinoma

These tumours are defined as malignant epithelial neoplasms with no evidence of glandular, squamous or neuroendocrine differentiation. Epithelial differentiation should be confirmed by immunohistochemistry and/or electron microscopy.[1,9]

[Level of evidence C – histological subtype provides a guide to appropriate management regarding guiding prognosis and response to therapy. This information is also important for cancer registration.]

5.3.2 Excision margins

In the surgical management of recurrent and residual anal cancer, completeness of excision (R0) is an important prognostic factor.[11,16] R1 represents residual microscopic disease and R2 residual macroscopic disease. For tumours reaching close to the deep plane of excision (i.e. within 1–2 mm) there are no data that would allow these to be allocated to further prognostic subgroups. However, for the purpose of discussion in the MDT and subsequent management, it is recommended that a qualifying statement is included to indicate closeness to the deep margin.

[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.[17] Therefore, the lymph node group and the number of lymph nodes affect the pN stage.[2] Where lymph nodes are included with the resected specimen it is recommended that all lymph nodes are evaluated.

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

6 Non-core data items

Non-core data items in College datasets are defined as those that are preferences of individual laboratories, items for clinical research or supplementary information that may contribute to management or treatment decisions in individual cases. These are not required for TNM staging and may be included in the free text of the report. Examples of these are given below.

6.1 Angiolymphatic and perineural invasion

Neither angiolymphatic invasion nor perineural invasion constitute a mandatory staging item under the TNM 8 classification.[2] There are no data in the literature relating to the relevance of these items regarding prognosis and treatment. However depending on specific clinical circumstances, it may be useful to include these items in the report.

6.2 Immunohistochemistry

In the histopathological assessment of anal cancers immunohistochemistry is not routinely required. There are, however, situations where this is helpful in ascertaining the precise tumour type particularly where there is poor differentiation. In this regard the expression of CK5/6, p63 and p40 show high specificity for squamous cell carcinoma.[9] Adenocarcinomas arising from colorectal type epithelium show positivity for CK20 and absent or weak staining for CK7 whereas the converse applies to adenocarcinoma from anal glands.[9,14] However there is an overlap in staining profile which reduces the usefulness of this approach.[13] Immunohistochemistry is naturally required in the diagnosis of undifferentiated carcinomas. These are malignant epithelial tumours showing no evidence of either glandular or squamous differentiation. Neuroendocrine markers should also be negative and the immunohistochemical panel should also allow for exclusion of melanomas, mesenchymal neoplasms and lymphomas.

6.2.1 Immunohistochemistry as biomarker of prognosis

There are currently no immunohistochemical markers which can be used as markers of prognosis or response to therapy. p16 is reliable as a surrogate immunohistochemical marker of HPV infection and is expressed in some 90% of anal squamous cell carcinomas. It is claimed that the expression of p16 is an independent prognostic factor, but because of heterogeneity of expression and the use of different cut-off points in assessing tumour samples, this cannot be recommended yet as part of routine practice[18–20] in relation to invasive squamous cell carcinoma. In the assessment of pre-invasive lesions (i.e. AIN), p16 is useful in confirming high-grade disease.

6.3 Predisposing lesions

In resected specimens for squamous cell carcinoma, precursor lesions may be present. These include evidence of HPV-associated condylomatous changes and AIN. With adenocarcinomas, evidence of association with Crohn's disease or an origin in the 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[2] is used (see Appendix A) for anal squamous cell carcinomas, adenocarcinomas, undifferentiated carcinomas and high-grade neuroendocrine carcinomas.

Well differentiated NETs are staged according to the TNM classification for large bowel and small intestinal NETs.[1,2] The site and histological diagnosis should be coded using SNOMED (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 for involvement by either invasive or in-situ disease.

