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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of primary bone tumours

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Contents

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.

The classification of sarcomas in this issue relates mainly to those in the *WHO Classification of Tumours of Soft Tissue and Bone (5th Edition)*.[1] A new issue of this book will be published soon, at which time these guidelines will be updated. The molecular classification of sarcomas is advancing rapidly and the entities that are recognised since the publication of the current WHO publication are largely found by searching PubMed using the search word 'sarcoma'. The majority of the new entities are published, although not exclusively, in the following journals: *The American Journal of Surgical Pathology*, *Genes Chromosomes and Cancer*, *Histopathology*, *Journal of Pathology*, *Journal of Pathology Clinical Research*, *Modern Pathology* and *Virchows Archiv*. Genetic alterations are found in COSMIC (Catalogue of Somatic Mutations in Cancer; www.sanger.ac.uk/science/tools/cosmic). Recent comprehensive overviews of the current classification of connective tumours can be found in *Genes, Chromosomes and Cancer*.[2,3]

Each dataset contains core data items (Appendix C) 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 recommendations made in this dataset are based on the authors' assessment of the relevant literature on bone tumour diagnosis and management, tumour grading and other predictive factors. In addition, the NICE guidelines were consulted.[4] The recommendations are in line with those of other national pathology organisations (College of American Pathologists, Royal College of Pathologists of Australasia and Canadian Partnership Against Cancer) and are detailed in the dataset produced by the International Collaboration on Cancer Reporting (ICCR). It is expected that most of the supporting evidence for cancer datasets will be grade C or D, or meet the good practice point (GPP) criteria. The level of evidence for the recommendations has been summarised in Appendix E. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in Appendix F.

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 advisor to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website

for two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group. It was placed on the College website for consultation with the membership from 12 November to 10 December 2020. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

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

1 Introduction

This dataset is intended to provide pathologists with a guide to the core data that should be included in histopathology reports of primary benign and malignant bone tumours. It also provides guidelines to assist in the provision of data required in histopathology reports of bone tumour specimens. The guidelines and core data can be used in conjunction with information from other pathological studies. Participation by bone histopathologists in an external quality assessment (EQA) scheme, to maintain a high standard of histological reporting of bone tumours, is required.

The guidelines in this dataset pertain to the histopathological techniques and reporting of specimens of primary bone tumours and do not apply to tumours metastatic to bone. The guidelines refer mainly to best practice related to bone tumours encountered in orthopaedic practice. Principles of specimen handling and reporting may need to be modified when bone tumours arise in specific sites that fall within the province of other specialist pathologists (e.g. head and neck, oral and maxillofacial pathologists) who will participate in an EQA that contains a relevant bone tumour component.

Recording of standardised histopathological data is important for the following reasons:

- accurate diagnosis and grading of bone tumours according to a recognised system is necessary for the appropriate treatment of patients with bone tumours
- it ensures consistency in histopathology reporting with respect to both terminology and report content
- it facilitates liaison at multidisciplinary team (MDT) meetings and collaboration between cancer networks, cancer centres and cancer units
- it provides histopathological information necessary to assist clinical decision making, patient management and treatment
- it is necessary for providing accurate prognostic information
- it provides consistent and standardised criteria for histopathology reporting, which can be used to provide a common database for audit of the clinical, radiological and pathological diagnosis and assessment of treatment effectiveness
- it provides a common database for epidemiological studies, including the monitoring of disease patterns and trends, as well as determining changes in outcome and survival
- it provides standardised data to assist in the stratification of patients for research studies and clinical/therapeutic trials; this allows meaningful comparison of data that pertain to groups of patients diagnosed with similar or different tumour types

- it provides core information for a common database in cancer registries; this information is incorporated in the COSD.

The guidance on cancer services issued by the National Institute for Health and Clinical Excellence (NICE) indicates that bone sarcomas should be either first reported or reviewed by a specialist bone sarcoma pathologist. This can be defined as a pathologist who regularly reports bone tumours as a significant component of their workload. A specialist pathologist should participate in EQA, normally through the bone pathology component of the UK national orthopaedic pathology EQA scheme, and should be a member of a properly constituted sarcoma MDT. All patients with a suspected malignant primary bone tumour should have their pathology reported by a specialist bone pathologist. Suspected benign primary bone tumours may be reported either by a specialist bone pathologist or a pathologist who has formal links to a specialist bone pathologist and a bone sarcoma MDT through a local diagnostic referral pathway.

1.1 Target users and health benefits of these guidelines

The target primary users are specialist trainees, fellows/consultants in training and established consultant cellular pathologists. The secondary users are surgeons, radiologists, oncologists, clinical nurse specialists involved in the clinical management of patients with primary bone tumours, advanced biomedical practitioners and clinical scientists involved in the reporting of molecular pathology, cancer registries and the National Cancer Registration and Analysis Service (NCRAS). Standardised cancer reporting and MDT assessment reduce the risk of histological misdiagnosis and help to ensure that clinicians have all the relevant pathological information required for tumour staging and management. Collection of standardised cancer-specific data also provides information for healthcare providers and cancer epidemiologists to facilitate international benchmarking and research.

2 Clinical and radiological information required for the diagnosis of bone tumours

As for any histopathology report, detailed information is required to identify the patient from whom the tissue is derived and to provide a record of the specimen receipt/specimen pathway. The diagnosis and management of bone tumours depends on close cooperation between the surgeon, oncologist, radiologist and pathologist. The protocol for the diagnostic evaluation of a bone tumour needs to take into account the clinical and radiological features of the lesion, the results of laboratory investigations and the histopathological findings. All members of the diagnostic team should be experienced in the assessment of these tumours. Diagnostic evaluation and treatment should be carried out at a unit or centre that specialises in the diagnosis and treatment of bone tumours.

