Primary Tumour in Bone
Histopathology Reporting Guide
Resection Specimens

Family/Last name | Date of birth DD – MM – YYYY

Given name(s)

Patient identifiers | Date of request DD – MM – YYYY | Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (select all that apply) (Note 1)

- ◯ Information not provided
- ☐ Pre-existing skeletal disease, *specify*
- ☐ Familial syndrome, *specify*
- ☐ Multifocal disease, *specify*
- ☐ Other (e.g., prior radiation therapy, implants, fracture), *specify*

NEOADJUVANT THERAPY (Note 2)

- ◯ Information not provided
- ◯ Not administered
- ◯ Administered
  - ☐ Neoadjuvant chemotherapy
  - ☐ Neoadjuvant radiotherapy
  - ☐ Other (e.g., denosumab), *describe*

Included in clinical trial

◯ No ◯ Not known

◯ Yes, *specify*

IMAGING FINDINGS (Note 3)

- ◯ Not provided
- ◯ Provided, *describe*

OPERATIVE PROCEDURE (select all that apply) (Note 4)

- ◯ Not specified
- ☐ En bloc resection
- ☐ Amputation
- ☐ Curettage
- ☐ Other (e.g., metastasectomy, lymph node dissection), *specify*

ANATOMICAL SITE (Note 5)

- ◯ Bone, not specified
- ◯ Bone, *specify*
- ◯ Other, *specify*

TUMOUR SITE (select all that apply) (Note 6)

- ☐ Epiphysis or apophysis
- ☐ Metaphysis
- ☐ Diaphysis
- ☐ Other, *specify*
- ☐ Not known

AND

- ☐ Cortex
- ☐ Medullary cavity
- ☐ Surface
- ☐ Not known

AND

- ☐ Tumour confined to bone
- ☐ Tumour involves joint
- ☐ Tumour extension into soft tissue
- ☐ Not known

TUMOUR LATERALITY

- ◯ Left
- ◯ Right
- ◯ Not specified/Not applicable

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TUMOUR DIMENSIONS (Note 7)

Maximum tumour dimension ____ mm

Additional dimensions ____ mm x ____ mm

OR

- ◯ No identifiable tumour (e.g., after preoperative therapy)
- ◯ Cannot be assessed, *specify*

Presence of skip metastases

- ◯ No
- ◯ Yes, *specify dimensions*

HISTOLOGICAL TUMOUR TYPE (Note 8)

(Value list based on the World Health Organization Classification of Soft Tissue and Bone Tumours (2020))

- ◯ Atypical cartilaginous tumour
- ◯ Central chondrosarcoma
- ◯ Peripheral chondrosarcoma
- ◯ Periosteal chondrosarcoma
- ◯ Clear cell chondrosarcoma
- ◯ Mesenchymal chondrosarcoma
- ◯ Dedifferentiated chondrosarcoma
- ◯ Low-grade central osteosarcoma
- ◯ Osteosarcoma (conventional, teleangiectatic, or small cell)
- ◯ Parosteal osteosarcoma
- ◯ Periosteal osteosarcoma
- ◯ High-grade surface osteosarcoma
- ◯ Secondary osteosarcoma
- ◯ Fibrosarcoma
- ◯ Epithelioid haemangioendothelioma
- ◯ Angiosarcoma
- ◯ Giant cell tumour of bone
- ◯ Giant cell tumour of bone, malignant
- ◯ Conventional chordoma (including chondroid)
- ◯ Poorly differentiated chordoma
- ◯ Dedifferentiated chordoma
- ◯ Adamantinoma of long bones
- ◯ Leiomyosarcoma of bone
- ◯ Undifferentiated pleomorphic sarcoma
- ◯ Ewing sarcoma
- ◯ Round cell sarcoma with *EWSR1*-non ETS fusions
- ◯ Sarcoma with *BCOR* genetic alterations
- ◯ Other, *specify*
- ◯ Indeterminate, *specify*

Comments

HISTOLOGICAL TUMOUR GRADE (Note 9)

- ◯ Not applicable
- ◯ Grade 1
- ◯ Grade 2
- ◯ Grade 3
- ◯ Cannot be assessed, *specify*

MICROSCOPIC EXTENT OF INVASION (select all that apply)

(Applicable to medullary tumours only) (Note 10)

