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

Standards and datasets for reporting cancers

Dataset for histopathology reports on primary bone tumours

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Authors: Professor Nicholas A Athanasou, Nuffield Orthopaedic Centre, Oxford

Dr David C Mangham, The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Trust, Oswestry

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Produced by	Nicholas A Athanasou, Professor of Musculoskeletal Pathology, University of Oxford, Nuffield Orthopaedic Centre, Oxford Dr David C Mangham, Consultant Histopathologist, The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Trust, Oswestry and The Royal Orthopaedic Hospital NHS Trust, Birmingham
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Comments	In accordance with the College's pre-publications policy, this document was on the College website for consultation from 8 September to 6 October 2014. Twenty-one items of feedback were received and the authors considered them and amended the document appropriately. Please email publications@rcpath.org if you wish to see the responses and comments. This edition replaces the 2010 edition of the *Dataset for histopathology reports on primary bone tumours.* **Dr David Bailey** **Vice-President for Communications**

The Royal College of Pathologists
2 Carlton House Terrace, London, SW1Y 5AF
Tel: 020 7451 67007
Fax: 020 7451 6701
Web: www.rcpath.org

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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. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

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 contents of this dataset were circulated to members of the UK National Bone and Soft Tissue Sarcoma Panel, from whom feedback was invited. The first version of the dataset was also discussed (as part of the consultation process) by the British Sarcoma Group and the National Cancer Intelligence Network (NCIN) Sarcoma Site-Specific Reference Group.

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,[1] the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*[2] and the *Protocol for the Examination of Specimens from Patients with Tumours of Bone*, produced by the College of American Pathologists,[3] were consulted. The recommendations are in line with those of other national pathology organisations (College of American Pathologists, The 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) at www.rcpa.edu.au/Publications/StructuredReporting/ICCR.htm. It is expected that most of the supporting evidence for cancer datasets will be grade C or D, or meet the GPP (good practice point criteria). Consensus of evidence in the datasets is achieved by expert review during the consultation process. Gaps in evidence were identified by Fellows via feedback received from consultation.

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 sub-specialty 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 Fellows' attention. If Fellows 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 Working Group on Cancer Services and was on the College website for consultation with the membership from 8 September to 6 October 2014. 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 Vice-President for Communications.

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.

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 where bone tumours arise in specific sites which fall within the province of other specialist pathologists (e.g. head and neck, oral 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 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 Cancer Outcomes and Services Dataset.

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.[1] This can be defined as a pathologist who regularly

reports bone tumours as a significant component of his/her workload. A specialist pathologist should participate in external quality assessment (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 multidisciplinary team (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.

The target primary users are training and consultant cellular pathologists. The secondary users are surgeons, radiologists and oncologists, cancer registries and NCIN. 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 health care providers and cancer epidemiologists to facilitate international bench marking 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 which 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.[4] 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/specimen pathway information on the request form or report should include:

- the patient name's, date of birth, gender, 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 authorising pathologist.

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 within bone
- laterality (right, left, mid-line)
- dimensions of the tumour
- additional relevant clinical information such as the nature and duration of signs and symptoms; the presence or absence of pain, swelling, deformity, and relation of the lesion to a traumatic episode, should also be provided

Where relevant, the following information should also be added:

- the presence or absence of a pre-existing or concomitant skeletal disease, history of a familial syndrome or other relevant disease predisposing to tumour development
- occupational or treatment history (e.g. chemotherapy, radiation therapy) that may predispose to bone 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. Where the radiological findings are not available, this should be recorded in the pathology report.

3 Receipt and preparation of specimens before dissection

It is often useful to receive specimens in a fresh (unfixed) state in the laboratory.[4] This permits the use of a number of specialised investigations, where appropriate. These include the provision of material for frozen section diagnosis, the use of specific fixatives for histochemistry and electron microscopy, and snap freezing of tissue for molecular genetic studies. Fresh tissue can also be sent for microbiological culture or cytogenetic studies.