2.1 Clinical information

Patient and specimen pathway information on the request form or report should include:

- the patient name's, date of birth, gender, NHS number (when available) and hospital (or other) patient identification number
- details of the referring and reporting organisation
- the name of the clinician requesting the investigation
- the date and time at which the procedure was undertaken
- the date and time the specimen was received in the laboratory
- if the specimen were received fixed or fresh; if received fresh, state whether it was stored at room temperature or at 4ºC, and how long the specimen was at this temperature before processing in formalin or other reagents and freezing

- the date the histopathology report was issued
- the name of the authorising pathologist(s).

Clinical information should be provided on the specimen request form and recorded fully in the pathology report. This should include information on:

- the type of bone tumour specimen received for pathological examination, for example:
  - closed (percutaneous) needle core biopsies
  - an open (surgical) biopsy
  - curettage tissue
  - a segmental (en bloc) resection
  - a large amputation specimen
  - other/specific, e.g. hemipelvectomy, limb salvage
- the anatomical bone sampled/involved by the lesion and the location of the lesion in or on the bone, skeletal maturity (open or closed epiphysis in a teenager/adolescent)
- laterality (right, left, midline)
- three dimensions of the tumour
- additional relevant clinical information should also be provided, such as the nature and duration of signs and symptoms; the presence or absence of pain, swelling or deformity; and relation of the lesion to a traumatic episode.

When relevant, the following information should also be added:

- the presence or absence of a pre-existing or concomitant skeletal disease, or history of a familial syndrome or other relevant disease predisposing to tumour development
- occupational or clinical treatment history (e.g. chemotherapy, ionising radiation and the type – photons [X-rays] or proton beam) that may predispose to bone and or other secondary malignancy
- the presence or absence of systemic features of disease
- the results of relevant laboratory investigations.

2.2 Radiological information

Radiological information is essential for bone tumour diagnosis and should be provided on the specimen request form. Pathologists should have access to radiology reports and imaging studies. It is strongly recommended that, wherever possible, the pathologist should personally view the radiological images of a bone tumour before issuing a diagnostic report. If the radiological findings are not available, this should be recorded in the pathology report.

3 Receipt and preparation of specimens before dissection

Ideally, all specimens should be received fresh/unfixed in the laboratory. Samples can be placed unfixed in a cold room/fridge for 48 hours or over the weekend since the quality of the morphology and DNA remains suitable for clinical reporting. Unfixed samples provide greater opportunities to perform specialised investigations, when required, including next-generation DNA and RNA sequencing and other molecular tests, as well as frozen section diagnosis, the use of specific fixatives for histochemistry and electron microscopy.

When there is likely to be a severe delay in processing (>48 hours when the sample is not held at 4ºC), the specimen should be fixed immediately in 10% neutral buffered formalin. It is important that whole specimens are not placed in a freezer as this may result in the formation of ice crystal artefacts.

Delays or problems in processing should also be recorded as this may indicate whether the tissue is suitable for subsequent use in molecular genetic studies.

Diagnostic biopsies of suspected malignancies should be regarded as urgent. Specimens may be processed fresh on receipt or fixed before routine processing, depending on the laboratory preferences, and decalcified appropriately.

4 Specimen handling of bone tumour biopsy and resection specimens

4.1 Introduction

The specimen handling and preparation protocol described below is based on previous and current practice and should be regarded as a guide only; it may need to be modified in individual cases.

4.1.1 Decalcification

The decalcification of tissue requires the use of acids and this process damages the tissue, including nucleic acids. When feasible, a small non-ossified or non-calcified component of the tumour should be removed prior to decalcification. This provides more opportunities for specialist diagnostic tests and allows the tissue to be processed more rapidly. If the whole specimen is calcified, a small piece of the least densely calcified component of the lesion should be decalcified in a chelating agent, such as EDTA (14% 250 g in 1,750 ml), in the shortest time possible. Although the use of EDTA takes longer than strong acids (either nitric 5% or formic acid 10%), it is less damaging. Furthermore, the morphology is better preserved, as is the tissue for immunohistochemistry and molecular tests. The remainder of the heavily calcified/ossified sample should be placed in nitric or formic acid and the decalcification process monitored by X-ray. The acid should be refreshed regularly to ensure that samples are processed as quickly as possible. Formic acid is slower but provides better preservation for cytological, immunophenotypic and molecular genetic analysis. In general, if ancillary studies are anticipated, a minimum of three cores may be needed.

4.2 Handling of biopsy specimens

A general gross description of the specimen should be given, including dimensions, consistency and colour. In addition, the presence of bone, cartilage, fibrous tissue, necrosis, haemorrhage and myxoid change should be noted. Soft areas of the tumour should be separated from densely calcified areas of the tumour, which allows processing for rapid histology without decalcification or light decalcification in EDTA (if required). The densely calcified/ossified component can be placed in formic or nitric acid as decalcification in EDTA would result in an unacceptable turnaround time.

Provision of fresh tissue for ancillary studies (e.g. molecular genetic analysis) or specific fixation should be considered before the specimen is fixed in formalin. When indicated, touch imprint preparations of the fresh biopsy specimen can be made. If a diagnosis of a low-grade tumour is made on a formalin-fixed haematoxylin and eosin section, for example a low-grade chondrosarcoma (grade I), frozen material should be thawed and examined for the presence of high-grade components as this would change clinical management.

Most specimens require fixation for at least three hours. Needle biopsy specimens, when fixed, are best decalcified overnight in EDTA. Decalcification in EDTA occurs more rapidly in an oven at 45ºC. A minimum of three cores may be needed.

4.3 Handling of curettage specimens

This is essentially similar to that for core needle biopsies with regard to gross description and specimen handling. If a large amount of curetted material is received, this should be sampled extensively (about one block per centimetre). When appropriate, mineralised parts of the tumour may be separated from non-calcified soft areas as ancillary investigations may need to be carried out. Specimens should be submitted for overnight formalin fixation and subsequent decalcification (see above for decalcification).