- ◯ Cannot be assessed
- ☐ Permeative (infiltrative) growth
- ☐ Cortical destruction
- ☐ Soft tissue extension

LYMPHOVASCULAR INVASION (Note 11)

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate

RESPONSE TO NEOADJUVANT THERAPY (Note 12)

- ◯ No prior treatment
- ◯ No response
- ◯ Response
  - % viable tumour ____ %
  - % response (e.g., necrosis, fibrosis, calcification) ____ %
- ◯ Cannot be assessed, *explain reasons*

MARGIN STATUS (Note 13)

- ◯ Cannot be assessed
- ◯ Not involved (R0)
  - Distance of tumour from closest margin ____ mm
  - Specify closest margin (e.g., distal), if possible
  - Specify type of tissue of closest margin
  - AND
  - Distance of tumour to osteotomy (if not the closest margin) ____ mm
- ◯ Microscopically involved (R1)
  - Specify margin(s), if possible
- ◯ Macroscopically involved (R2)
  - Specify margin(s), if possible

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LYMPH NODE STATUS (Note 14)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Number of lymph nodes examined

- ◯ Not involved
- ◯ Involved

Number of involved lymph nodes

- ◯ Number cannot be determined

COEXISTENT PATHOLOGY[a] (Note 15)

- ◯ None identified
- ◯ Present, *specify*

[a] *Found at histological examination.*

ANCILLARY STUDIES (Note 16)

- ◯ Not performed
- ◯ Performed
  - ☐ Immunohistochemistry, *specify test(s) and result(s)*
  - ☐ Molecular findings, *specify test(s) and result(s)*
  - ☐ Other, *specify test(s) and result(s)*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[b] (Note 17)

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

Primary tumour (pT)

- ◯ Inadequate specimen for assessment
- ◯ 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

- ◯ T1 Tumour confined to a single vertebral segment or two adjacent vertebral segments[c]
- ◯ T2 Tumour confined to three adjacent vertebral segments[c]
- ◯ T3 Tumour confined to four adjacent vertebral segments[c]
  - ◯ T4a Tumour invades into the spinal canal
  - ◯ T4b Tumour invades the adjacent vessels or tumour thrombosis within the adjacent vessels

PELVIS

- ◯ T1a A tumour 8 cm or less in size and confined to a single pelvic segment[d] with no extraosseous extension
- ◯ T1b A tumour greater than 8 cm in size and confined to a single pelvic segment[d] with no extraosseous extension
- ◯ T2a A tumour 8 cm or less in size and confined to a single pelvic segment with extraosseous extension or confined to two adjacent pelvic segments[d] without extraosseous extension
- ◯ T2b A tumour greater than 8 cm in size and confined to a single pelvic segment with extraosseous extension or confined to two adjacent pelvic segments[d] without extraosseous extension
- ◯ T3a A tumour 8 cm or less in size and confined to two pelvic segments[d] with extraosseous extension
- ◯ T3b A tumour greater than 8 cm in size and confined to two pelvic segments[d] with extraosseous extension
- ◯ T4a Tumour involving three adjacent pelvic segments[d] 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 (pN)

- ◯ No nodes submitted or found
- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

[b] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 6th October 2020).*

[c] *The five vertebral segments are the: Right pedicle, Right body, Left body, Left pedicle and Posterior element.*

[d] *The four pelvic segments are the: Sacrum lateral to the sacral foramen, Iliac wing, Acetabulum/periacetabulum and Pelvic rami, symphysis and ischium.*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the Dataset Authoring Committee.

⬆ **Back**

Scope

The dataset has been developed for the pathology reporting of resection specimens of primary tumour in bone. Ewing sarcoma and related round cell sarcomas with primary bone presentation are also covered in this dataset. A separate dataset is available for reporting of biopsy specimens of primary tumour in bone. Some types of soft tissue sarcoma may on rare occasion arise primarily in bone and should be reported using the primary tumour in bone dataset, rather than the soft tissue sarcoma dataset.

Haematologic malignancies and metastatic specimens are excluded from this dataset.

The authors of this dataset can be accessed here.

⬆ **Back**

Note 1 – Clinical information (Non-core)

For accurate diagnosis of bone tumours, a multidisciplinary approach is imperative. It is the responsibility of the clinician or radiologist requesting the pathological examination of a specimen to provide information to the pathologist that will have an impact on the diagnostic process or affect its interpretation. The use of a standard pathology requisition/request form including a checklist of

important clinical information is strongly encouraged to help ensure that important clinical data is provided by the clinicians with the specimen.