Where the above studies are not anticipated or where there is likely to be a delay in processing, the specimen should be immediately fixed 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.

It should be specified whether the specimen is received fresh or in fixative. In some cases, it may also be useful to record for specimen resections the time of vessel ligation and specimen despatch as well as specimen receipt in the laboratory. Delays or problems in processing should also be recorded as this may indicate whether the tissue is suitable for subsequent use in tissue microarrays or other preparations.

Diagnostic biopsies of suspected malignancies should be regarded as urgent. All specimens should be adequately fixed before routine processing and decalcified appropriately. It should be noted that most ancillary stains can be employed without modification on tissues that are decalcified even in strong acids.[5] However, strong acids can interfere with molecular genetic analysis due to fragmentation of DNA and RNA.[6]

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[3,4,7,8] and should be regarded as a guide only; it may have to be modified in individual cases.

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 calcified areas of the tumour and may be submitted for frozen section or rapid histology (if required).

Provision of fresh tissue for ancillary studies (e.g. cytogenetic and molecular genetic analysis) or specific fixation (e.g. glutaraldehyde for electron microscopy) should be considered before the specimen is fixed in formalin. Where indicated, touch imprint preparations of the fresh biopsy specimen can be made.

Most specimens require at least three hours' fixation. Needle biopsy specimens, if properly fixed, may be decalcified overnight in acid or in a chelating agent (EDTA); the latter is slower but provides better preservation for cytological, immunophenotypic and molecular genetic analysis. If the core is 5 mm or more in thickness, it should be divided longitudinally. In general, if ancillary studies are anticipated, a minimum of three cores may be needed.

4.3 Handling of curettage specimens

This is essentially similar to that described above 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). Where appropriate, mineralised parts of the tumour may be separated from non-calcified soft areas. Ancillary investigations may need to be carried out on fresh specimens (as described above). Specimens should be submitted for overnight formalin fixation and subsequent decalcification.

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

4.4.1 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 The following tumour characteristics should be recorded, where relevant:

- anatomical location of the tumour within 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, 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/absence of a pathological fracture should be noted
- tumour invasion across the growth plate, if present
- elevation of the periosteum by the tumour
- tumour breaching the periosteum and extending 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 away from main tumour including the presence of satellite lesions
- abnormalities of 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 a bandsaw, a slab of the whole tumour in bone should be taken and blocked out; additional blocks may be taken from non-slab areas of tumour or surrounding bone where the macroscopic appearance is dissimilar or unusual
- blocks of the previous incision site and biopsy tract (where appropriate)
- blocks of the proximal bone resection margin at the site of amputation (where 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 bone, soft tissues, or skin
- lymph nodes (where relevant)
- major vessels at the soft tissue amputation site (where appropriate).

4.4.4 Specimen photography and radiography

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. Consideration should be given to obtaining plain radiographs of the intact and slab specimens.

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/ specimen pathway identification:

- patient name, date of birth, gender, 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 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. whether closed (percutaneous) needle core biopsy, open (surgical) biopsy, curettage tissue, segmental (en-bloc) resection, amputation or other specimen
- the anatomical bone involved
- the location of the tumour within 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, mid-line).

5.2 Pathological data

- Specimen and tumour size.
- Histological diagnosis: tumour type (and subtype).
- Tumour grade.
- Extent of local tumour spread.
- Excision margin status.
- Cytogenetic and molecular genetic analysis of small round cell tumours of bone.
- Tumour necrosis (approximate percentage) in response to pre-operative therapy, where relevant.

5.3 Additional notes on core pathology data items

5.3.1 Size

The macroscopic measurements of the tumour should be given in mm 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). The histogenesis of many primary bone tumours, however, is not known 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).

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 2013 World Health Organization (WHO) classification of bone tumours, 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.[2] It provides a histogenetic and morphological categorisation of benign, malignant and intermediate (locally aggressive and rarely metastasing) lesions. It is recommended that this classification system (see Appendix A) forms the basis of histological reporting of bone tumours as it is well-recognised and widely employed internationally.