9 Specific aspects of individual tumours not covered elsewhere

9.1 AIN and microinvasive squamous cell carcinoma

The diagnosis and management of AIN is beyond the scope of this dataset, which deals only with invasive anal cancers. However, pre-invasive neoplastic lesions are not uncommonly encountered in anal cancer resection specimens and in biopsies of presumed cancers. Where neoplastic squamous cells have not penetrated the basement membrane, these lesions have traditionally been graded as AIN1, AIN2 and AIN3. The AJCC recommends that the terms low-grade squamous intra-epithelial lesion and high-grade squamous intra-epithelial lesion are used instead. In the WHO classification the favoured terms are AIN and anal squamous intra-epithelial neoplasia and a two-tier grading system (high grade/low grade) is then employed such that AIN2 and AIN3 lesions correspond to high-grade changes and are staged as Tis in the TNM classification, whereas AIN1 corresponds to a low-grade lesion.

The term 'microinvasive squamous cell carcinoma' is not recommended[21] and is not recognised in the WHO classification,[1] and there are no data to support this as a separate subgroup from a pT1 tumour in terms of prognosis and treatment. Where there is difficulty in ascertaining invasion, multiple levels are recommended, and care should be taken not to mistake involvement of adnexal structures for invasion.

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 from 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 and this should be documented in the main text of the histology report. Immunohistochemistry is useful in determining the likely site of origin since tumours of anorectal origin are CK20+, CK7- and GCDFP-15-.

9.3 Perianal cancers

This dataset deals only with tumours that are classified as anal cancers according to the WHO (2010) classification. It is often difficult to separate anal cancers from perianal cutaneous tumours and these indeed share a common classification and staging system under the TNM 8 classification of malignant tumours. A detailed classification of primary cutaneous cancers (e.g. basal cell carcinoma) that do not overlap with anal cancers is not

provided here. The relevant histological features and grading of these tumours is discussed in the RCPath datasets of primary cutaneous adnexal tumours[22] and basal cell carcinoma.[23]

10 Criteria for audit

As recommended by the RCPath as key performance indicators (see *Key Performance Indicators – Proposals for implementation,* July 2013*,* http://www.rcpath.org/resourceLibrary/key-performance-indicators---proposals-forimplementation-.html):

- 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 by January 2016.
  - 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 seven and ten calendar days of the procedure shall be published and recorded.
  - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

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Appendix A Anal cancer – TNM staging (UICC TNM 8)[2]

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 not more than 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
Neuroendocrine tumour (grade 1)	M82403	Carcinoid tumour (morphologic abnormality) NET grade 1	81622000
Neuroendocrine tumour (grade 2)	M82493	Carcinoid tumour (morphologic abnormality) NET grade 2	128658008
Small cell carcinoma	M80143	Small cell carcinoma (morphologic abnormality)	74364000
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 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 □ 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 □
Mucinous adenocarcinoma □ Neuroendocrine carcinoma □
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 □
Present □ Grade of AIN: 1 □ 2 □ 3 □
Completeness of excision of dysplasia: N/A □ Yes □ No □

Maximum microscopic size of tumour: ….. mm or □ N/A (more than 20 mm see macroscopic description)
Depth of invasion: invades Lamina propria □ Submucosa □ Muscularis propria □
Smooth muscle □ 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:…

Summary:

Tumour type: Grade and stage: (e.g. pT1N0R0Mx)

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
Maximum diameter of specimen: .... mm
Length of perianal skin: .... mm
Distance from perianal resection margin to dentate line:
Surgical plane of excision: Extra-sphincteric □ Inter-sphinteric □ Intra-sphinteric □
Depth of perianal connective tissue (to include sphincter muscle): .... mm
Depth of mesorectum: .... mm
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 dentate line: .... mm
Distance of tumour to anal verge: .... mm
Distance of tumour to deep margin: .... mm

Histology
Tumour type: Squamous cell carcinoma □ Adenocarcinoma □
Mucinous adenocarcinoma □ Neuroendocrine carcinoma □
Undifferentiated carcinoma □ Verrucous carcinoma □

Differentiation: Well differentiated □ Moderately differentiated □
Poorly differentiated □ Undifferentiated □
Adjacent surface squamous dysplasia: Not identified □
Present □ AIN grade: 1 □ 2 □ 3 □
Completeness of excision of dysplasia: N/A □ Yes □ No □
Maximum microscopic size of tumour: ….. mm or □ N/A (more than 20 mm see macroscopic description)
Depth of invasion: invades 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:…