4.4 Handling of large segmental (en bloc) resection and amputation specimens for primary bone tumour

4.4.1 Specimen characteristics

The following specimen characteristics should be noted:

- laterality (left/right) of amputation or bone resection specimen and any markers of specimen orientation
- the dimensions of the total segmental resection specimen or amputation specimen (the total length of the extremity)
- the presence or absence of exposed tumour in bone or soft tissues
- the presence and dimensions of the bone containing the tumour and the nature and dimensions of attached soft tissues
- the presence of previous biopsy sites and surgical scars on attached skin.

4.4.2 Tumour characteristics

The following tumour characteristics should be recorded, when relevant:

- anatomical location of the tumour within the bone. It should be noted whether the tumour involves the diaphysis, metaphysis or epiphysis (or more than one region) of a long bone and whether it is predominantly located in the medulla or cortex or on the bone surface.
- gross appearance of the tumour including size in three dimensions, shape, colour, border (well or poorly defined), consistency, and the presence of areas of cystic change, haemorrhage or necrosis (give percentage). It should be noted whether the tumour appears to be bone-forming or predominantly cartilaginous, fibrous or myxoid in nature. The presence or absence of a pathological fracture should be noted.
- tumour invasion across the growth plate, if present
- elevation of the periosteum by the tumour
- whether the tumour breaches the periosteum and extends into the soft tissues
- tumour involvement of the articular cartilage or joint cavity
- evidence of tumour invasion along a previous incision
- distance of tumour to the osseous margin of resection
- appearance of bone distant from the main tumour, including the presence of satellite lesions
- abnormalities of the skin, subcutaneous fat, muscle, major vessels and nerves, other bones, joints and the remainder of the resection or amputated extremity
- the presence, number and appearance of lymph nodes.

4.4.3 Tissue sampling of an amputation or excision specimen of a bone tumour

Representative tissue blocks for histology should include:

- blocks of tumour: using the appropriate cutting equipment (band-saw, Exakt saw), a slab of the whole tumour in bone should be taken and blocked out. Additional blocks may be taken from non-slab areas of the tumour or surrounding bone where the macroscopic appearance is dissimilar or unusual.
- blocks of the previous incision site and biopsy tract (when appropriate)
- blocks of the proximal bone resection margin at the site of amputation (when relevant). For excision specimens, the closest margins should be taken. It is good practice to take blocks of superior, inferior, lateral, medial, anterior and posterior margins as a minimum.
- any abnormal-looking areas elsewhere in the bone, soft tissues or skin
- lymph nodes (when relevant)
- major vessels at the soft tissue amputation site (when appropriate).

4.4.4 Specimen photography

The bone tumour specimen should be photographed before dissection. The slab specimen of tumour should also be photographed, and the nature and location of blocks taken for histology recorded on the slab specimen photograph.

5 Core data items for bone tumour surgical pathology reports

5.1 Clinical data

Core clinical data includes the information required for secure patient and specimen pathway identification:

- patient name, date of birth, gender, NHS number (when available) and hospital (or other) patient identification number
- details of the referring and reporting organisation
- the name of the clinician requesting the investigation
- the date and time at which the procedure was undertaken
- the date and time the specimen was received in the laboratory
- the date the histopathology report was issued
- the name of the reporting/authorising pathologist.

Core clinical data also includes information on the nature of the bone specimen received. This should specify:

- the type of specimen received, i.e. closed (percutaneous) needle core biopsy, open (surgical) biopsy, curettage tissue, segmental (en bloc) resection, amputation or another specimen
- the anatomical bone involved
- the location of the tumour within the bone in terms of whether it is in the epiphysis, metaphysis or diaphysis of a long bone, located in the medulla, cortex or periosteum (bone surface), extraosseous (in adjacent soft tissues), or a joint-based tumour involving bone
- laterality (right, left, midline).

5.2 Pathological data

Core pathological data should include:

- specimen and tumour size
- histological diagnosis: tumour type (and subtype)
- histochemistry and Immunohistochemistry tests performed
- molecular genetic analysis, if undertaken
- extent of local tumour spread
- excision margin status
- tumour necrosis (approximate percentage) in response to preoperative therapy, when relevant

5.3 Additional notes on core pathology data items

5.3.1 Size

The macroscopic measurements of the tumour should be given in millimetres for three dimensions.

5.3.2 Histological diagnosis: tumour type (and subtype)

The nomenclature and classification of bone tumours is based mainly on the pathway of cell or tissue differentiation exhibited by a particular tumour; this is often evidenced by the type of connective tissue matrix, which is formed by the tumour cells found within the lesion (e.g. a lesion in which tumour cells produce osteoid/bone is classified as a bone-forming tumour). However, the histogenesis of many primary bone tumours is unknown and a number of bone tumours are by convention classified by distinct morphological and clinicopathological features (e.g. giant cell tumour of bone) and, in some cases, characteristic cytogenetic abnormalities (e.g. Ewing sarcoma and other small round cell tumours).

The use of a standardised system of classification and nomenclature for the diagnosis of bone tumours is essential for effective communication between pathologists and clinicians who deal with bone tumours. It is also required for the meaningful assessment of research and comparative studies in multicentre trials. The 5th edition of the *WHO Classification of Tumours of Soft Tissue and Bone*, produced by an international working group of bone pathologists, incorporates clinical, morphological and genetic data to provide a uniform system of classification and standardised nomenclature for the diagnosis of benign and malignant bone tumours.[1] It provides a morphological categorisation of benign, malignant and intermediate (locally aggressive and rarely metastasising) lesions. It is recommended that this classification system (see Appendix A) forms the basis of histological reporting of bone tumours since it is well recognised and widely employed internationally.