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

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. In 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 1 chondrosarcoma, which is a locally aggressive and destructive tumour that commonly recurs if incompletely excised but does not typically metastasise, and giant cell tumour of bone, which is commonly destructive locally, but can rarely give rise to metastatic lesions, mostly commonly in the lung.

Histological grading of a bone sarcoma provides a guide as 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 or four-tier histological grading system is commonly used. The utility of any histological grading system is limited by interobserver variability and by the fact that many of the tumours fall 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 2013 WHO Classification describes a three-tier grading system:[2]

- Grade I (low-grade) tumours include Grade 1 chondrosarcoma, clear cell chondrosarcoma, parosteal osteosarcoma, low-grade intramedullary osteosarcoma
- Grade II sarcomas include, classic adamantinoma, grade 2 chondrosarcoma, periosteal osteosarcoma and chordoma
- Grade III (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.

[Histological grade provides important prognostic information; it provides a guide to appropriate management and is a major determinant of stage – Level of evidence B.]

5.3.4 Extent of local tumour spread

The extent of local bone and soft tissue spread should include 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 (in order to guide block selection) and confirmed or amended microscopically. The extent of local spread will determine whether the tumour is intracompartmental or extracompartmental.

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

5.3.5 Excision margin status with regard to tumour involvement

This should include a measure (in millimetres) of tumour proximity to proximal, distal and other relevant bone resection margins and the closest soft tissue resection margin; 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.

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

5.3.6 Cytogenetic and molecular genetic findings for small round cell tumours of bone

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

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

6.1 Clinical data

- Submission of tissue for other investigations or research (e.g. frozen section, molecular genetics) should be specified.
- Clinical details (e.g. signs, symptoms, history of previous surgery, radiation, chemotherapy, past medical history, radiological findings).
- Specimen fixation status: whether tissues were received fixed or unfixed.
- Radiological findings.

6.2 Pathological data

6.2.1 Macroscopic features

- The gross appearance of the tumour include 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).
- Involvement or invasion of major structures (e.g. nerve, major blood vessels).
- Presence of satellite lesions of tumour away from the main tumour mass.
- Presence of lymph nodes and description of 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, electron microscopy, flow cytometry).

7 Diagnostic coding

SNOMED coding is incorporated in the 2013 WHO classification of bone and soft tissue tumours.[2] A list of SNOMED morphology codes is shown in Appendix A.

8 Stage

Bone sarcomas are staged using either the International Union against Cancer (UICC) TNM staging system or the Musculoskeletal Tumour Society (MSTS) Staging System[9-11] (see Appendices B and C).

The UICC and MSTS systems have many features in common, but the most recent version of the UICC staging of primary malignancies of bone have subdivided Stage I and Stage II tumours on the basis of tumour size rather than intraosseous or extraosseous extent of the tumour (as in the MSTS system). Specifically, tumour size of less than 8 cm maximum 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 lung (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. MSTS staging uses a two-grade system of histological grading whereas UICC staging uses a four-grade system, with grade 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 only be carried out by pathologists who have some experience of osteoarticular pathology and who have knowledge of the clinical background and radiological appearances of the lesion.[4,7,8] The usefulness of frozen section histological examination is predicated on close cooperation between the surgeon, radiologist and pathologist. Frozen section histology provides information on:

- the adequacy of the biopsy specimen
- the nature of the lesion
- ancillary investigations required for diagnosis
- the adequacy of resection margins

Whether or not frozen section investigation is appropriate should be at the discretion of the reporting pathologist and should only be carried out after discussion with relevant clinicians, including the surgeon and radiologist.

Fine needle, aspiration cytology has a limited diagnostic role even in specialist centres. It can be of use in confirming recurrence or metastasis in a patient with a previously diagnosed tumour.