Summary:
Tumour type:
Grade: Not assessable □ Well differentiated □ Moderately differentiated □
Poorly differentiated □ Undifferentiated □
Stage: pTX cannot be assessed □ No evidence of tumour pT0
pTis AIN II or III □ pT1 (2 cm or less) □
pT2 (2–5 cm) □ pT3 more than 5 cm □
pT4 invasion of adjacent organs excluding invasion of sphincter muscle □
Excision: N/A pT0 □ RO complete excision □
R1 microscopic residual tumour □ R2 macroscopic residual tumour □
Post-treatment: y for neoadjuvant therapy No □ Yes □
Distant metastasis/es: N/A □ No □ Yes □

Final summary of stage: (e.g. ypT1N0R0Mx)
Signature: **Date:** **SNOMED CODE:**

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

Element name	Values	Implementation notes
Specimen type	Single selection value list: • Anal canal • 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	
Tumour type	Single selection value list: • Squamous cell carcinoma • Adenocarcinoma • Mucinous adenocarcinoma • Neuroendocrine carcinoma • Undifferentiated carcinoma • Verrucous carcinoma	
Differentiation	Single selection value list: • Well differentiated • Moderately differentiated • Poorly differentiated • Undifferentiated	
Background epithelium	Multiple selection value list: • Non-keratinising squamous • Keratinising squamous • Columnar	
Adjacent squamous dysplasia	Single selection value list: • Not identified • Present	
Adjacent squamous dysplasia, grade	Single selection value list: • 1 • 2 • 3	Only applicable if ‘Adjacent squamous dysplasia, Present’ is selected.
Completeness of excision of 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	
Peripheral margins	Single selection value list: • Involved • Not involved	
Distance to nearest peripheral margin	Distance in mm or N/A	
Deep (CRM) margin	Single selection value list: • Involved • Not involved	
Distance to deep margin	Distance in mm	
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	
UICC TNM version 8 pN category	Single selection value list: • pNX • pN0 • pN1a • pN1b • pN1c	
Excision	Single selection value list: • N/A pT0 • R0 • R1 • R2	
Post-treatment y for neoadjuvant therapy	Single selection value list: • Yes • No	
Distant metastasis/es	Single selection value list: • N/A • Yes (M1) • No	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

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

Element name	Values	Implementation notes
Length of specimen	Distance in mm	
Maximum diameter of specimen	Distance in mm	
Length of perianal skin	Distance in mm	
Distance from perianal resection margin to dentate line	Distance in mm	
Surgical plane of excision	Single selection value list: • Extra-sphincteric • Inter-sphinteric • Intra-sphinteric	
Depth of perianal connective tissue (to include sphincter muscle)	Distance in mm	
Depth of mesorectum	Distance in mm	
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	
Distance of tumour to dentate line	Distance in mm	
Distance of tumour to anal verge	Distance in mm	
Distance of tumour to deep margin, macroscopic	Distance in mm	
Tumour type	Single selection value list:	

	• Squamous cell carcinoma • Adenocarcinoma • Mucinous adenocarcinoma • Neuroendocrine carcinoma • Undifferentiated carcinoma • Verrucous carcinoma	
Differentiation	Single selection value list: • Well differentiated • Moderately differentiated • Poorly differentiated • Undifferentiated	
Adjacent squamous dysplasia	Single selection value list: • Not identified • Present	
Adjacent squamous dysplasia, grade	Single selection value list: • 1 • 2 • 3	Only applicable if 'Adjacent squamous dysplasia, Present' is selected.
Completeness of excision of 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	
Distance to deep margin	Distance in mm	
Total lymph nodes with main specimen	Integer	
Positive lymph nodes with main specimen	Integer	
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	
Excision	Single selection value list: • N/A pT0 • R0 • R1 • R2	
Post-treatment y for neoadjuvant therapy	Single selection value list: • Yes • No	
Distant metastasis/es	Single selection value list: • N/A	

	• Yes • No	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.	

Appendix G Anal cancer tumour regression (post chemoradiotherapy)

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 one 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 cancer type 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 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 I AGREE guideline monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this dataset 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