[Level of evidence B – histological type/subtype is important for cancer registration and for grading, prognosis and prediction of response to therapy.][5–9]

5.3.3 Grade

Primary benign and malignant bone tumours vary widely in their clinical behaviour and pathological appearances. Benign bone tumours are distinguished by the fact that they do not metastasise and have a limited capacity for local recurrence. By contrast, malignant bone tumours (bone sarcomas) commonly recur if incompletely excised and have a variable but often significant risk of distant metastasis. There are some bone tumours that can exhibit limited malignant behaviour such as grade I chondrosarcoma, which is a locally aggressive and destructive tumour that commonly recurs if incompletely excised but does not typically metastasise. For this reason, grade I chondrosarcoma and atypical cartilaginous tumours are now grouped together as atypical cartilaginous tumour/chondrosarcoma grade I in the long

bones and small bones of the hand and feet. However, when these lesions present in the axial skeleton and scapula, they are referred to as well-differentiated chondrosarcoma to indicate their risk of local recurrence and worse prognosis. A giant cell tumour of the bone is commonly destructive locally but rarely metastasises. However, it can rarely give rise to benign metastatic lesions, mostly commonly in the lung, and can transform into a high-grade sarcoma.

Histological grading of a bone sarcoma provides a guide to its biological behaviour based on morphological and cytological features. This is assessed in terms of the degree of cellularity and cytological/nuclear atypia, mitotic activity and the extent of tumour necrosis. A three-level histological grading system is commonly used. The utility of any histological grading system is limited by interobserver variability and by many of the tumours falling cytologically into the intermediate range. For this reason, a tumour is often classified simply as low grade or high grade, indicating that the tumour has a low (less than 25%) or high (more than 25%) risk of distant metastasis, respectively.

The 2020 WHO classification describes a three-tier grading system:[1]

- grade 1 (low-grade) tumours include grade I chondrosarcoma, clear cell chondrosarcoma, parosteal osteosarcoma and low-grade central osteosarcoma
- grade 2 sarcomas include classic adamantinoma, grade II chondrosarcoma, periosteal osteosarcoma and chordoma
- grade 3 (high-grade) tumours include conventional, telangiectatic, small-cell and high-grade surface osteosarcoma, Ewing sarcoma, undifferentiated high-grade pleomorphic sarcoma, grade 3 chondrosarcoma, mesenchymal chondrosarcoma, dedifferentiated chondrosarcoma, dedifferentiated chordoma and malignant giant cell tumour of bone
- historically, chondrosarcomas are graded as I, II and III whereas 1, 2 and 3 is used for other sarcomas.

[Level of evidence B – histological grade provides important prognostic information, guides appropriate management and is a major determinant of stage.]

5.3.4 Extent of local tumour spread

The extent of local bone and soft tissue spread should include a comment on tumour involvement of specific anatomical components or compartments, e.g. medulla, cortex, joints and extraosseous soft tissues. This assessment is primarily made at the macroscopic level (to guide block selection) and confirmed or amended microscopically. The extent of local spread will determine whether the tumour is intracompartmental or extracompartmental.[1]

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

5.3.5 Excision margin status with regard to tumour involvement

The proximity of the tumour to proximal, distal and other relevant bone resection margins and the closest soft tissue resection margin should be measured in millimetres. The details of the location and nature of the soft tissue at the closest soft tissue margin (e.g. fat, muscle, loose or dense fibrous tissue) should be noted.

[Level of evidence B – adequacy of clearance of excision margins is important for predicting local recurrence.]

5.3.6 Molecular genetic findings

Results from molecular genetic studies should be incorporated into the final histopathological report.

[Level of evidence B – provides diagnostic information and has prognostic significance.][5]

6 Non-core data items for bone tumour surgical pathology reports

6.1 Clinical data

Non-core clinical data should include:

- submission of tissue for other investigations or research (e.g. frozen section, molecular genetics)
- clinical details (e.g. signs, symptoms, history of previous surgery, radiation, chemotherapy, past medical history, radiological findings)
- specimen fixation status, i.e. whether tissues were received fixed or unfixed
- radiological findings.

6.2 Pathological data

6.2.1 Macroscopic features

- The gross appearance of the tumour, including the presence or absence of necrosis and other descriptive characteristics (e.g. colour, calcification, hardness, gritty, haemorrhagic, cystic), and the presence or absence of chemotherapy or radiotherapy effect.
- The presence or absence of a previous biopsy site or scar on the skin surface (with dimensions and relation to resection margins).
- The involvement or invasion of major structures (e.g. nerve, major blood vessels).
- The presence of satellite lesions of the tumour away from the main tumour mass.
- The presence of lymph nodes and a description of the cut surface of the nodes.

6.2.2 Microscopic features

- Morphological and cytological description of the tumour; this may include details of the mitotic count, degree of pleomorphism and other histological features (e.g. vascular/lymphatic invasion).
- Additional comments on the nature of the tumour with regard to the histological appearances in a biopsy or previous specimen. The clinical context in which the tumour has arisen or observations made at the time of surgery may also be useful.
- Results of ancillary investigations (e.g. immunohistochemistry, molecular genetics).

7 Diagnostic coding

SNOMED coding is incorporated in the 2020 *WHO Classification of Tumours of Soft Tissue and Bone*.[1] However, it is noted that SNOMED is now in a practical transition phase, as part of the intended full implementation by the NHS and Public Health England of SNOMED-CT. SNOMED ceased to be licensed by the International Health Terminology Standards Development Organisation from 26 April 2017.

A list of applicable T and M SNOMED and SNOMED-CT codes is provided in Appendix A. Mapping SNOMED-CT terminology is provided.

8 Staging

Bone sarcomas are staged using the International Union against Cancer (UICC) TNM staging system (see Appendix B).[10] The UICC system for primary malignancies of bone subdivides stage I and stage II tumours on the basis of tumour size. Specifically, a tumour size of less than 8 cm in greatest dimension is considered a favourable prognostic indicator. The current UICC system also recommends that tumours with skip metastases are classified separately as stage III and that stage IV tumours associated with distant metastases are subdivided on the basis of whether these are only to the lungs (stage IVA) or to other sites, including bone (stage IVB).