It is also the responsibility of the pathologist to verify that all radiological and clinical information that is essential to make a diagnosis is available to guarantee that the final diagnosis is made within the appropriate clinical/imaging context. This often achieved through discussion at a multidisciplinary tumour board meeting.

⬆ **Back**

Note 2 – Neoadjuvant therapy (Core and Non-core)

Information about treatment or other clinical information aids interpretation of the microscopic findings and accurate pathological diagnosis. Pre-operative radiation and/or other therapy may have a profound effect on the morphology of both the cancer and benign tissue. Knowledge of such prior therapy may help to interpret changes such as necrosis, vasculature changes, cellular atypia and inflammatory cells. For this reason, information about any previous therapy is important for the accurate assessment of bone specimens. Different scoring systems are being used, and are discussed in **Note 12 RESPONSE TO NEOADJUVANT THERAPY**. Moreover, the use of denosumab in giant cell tumour of bone induces bone formation, and disappearance of the giant cells, therefore, this information is crucial. Also, previous embolization may cause areas of necrosis. In addition, many novel therapies, such as tyrosine kinase inhibitors and immunotherapy, may cause histological effects when used in a neoadjuvant setting, and need to be fully described.

⬆ **Back**

Note 3 – Imaging findings (Core)

The correlation between the histology and imaging findings is critical in the diagnosis of bone tumours. For instance, aggressive features identified radiographically (permeative/moth-eaten growth, cortical destruction, soft tissue extension, periosteal reaction) should be mentioned here, as well as multifocality, evidence of matrix deposition, presence of fluid-fluid levels etc. It is important for the pathologist to be aware of the radiological differential diagnosis, and to be aware of previous radiological findings, if applicable. The presence of a pathologic fracture may influence the histological evaluation and should be documented. Certain bone tumours (cartilaginous tumour, vascular tumours) tend to occur multifocally, and skip metastases can be present. This is important knowledge for the pathologist when working up the resection specimen. Finally, in the case of neoadjuvant therapy, the radiological response evaluation should be recorded.

⬆ **Back**

Note 4 – Operative procedure (Core)

This element includes the type and intent of the operative procedure, independent of the final margin assessment by the pathologist. On the rare occasion that lymph nodes are included with the specimen, these should be listed under ‘other’. Metastasectomy specimens can also be listed under ‘other’.

⬆ **Back**

Note 5 – Anatomical site (Core)

Recording anatomical site of the tumour is important as certain bone tumours have a preference for specific bones and do not occur in others, and there is a strong association between site and outcome. The latter is especially true for cartilaginous tumours, and as a consequence in the World Health Organization (WHO) Classification of Tumours, Soft Tissue and Bone Tumours, 5th edition, 2020,[2] a diagnosis of atypical cartilaginous tumours/chondrosarcoma grade 1, depends on whether the tumour is located in the appendicular or the axial skeleton, respectively. In the long and short tubular bones these tumours behave in a locally aggressive manner and do not metastasize, can be treated locally, and should not be classified as having full malignant potential. Therefore, the term 'atypical cartilaginous tumour' is used for these cartilaginous tumours in the appendicular skeleton (long and short tubular bones). In contrast, the term chondrosarcoma grade 1 is used for histologically similar tumours of the axial skeleton, including the pelvis, scapula and skull base (flat bones) – reflecting the poorer clinical outcome and the necessity of more aggressive treatment of these tumours at these sites. Please note that here we consider the scapula and skull base to be part of the axial skeleton. It should be noted that the definition of axial versus appendicular is not universally accepted; while the 2020 WHO Classification[2] categorises the scapula, and skull base as part of the axial skeleton, the Union for International Cancer Control (UICC)[3]/American Joint Committee on Cancer (AJCC)[4] TNM 8th editions include these with appendicular skeleton.