11 Tumour-specific aspects

11.1 Assessment of pre-operative chemotherapy

Pre-operative 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.[12-14] For Ewing sarcoma, significant necrosis is defined as between 90% and 100% of the microscopic tumour mass.[12,15,16] 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.[3,4] A photograph or radiograph 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. As indicated earlier, 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 in order 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.[12] 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

Although the vast majority of Ewing sarcomas show the standard cyto/histomorphology of a malignant round cell tumour, there are cases with variant features.[2,17] PAS and silver stains are useful to demonstrate glycogen and the scanty reticulin in these tumours. In general, it is best practice to supplement the morphological diagnosis of Ewing sarcoma with ancillary techniques. Immunohistochemistry should be carried out to determine expression of CD99, which is usually strong and diffuse. 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, neurofilament, desmin and smooth muscle actin can be seen in some case of Ewing sarcoma. Appropriate leukocyte markers should be employed to exclude lymphoma.[18]

Cytogenetic or molecular analysis techniques should ideally be used to identify the presence of a characteristic Ewing sarcoma-associated translocation. Cytogenetic karyotyping is performed using fresh tissue samples, but there is often a delay in diagnosis using this method. Fluorescence *in situ* hybridization (FISH) or more specifically reverse transcriptase-polymerase chain reaction (RT-PCR) 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.[6,19,20] Recently, Ewing sarcoma-like sarcomas with BCOR-CCNB3 and CIC-DUX4 gene fusions have been described.[21] 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.[2] Immunohistochemical identification of bone matrix proteins, such as Dentine Matrix-Protein 1, is useful in this regard.[22] 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; 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 well-differentiated osteosarcoma, should be recognised as they have prognostic and therapeutic significance.[2] Similarly, surface osteosarcomas should be distinguished from medullary 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. A biopsy should optimally sample the bone-tumour interface. 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;[2] the cartilage cap of an osteochondromatous surface cartilage tumour should be measured and carefully assessed histologically, in particular for evidence of bone invasion.[23] Histological grading of chondrosarcoma is important in predicting prognosis. Chondrosarcomas are classified as atypical cartilaginous tumours/grade 1 (low grade), grade 2 (intermediate grade) or grade 3 (high-grade) on the basis of the grade of cellularity, nuclear atypia, myxoid change within the matrix and other features.[2] 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.[24] Atypical cartilaginous tumour/grade 1 chondrosarcoma behaves as a locally aggressive lesion and rarely metastasises. This tumour has a good prognosis and can be treated locally by excision/curettage (+/- local adjuvants). Grade 2 and Grade 3 chondrosarcomas require complete excision. Recognition of specific subtypes of chondrosarcoma, including periosteal, mesenchymal, clear cell and dedifferentiated chondrosarcomas, is important as this has prognostic and treatment implications.[2]

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.[25] Tumour cell expression of cytokeratin, as well as EMA, S100 and brachyury is seen in

chordoma.[26,27] Malignant vascular tumours of bone express endothelial cell markers such as CD31, CD34, factor VIII, podoplanin and LYVE1.[28] Primary lymphomas of bone express CD45 and specific B cell, T cell or other leukocyte markers. Myelomas should be assessed for light chain restriction. 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.[2] A proforma for bone tumour reports is shown in Appendix D.

12 Criteria for audit of the dataset

Recommended by the RCPath as key performance indicators (KPIs) (see *Key Performance Indicators – Proposals for implementation* (July 2013) on www.rcpath.org/clinical-effectiveness/kpi/KPI):

- 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 2014.

  Standard: 95% of reports must contain structured data.