Formal staging of a bone tumour should be carried out at a sarcoma MDT meeting where clinical, radiological and histological information can be correlated. UICC staging uses a four-grade system, with grades 1 and 2 effectively considered low grade and grades 3 and 4 considered high grade.

9 Reporting of small biopsy specimens

The report should include histological diagnosis (type and subtype) and grade (if relevant) with the caveat that the excised lesion may be found to exhibit a higher grade of malignancy. Information from relevant immunohistochemical investigation should be included. Results of molecular genetic investigations, which may not be immediately available, can be issued in a supplementary report.

10 Reporting frozen section and aspiration cytology of bone tumours

Frozen section examination of bone tumours should not be carried out for diagnostic purposes and pathologists should discourage surgeons from requesting such a procedure. Similarly, fine needle aspiration cytology has a very limited diagnostic role even in specialist centres.

11 Tumour-specific aspects

11.1 Assessment of preoperative chemotherapy

Preoperative chemotherapy is commonly used with limb salvage procedures for the treatment of high-grade sarcomas, particularly osteosarcoma and Ewing sarcoma. To determine the effect of chemotherapy, the extent of tumour necrosis should be quantified as a percentage of the total tumour area. For osteosarcomas, chemotherapy-induced necrosis of 90% or more has a greater than 90% disease-free survival, compared with less than 50% survival in patients with less than 90% tumour necrosis. For Ewing sarcoma, significant necrosis is defined as between 90% and 100% of the microscopic tumour mass. Tumours demonstrating such massive necrosis are associated with a favourable prognosis, whereas those with less necrosis are associated with poor survival.

To determine the extent of necrosis in an osteosarcoma or Ewing sarcoma, the slab specimen of resected bone is submitted for histological analysis. A photograph of the slice is taken and the site of each numbered block is marked on the image or an accompanying diagram. Additional blocks are taken in a plane at right angles to the slab to determine the full extent of the tumour. Blocks should also be taken from other representative areas of the specimen, including areas of unusual appearance in bone and soft tissue surrounding the tumour and possible satellite lesions, to get a clear picture of the volume and extent of the tumour. Treated osteosarcomas may contain large atypical cells with hyperchromatic nuclei, smudged or clumped chromatin, and vacuolated cytoplasm in areas of necrosis, calcification or fibrosis.

The nature of these cells is not certain, but they are currently considered to represent viable tumour cells when assessing the extent of tumour necrosis. Other effects of chemotherapy on tumour histology include ghost-like cells with loss of nuclear and cytoplasmic detail, granulation tissue, fibrosis, haemosiderin deposition, mucinous change and inflammation.

11.2 Ewing sarcoma

The diagnosis of Ewing sarcoma must be confirmed by ancillary techniques. Immunohistochemistry should be carried out to determine expression of CD99, which is usually strong and diffuse with a peri-membranous pattern. CD99 can be expressed in other round cell tumours such as in lymphoblastic lymphoma, small cell osteosarcoma and mesenchymal chondrosarcoma. CD99 is therefore not specific for Ewing sarcoma, but this diagnosis should be questioned if CD99 is absent, weak or patchy. Focal immunoreactivity for broad-spectrum cytokeratins, desmin and S100 can be seen in some cases of Ewing sarcoma. Appropriate leukocyte markers, such as CD45 and TdT, should be employed to exclude a lymphoma. Molecular genetic techniques should ideally be used to identify the presence of a characteristic Ewing sarcoma-associated translocation. Fluorescence in situ hybridisation or reverse transcriptase-polymerase chain reaction can be used to identify genetic abnormalities involving Ewing-associated genes and can be carried out on either fresh tissue or formalin-fixed paraffin-embedded tissue. Recently, Ewing-like sarcomas with *BCOR-CCNB3* and *CIC-DUX4* gene fusions have been described.[11,12] The existence of these tumours highlights the increasing importance of utilising molecular pathological techniques.

11.3 Osteosarcoma

The morphological diagnosis of osteosarcoma requires the demonstration of osteoid or bone formation by malignant tumour cells. Imprint or frozen section preparations of osteosarcoma are useful to demonstrate alkaline phosphatase activity in tumour cells. In general, the use of the unqualified term ‘osteosarcoma’ refers to primary conventional high-grade intramedullary osteosarcoma. Secondary osteosarcoma, developing as a consequence of treatment or on the basis of a known bone condition, is qualified accordingly (e.g. Paget’s osteosarcoma, radiation-induced osteosarcoma). Most osteosarcomas arise in the medulla, and these tumours are often described as osteoblastic, fibroblastic or chondroblastic on the basis of the predominant type of matrix.

Specific morphological subtypes of intramedullary osteosarcoma, such as telangiectatic osteosarcoma, small cell osteosarcoma, giant cell-rich osteosarcoma and low-grade central osteosarcoma, should be recognised. Similarly, surface osteosarcomas should be distinguished from central osteosarcoma and subclassified as either parosteal, periosteal or high-grade surface osteosarcoma.

11.4 Chondrosarcoma

Clinical and radiological features of a suspected cartilage tumour should be carefully correlated with the pathological findings. Conventional chondrosarcomas arise as primary tumours within the medulla. Peripheral chondrosarcomas arise on the bone surface where they may develop as a secondary chondrosarcoma from a pre-existing osteochondroma; the cartilage cap of an osteochondroma should be measured and carefully assessed histologically, in particular for evidence of bone invasion. Histological grading of chondrosarcoma is important in predicting prognosis. Chondrosarcomas are classified as atypical cartilaginous tumours/chondrosarcoma grade 1 (low grade), grade 2 and grade 3 (high grade) on the basis of the grade of cellularity, nuclear atypia, myxoid change within the matrix and other features. There is a degree of subjectivity in distinguishing grade 1 and grade 2 chondrosarcomas, and even greater variability in distinguishing enchondroma from atypical cartilaginous tumour/chondrosarcoma grade 1. Atypical cartilaginous tumour/grade 1 chondrosarcoma behaves as a locally aggressive lesion, but has little or no metastatic potential. This tumour has a good prognosis and can be treated locally by excision or curettage. Grade 2 and grade 3 chondrosarcomas

require complete excision. Tumours in the appendicular skeleton (long and short tubular bones) are termed atypical cartilaginous tumours, whereas tumours with similar morphology in the axial skeleton and flat bones should be called grade 1 chondrosarcoma because at these anatomical locations there is a significant risk of local recurrence.[1] Recognition of specific subtypes of chondrosarcoma, including periosteal, mesenchymal, clear cell and dedifferentiated chondrosarcomas, is important as this has prognostic and treatment implications.