⬆ **Back**

Note 6 – Tumour site (Core)

It is important to know the exact tumour site within the bone; for intramedullary tumours and those arising primary at the surface of bone, the histological differential diagnosis will differ. Also, some tumours almost exclusively occur in the epiphysis of the bone (e.g., clear cell chondrosarcoma, giant cell tumour of bone), while others prefer the metaphysis (osteosarcoma) or diaphysis (Ewing sarcoma, adamantinoma). Moreover, primary soft tissue sarcomas may be in close proximity and even invade the bone, while primary bone sarcomas may have an extensive soft tissue component; in these cases, radiological information is required to decide whether the tumour originates primarily from bone or soft tissue.

⬆ **Back**

Note 7 – Tumour dimensions (Core and Non-core)

The size of the largest tumour mass should be measured on the resection specimen, preferably in three dimensions as this is important to evaluate the tumour volume.

⬆ **Back**

Note 8 – Histological tumour type (Core)

Histologic diagnosis is based on the WHO Classification of Tumours, Soft Tissue and Bone Tumours, 5th edition, 2020 (Table 1).[2] The diagnosis is usually made on biopsy before resection. A comment should be included if the final diagnosis based on the resection specimen is discordant with the previous diagnosis on the biopsy.

Table 1: World Health Organization classification of intermediate and malignant bone tumours and undifferentiated small round cell sarcomas.[2]

Descriptor	ICD-O codes[a]
Chondrogenic tumours	
Intermediate (locally aggressive)	
Atypical cartilaginous tumour	9222/1
Malignant	
Chondrosarcoma, grade 1	9222/3*
Chondrosarcoma, grade 2	9220/3
Chondrosarcoma, grade 3	9220/3
Periosteal chondrosarcoma	9221/3
Clear cell chondrosarcoma	9242/3
Mesenchymal chondrosarcoma	9240/3
Dedifferentiated chondrosarcoma	9243/3
Osteogenic tumours	
Malignant	
Low-grade central osteosarcoma	9187/3
Osteosarcoma	9180/3
Conventional osteosarcoma	
Telangiectatic osteosarcoma	
Small cell osteosarcoma	
Parosteal osteosarcoma	9192/3
Periosteal osteosarcoma	9193/3
High-grade surface osteosarcoma	9194/3
Secondary osteosarcoma	9184/3
Fibrogenic tumours	
Malignant	
Fibrosarcoma NOS	8810/3
Vascular tumours of bone	
Malignant	
Epithelioid haemangioendothelioma NOS	9133/3
Angiosarcoma	9120/3
Osteoclastic giant cell–rich tumours	
Intermediate (locally aggressive, rarely metastasizing)	
Giant cell tumour of bone	9250/1
Malignant	
Giant cell tumour of bone, malignant	9250/3
Notochordal tumours	
Malignant	
Conventional chordoma	9370/3
Chondroid chordoma	
Poorly differentiated chordoma	9370/3
Dedifferentiated chordoma	9372/3

Descriptor	ICD-O codes[a]
Other mesenchymal tumours of bone	
Malignant	
Adamantinoma of long bones	9261/3
Dedifferentiated adamantinoma	
Leiomyosarcoma NOS	8890/3
Pleomorphic sarcoma, undifferentiated	8802/3
Haematopoietic neoplasms of bone	
Plasmacytoma of bone	9731/3
Malignant lymphoma, non-Hodgkin, NOS	9591/3
Hodgkin disease NOS	9650/3
Diffuse large B-cell lymphoma NOS	9680/3
Follicular lymphoma NOS	9690/3
Marginal zone B-cell lymphoma NOS	9699/3
T-cell lymphoma NOS	9702/3
Anaplastic large cell lymphoma NOS	9714/3
Malignant lymphoma, lymphoblastic, NOS	9727/3
Burkitt lymphoma NOS	9687/3
Langerhans cell histiocytosis NOS	9751/1
Langerhans cell histiocytosis, disseminated	9751/3
Erdheim–Chester disease	9749/3
Rosai–Dorfman disease	
Undifferentiated small round cell	
Ewing sarcoma	9364/3
Round cell sarcoma with *EWSR1*–non-ETS fusions	9366/3*
CIC-rearranged sarcoma	9367/3*
Sarcoma with *BCOR* genetic alterations	9368/3*

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-O-3.2).[5] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site.
* Codes marked with an asterisk were approved by the International Agency for Research on Cancer/WHO Committee for ICD-O at its meeting in January 2020. Incorporates all relevant changes from the 5th Edition Corrigenda October 2020.