- Histopathology cases that are 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

Morphological codes	SNOMED code	SNOMED CT terminology	SNOMED CT code
CHONDROGENIC TUMOURS			
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 metastasizing)			
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			
Benign			
Osteoma	M-91800	Osteoma, no ICD-O subtype (morphologic abnormality)	83612000
Osteoid osteoma	M-91910	Osteoid osteoma (morphologic abnormality)	71666005

Morphological codes (continued)	SNOMED code	SNOMED CT terminology	SNOMED CT code
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
Telangiectactic 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			
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

Morphological codes (continued)	SNOMED code	SNOMED CT terminology	SNOMED CT code
HAEMATOPOIETIC NEOPLASMS			
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			
Intermediate (locally aggressive, rarely metastasizing)			
Giant cell tumour of bone	M-92501	Giant cell tumor 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			
Benign			
Benign notochordal tumour	M-93700	No code	No code
Malignant			
Chordoma	M-93703	Chordoma (morphologic abnormality)	50007008
VASCULAR TUMOURS			
Benign			
Haemangioma	M-91200	Hemangioma, no ICD-O subtype (morphologic abnormality)	2099007
Intermediate (locally aggressive, rarely metastasizing)			
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

Morphological codes (continued)	SNOMED code	SNOMED CT terminology	SNOMED CT code
MYOGENIC TUMOURS			
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			
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			
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			
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 Staging system for bone tumours of the International Union against Cancer[10,11]

T – Primary tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

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

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M – Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

M1a Lung

M1b Other distant sites

G – Histologic grade

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

Stage	Tumour (T)	Node (N)	Metastasis (M)	Grade (G)
Stage IA	T1	N0	M0	G1, 2 low grade
Stage IB	T2	N0	M0	G1, 2 low grade
Stage IIA	T1	N0	M0	G3, 4 high grade
Stage IIB	T2	N0	M0	G3, 4 high grade
Stage III	T3	N0	M0	Any G
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Residual tumour (R)

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

RX Presence of residual tumour cannot be assessed

R0 No residual tumour

R1 Microscopic residual tumour

R2 Macroscopic residual tumour

Appendix C Musculo-skeletal Tumour Society staging system for bone tumours[9]

Benign tumours (G0)

Stage I Inactive, latent (G0)

Stage II Active (G0)

Stage III Aggressive (G0)

Malignant tumours

Stage I Low grade (G1)

Stage II High grade (G2)

Stage III Low or high grade tumours with metastases

Subdivisions

A Intracompartmental

B Extracompartmental

Appendix D 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 □ Mid-line □ 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 pre-operative therapy: ……% Not applicable □

UICC TNM (7th edition): (y)pT …….. (y)pN …….. (y)pM ……..

SNOMED codes: T…… M……..

COMMENTS

Pathologist …….. **Date……**

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 compliance monitoring sheet

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

AGREE standard	Section of dataset
SCOPE AND PURPOSE	
1. The overall objective(s) of the guideline is (are) specifically described.	Foreword, 1
2. The clinical question(s) covered by the guidelines is (are) specifically described.	1
3. The patients to whom the guideline is meant to apply are specifically described.	1
STAKEHOLDER INVOLVEMENT	
4. The guideline development group includes individuals from all the relevant professional groups.	Foreword
5. The patients' views and preferences have been sought.	N/A
6. The target users of the guideline are clearly defined.	1
7. The guideline has been piloted among target users.	Through previous version
RIGOUR OF DEVELOPMENT	
8. Systematic methods were used to search for evidence.	Foreword
9. The criteria for selecting the evidence are clearly described.	Foreword
10. The methods used for formulating the recommendations are clearly described.	Foreword
11. The health benefits, side effects and risks have been considered in formulating the recommendations.	Foreword
12. There is an explicit link between the recommendations and the supporting evidence.	2–7
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.	2–12
16. The different options for management of the condition are clearly presented.	2–12
17. Key recommendations are easily identifiable.	Throughout
18. The guideline is supported with tools for application.	Appendices A–D
APPLICABILITY	
19. The potential organisational barriers in applying the recommendations have been discussed.	Foreword
20. The potential cost implications of applying the recommendations have been considered.	Foreword
21. The guideline presents key review criteria for monitoring and/or audit purposes.	12
EDITORIAL INDEPENDENCE	
22. The guideline is editorially independent from the funding body.	Foreword
23. Conflicts of interest of guideline development members have been recorded.	Foreword

***** The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised the Publications Department that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.