11.5 Assessment of other primary bone sarcomas

A large number of other malignant tumours can arise in bone. These may require particular immunohistochemical investigations or the use of other specific diagnostic methods. Adamantinoma of long bones and osteofibrous dysplasia exhibit cytokeratin expression. Tumour cell expression of cytokeratin, as well as EMA, S100 and brachyury, is seen in chordoma. Malignant vascular tumours of bone express endothelial cell markers such as CD31, CD34 and ERG. Haematological malignancies such as lymphoma and myeloma can occur in bone. They should be confirmed by appropriate immunohistochemistry and reviewed by a haematopathologist. Other sarcomas that rarely develop in bone (e.g. clear cell sarcoma, synovial sarcoma) are identified by immunohistochemistry and other investigations in the same way as for their counterparts in soft tissue. A proforma for bone tumour reports is shown in Appendix C.

12 Criteria for audit of the dataset

As recommended by the RCPath as key performance indicators (KPIs) (see *Key Performance Indicators – Proposals for implementation* [July 2013] on www.rcpath.org/profession/quality-improvement/kpis-for-laboratory-services.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 NHS Trusts are required to implement the structured recording of core pathology data in the COSD by January 2016 and to update their systems in line with subsequent COSD updates
  - standard: 95% of reports must contain structured data
- histopathology cases must be reported, confirmed and authorised within seven and ten calendar days of the procedure
  - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

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Appendix A Histological types of bone tumour with SNOMED coding

Chondrogenic tumours

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Benign			
Osteochondroma	M-92100	Osteochondroma (morphologic abnormality)	52299001
Chondroma	M-92200	Chondroma (morphologic abnormality)	31186001
Enchondroma	M-92200	Chondroma (morphologic abnormality)	31186001
Periosteal chondroma	M-92210	Juxtacortical chondroma (morphologic abnormality)	9266000
Osteochondromyxoma	M-92110	No code	No code
Subungual exostosis	M-92130	No code	No code
Bizarre parosteal osteochondromatous proliferation	M-92120	No code	No code
Synovial chondromatosis	M-92200	Chondroma (morphologic abnormality)	31186001
Intermediate (locally aggressive)			
Chondromyxoid fibroma	M-92410	Chondromyxoid fibroma (morphologic abnormality)	39553005
Atypical cartilaginous tumour/ chondrosarcoma grade 1	M-92221	No code	No code
Intermediate (rarely metastasising)			
Chondroblastoma	M-92301	No code	No code
Malignant			
Chondrosarcoma grade 2, grade 3	M-92203	Chondrosarcoma, no ICD-O subtype (morphologic abnormality)	14990007
Dedifferentiated chondrosarcoma	M-92433	Dedifferentiated chondrosarcoma (morphologic abnormality)	128776008
Mesenchymal chondrosarcoma	M-92403	Mesenchymal chondrosarcoma (morphologic abnormality)	56565002
Clear cell chondrosarcoma	M-92423	Clear cell chondrosarcoma (morphologic abnormality)	128775007

Osteogenic tumours

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Benign			
Osteoma	M-91800	Osteoma, no ICD-O subtype (morphologic abnormality)	83612000
Osteoid osteoma	M-91910	Osteoid osteoma (morphologic abnormality)	71666005
Intermediate (locally aggressive)			
Osteoblastoma	M-92000	Osteoblastoma (morphologic abnormality)	55333008
Malignant			
Low-grade central osteosarcoma	M-91873	Intraosseous well-differentiated osteosarcoma (morphologic abnormality)	128771003
Conventional osteosarcoma	M-91803	Osteosarcoma, no ICD-O subtype (morphologic abnormality)	21708004
Chondroblastic osteosarcoma	M-91813	Chondroblastic osteosarcoma (morphologic abnormality)	76312009
Fibroblastic osteosarcoma	M-91823	Fibroblastic osteosarcoma (morphologic abnormality)	12690005
Osteoblastic osteosarcoma	M-91803	Osteosarcoma, no ICD-O subtype (morphologic abnormality)	21708004
Telangiectatic osteosarcoma	M-91833	Telangiectatic osteosarcoma (morphologic abnormality)	78453009
Small cell osteosarcoma	M-91853	Small cell osteosarcoma (morphologic abnormality)	12302002
Secondary osteosarcoma	M-91843	Osteosarcoma in Paget's disease of bone (morphologic abnormality)	33681003
Parosteal osteosarcoma	M-91923	Parosteal osteosarcoma (morphologic abnormality)	128918008
Periosteal osteosarcoma	M-91933	Periosteal osteosarcoma (morphologic abnormality)	128772005
High-grade surface osteosarcoma	M-91943	High-grade surface osteosarcoma (morphologic abnormality)	128773000

Fibrogenic tumours

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Intermediate (locally aggressive)			
Desmoplastic fibroma of bone	M-88231	No code	No code
Malignant			
Fibrosarcoma of bone	M-88103	Fibrosarcoma (morphologic abnormality)	53654007
Fibrohistiocytic tumours			
Benign fibrous histiocytoma/ non-ossifying fibroma	M-88300	Benign fibrous histiocytoma (morphologic abnormality)	25889007

Haematopoietic neoplasms

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Malignant			
Plasma cell myeloma	M-97323	Multiple myeloma, no ICD-O subtype (morphologic abnormality)	55921005
Solitary plasmacytoma of bone	M-97313	Solitary plasmacytoma of bone (morphologic abnormality)	10639003
Primary non-Hodgkin's lymphoma of bone	M-95913	Non-Hodgkin's lymphoma, no ICD-O subtype (morphologic abnormality)	1929004

Osteoclastic giant cell-rich tumours

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Intermediate (locally aggressive, rarely metastasising)			
Giant cell tumour of bone	M-92501	Giant cell tumour of bone (morphologic abnormality)	57500000
Malignant			
Malignancy in giant cell tumour of bone	M-92503	Giant cell sarcoma (except of Bone, M-92503) (morphologic abnormality)	87992000

Notochordal tumours

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Benign			
Benign notochordal tumour	M-93700	No code	No code
Malignant			
Chordoma	M-93703	Chordoma (morphologic abnormality)	50007008

Vascular tumours

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Benign			
Haemangioma	M-91200	Hemangioma, no ICD-O subtype (morphologic abnormality)	2099007
Intermediate (locally aggressive, rarely metastasising)			
Epithelioid haemangioma	M-91250	Epithelioid hemangioma (morphologic abnormality)	33929001
Malignant			
Epithelioid haemangioendothelioma	M-91333	Epithelioid hemangio-endothelioma, malignant (morphologic abnormality)	54124005
Angiosarcoma	M-91203	Hemangiosarcoma (morphologic abnormality)	39000009

Myogenic tumours

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Benign			
Leiomyoma of bone	M-88900	Leiomyoma, no ICD-O subtype (morphologic abnormality)	44598004
Malignant			
Leiomyosarcoma of bone	M-88903	Leiomyosarcoma, no subtype (morphologic abnormality)	51549004

Lipogenic tumours

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Benign			
Lipoma of bone	M-88500	Lipoma, no ICD-O subtype (morphologic abnormality)	46720004
Malignant			
Liposarcoma of bone	M-88503	Liposarcoma, no ICD-O subtype (morphologic abnormality)	49430005

Tumours of undefined neoplastic nature

Morphological codes	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Benign			
Fibrous dysplasia	M-88180	No code	No code
Intermediate (locally aggressive)			
Aneurysmal bone cyst	M-92600	No code	No code

Langerhans cell histiocytosis, monostotic	M-97521	Langerhans cell histiocytosis, unifocal (morphologic abnormality)	128810002
Langerhans cell histiocytosis, polystotic	M-97531	Langerhans cell histiocytosis, multifocal (morphologic abnormality)	128811003
Erdheim-Chester disease	M-97501	No code	No code

Miscellaneous tumours

Morphological codes	**SNOMED code**	**SNOMED-CT terminology**	**SNOMED-CT code**
Ewing sarcoma	M-93643	Peripheral neuroectodermal tumour (morphologic abnormality)	73676002
Adamantinoma	M-92613	Adamantinoma of long bones (morphologic abnormality)	56763007
Undifferentiated high-grade pleomorphic sarcoma of bone	M-88303	Fibrous histiocytoma, malignant (morphologic abnormality)	34360000

Procedure codes (P)

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

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

Appendix B TNM classification of bone tumours (UICC TNM 8)

Appendix B provides updated information on staging using UICC TNM 8,[10] which should be used for all tumours diagnosed after 1 January 2018.

Primary tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Appendicular skeleton, trunk, skull and facial bones

T1 Tumour 8 cm or less in greatest dimension

T2 Tumour more than 8 cm in greatest dimension

T3 Discontinuous tumours in the primary bone site

Spine
The five vertebral segments are the: right pedicle; right body; left body; left pedicle; and posterior element.

T1 Tumour confined to a single vertebral segment or two adjacent vertebral segments

T2 Tumour confined to three adjacent vertebral segments

T3 Tumour confined to four adjacent vertebral segments

T4a Tumour invades into the spinal canal

T4b Tumour invades the adjacent vessels or tumour thrombosis within the adjacent vessels

Pelvis
The four pelvic segments are the: sacrum lateral to the sacral foramen; iliac wing; acetabulum/periacetabulum; and pubic rami/symphysis/ischium.

T1a Tumour 8 cm or less in size and confined to a single pelvic segment with no extraosseous extension

T1b Tumour greater than 8 cm in size and confined to a single pelvic segment with no extraosseous extension

T2a Tumour 8 cm or less in size and confined to a single pelvic segment with extraosseous extension or confined to two adjacent pelvic segments without extraosseous extension

T2b Tumour greater than 8 cm in size and confined to a single pelvic segment with extraosseous extension or confined to two adjacent pelvic segments without extraosseous extension

T3a Tumour 8 cm or less in size and confined to two pelvic segments with extraosseous extension

T3b Tumour greater than 8 cm in size and confined to two pelvic segments with extraosseous extension

T4a Tumour involving three adjacent pelvic segments or crossing the sacroiliac joint to the sacral neuroforamen

T4b Tumour encasing the external iliac vessels or gross tumour thrombus in major pelvic vessels

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

- M1a: Lung
- M1b: Other distant sites

Histologic grade (G)

GX Grade cannot be assessed

G1 Well differentiated – low grade

G2 Moderately differentiated – low grade

G3 Poorly differentiated – high grade

G4 Undifferentiated – high grade*

*Ewing sarcoma is classified as high grade.

Stage grouping

Appendicular skeleton, trunk, skull and facial bones

Stage IA	T1	N0	M0	G1, GX low grade
Stage IB	T2, T3	N0	M0	G1, GX low grade
Stage IIA	T1	N0	M0	G2, G3 high grade
Stage IIB	T2	N0	M0	G2, G3 high grade
Stage III	T3	N0	M0	G2, G3 high grade
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Spine and pelvis

There is no stage for bone sarcomas of the spine or pelvis.

Residual tumour (R)

An R classification can be used to record the presence/absence of tumour remaining after curative therapy.[3]

RX	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

Appendix C Reporting proforma for bone tumour reports

Surname*…… Forenames*…… Date of birth*…… Sex*…....

Hospital*…… Hospital no*…… NHS/CHI no……

Referring organisation* …… Reporting organisation* ……

Authorising pathologist*…… Surgeon*……

Date of receipt*…… Date of reporting*……

Report no…… Report type ……

CLINICAL INFORMATION

Specimen type*: Closed (needle) biopsy □ Open (surgical) biopsy □ Curettage □ Excision □

Specimen size (in three dimensions in mm): ……

Anatomical bone sampled*: ……

Tumour location in bone*: Epiphysis/apophysis □ Metaphysis □ Diaphysis □ Cortex □ Medulla □ Periosteal □ Extraosseous (soft tissue) □ Joint-based tumour involving bone □ Not definable □

Laterality*: Left □ Right □ Midline □ Not known □ Not applicable □

PATHOLOGICAL INFORMATION

Tumour size (in three dimensions in mm):* ……

Histological diagnosis of tumour type*: ……

Tumour grade*: Low grade (G1) □ Low grade (G2) □ High grade (G3) □

Extent of local tumour spread (for medullary tumours only)*: Intracompartmental □ Extracompartmental □

If extracompartmental: Joints □ Extraosseus soft tissues □

Distance to proximal bone margin: ……mm

Distance to distal bone margin: ……mm

Distance to other relevant bone resection margin: ……mm (please specify……)

Distance to closest soft tissue resection margin: ……mm

Type of tissue at closest soft tissue margin*: Muscle □ Fat □ Loose fibrous tissue □ Dense fibrous tissue □ Tumour □

Is the histological diagnosis confirmed by cytogenetic or molecular tests?*

Yes, confirmed □ No, not confirmed □ Test not done □

Cytogenetic and molecular genetic findings (where applicable): ……

Tumour necrosis in response to preoperative therapy: ……%* Not applicable □

UICC TNM (8th edition)*: (y)pT …….. (y)pN …….. (y)pM ……..

SNOMED codes*: T…… M……..

COMMENTS* = required for COSD

Pathologist …….. **Date……**

Appendix D Reporting proforma for bone tumour reports in list format

Element name	Values	Implementation notes	COSD v8	COSD v9
Specimen type	• Closed (needle) biopsy • Open (surgical) biopsy • Curettage • Excision		CR0760 Closed (needle) biopsy = BU Open (surgical) biopsy = BU Curettage = CU Excision = EX	pCR0760 Closed (needle) biopsy = BU Open (surgical) biopsy = BU Curettage = CU Excision = EX
Specimen size	Free text (in three dimensions in mm)			
Anatomical bone sampled	Free text			
Tumour location in bone	• Epiphysis/apophysis • Metaphysis • Diaphysis • Cortex • Medulla • Periosteal • Extraosseous (soft tissue) • Joint-based tumour involving bone • Not definable			
Laterality	• Left • Right • Midline • Not known • Not applicable		CR0820 Left = L Right = R Midline = M Not known = 9 Not applicable = 8	pCR0820 Left = L Right = R Midline = M Not known = 9 Not applicable = 8
Tumour size	Free text (in three dimensions in mm)		CR0830	pCR0830
Histological diagnosis of tumour type	Free text			
Tumour grade	• Low grade (G1) • Low grade (G2) • High grade (G3)		CR0860 Low grade (G1) = G1 Low grade (G2) = G2 High grade (G3) = G3	pCR0860 Low grade (G1) = G1 Low grade (G2) = G2 High grade (G3) = G3

Extent of local tumour spread (for medullary tumours only)	• Intracompartmental • Extracompartmental	If extra-compartmental: • Joints • Extraosseus soft tissues	SA11130 Intra-compartmental = I Extra-compartmental = E	pSA11130 Intra-compartmental = I Extra-compartmental = E
Distance to proximal bone margin	Free text (in mm)		CR0880 Use smallest value to determine the most appropriate code to use >5 mm = 02 >1 to 5 mm = 03 < or equal to 1 mm = 04 0 mm = 05 All values blank = 99	pCR0880 Use smallest value to determine the most appropriate code to use >5 mm = 02 >1 to 5 mm = 03 < or equal to 1 mm = 04 0 mm = 05 All values blank = 99
Distance to distal bone margin	Free text (in mm)			
Distance to other relevant bone resection margin	Free text (in mm)	Specify margin		
Distance to closest soft tissue resection margin	Free text (in mm)			
Type of tissue at closest soft tissue resection margin	• Muscle • Fat • Loose fibrous tissue • Dense fibrous tissue • Tumour			
Is the histological diagnosis confirmed by cytogenetic or molecular tests?	• Yes, confirmed • No, not confirmed • Test not done		SA11170 Yes = Y No = N Test not done = X	pSA11170 Yes = Y No = N Test not done = X
Cytogenetic and molecular genetic findings	Free text			
Tumour necrosis in response to preoperative therapy	Integer (%) • Not applicable		SA11140	pSA11140
UICC TNM (8th edition)	• (y)pT and free text • (y)pN and free text • (y)pM and free text		CR0910 CR0920 CR0930	pCR0910 pCR0920 pCR0930

SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.		CR6410	pCR6410
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.		CR6420	pCR6420

Appendix E Summary table – explanation of levels of evidence

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

Level of evidence	Nature of evidence
Level 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.
Level 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.
Level 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.
Level 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 F AGREE II 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	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
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	Introduction
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 and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–11
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	2–11
16 The different options for management of the condition or health issue are clearly presented	2–11
17 Key recommendations are easily identifiable	2–11
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendix C
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	12
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