⬆ Back

Note 9 – Histological tumour grade (Core)

In bone sarcomas, the histotype mostly determines grade, as indicated in the list below (based on the 2020 WHO Classification[2]), with only a very few exceptions.

Bone sarcomas in which grade is determined by histotype:

Grade 1 (low grade):

- Low grade intramedullary osteosarcoma
- Parosteal osteosarcoma
- Clear cell chondrosarcoma

Grade 2 (intermediate grade):

- Periosteal osteosarcoma

Grade 3 (high grade):

- Osteosarcoma (conventional, telangiectatic, small cell, secondary, high grade surface)
- Undifferentiated high grade pleomorphic sarcoma
- Ewing sarcoma and BCOR-rearranged sarcoma
- Dedifferentiated chondrosarcoma
- Mesenchymal chondrosarcoma
- Dedifferentiated chordoma
- Poorly differentiated chordoma
- Angiosarcoma

Variable:

- Conventional chondrosarcoma (Grade 1-3 according to Evans)[2,6]
- Leiomyosarcoma of bone (Grade 1-3 no established grading system)
- Low and high grade malignancy may occur in giant cell tumour of bone

Not applicable:

- Adamantinoma and conventional chordoma.

Back

Note 10 – Microscopic extent of invasion (Core)

For correlation with imaging, histological evidence of permeative growth, cortical invasion and destruction or soft tissue extension should be recorded. This is facilitated when gross examination is aligned with the radiological imaging.

Back

Note 11 – Lymphovascular invasion (Non-core)

Lymphovascular invasion (LVI) is extremely rare in bone tumours. However, it is important to report if identified in the specimen.

Back

Note 12 – Response to neoadjuvant therapy (Core)

The response to pre-operative chemotherapy is of prognostic value, especially in Ewing and osteosarcoma, and needs to be evaluated in a standardised way. At least one complete central slab of tumour through its largest dimension should be submitted for histological evaluation. Additional sections can be taken from the remaining two hemispheres of the specimen, especially near the periosteum/soft tissue extension. The amount of remaining viable tumour cell should be estimated on each histological slide to obtain an average score reflecting the overall percentage of response. Response does not always consist of necrosis, very often extensive fibrosis and calcification can be seen, which is also considered response. In osteosarcoma, a cut-off of 10% viable tumour cells/90% or more response (tumour necrosis, fibrosis and calcification) is used to indicate a good response.[7] For Ewing sarcoma the cut-off is less well defined. Grimer and colleagues (2016) recently showed 100% response was most optimal to define a good tumour response in Ewing sarcoma.[8] In earlier reports (the Bologna system[9] as well as the van der Woude scoring system[10]) a good response was defined as the percentage of necrosis of the microscopic tumour mass between 90% and 100%. In the literature different cut-offs are used to evaluate chemotherapy-induced necrosis.[11-14]

⬆ **Back**

Note 13 – Margin status (Core and Non-core)

There is no generally accepted way of reporting margins for bone tumours. If margins are involved, a distinction is often made between microscopic involvement (R1) and resections in which it is evident macroscopically that the tumour is incompletely resected (R2). In the case of negative margins (R0), the minimum that should be documented is the distance of tumour to the closest margin. The type of tissue comprising the resection margin should also be recorded (e.g., pseudocapsule, loose fibrous/ fibroadipose tissue, bone, skeletal muscle, dense regular connective tissue (fascia/aponeurosis/ periosteum/vascular sheath/perineurium) since it might be that bone/fascia are more robust marginal tissues than other tissue types. In addition, the distance to the closest osteotomy margin should also be recorded even if it is not the closest margin. Some guidelines recommend that all margins less than 20 millimetres (mm) should be documented in terms of depth and the tissue comprising each that is less than 20 mm.

⬆ **Back**

Note 14 – Lymph node status (Non-core)

Lymph nodes are very rarely submitted or found with bone specimens and it is not necessary to undertake an exhaustive search for nodes in the specimen. Though regional lymph node metastasis is very rare in adult bone sarcomas, its presence has prognostic importance and it is important to report.

⬆ **Back**

Note 15 – Coexistent pathology (Non-core)

If present, the pathologist should report other abnormalities that are relevant for the diagnosis and any other significant pathologic finding, even if not directly relevant or unrelated. For instance, the presence of precursor lesions for chondrosarcoma, such as multiple enchondromas, osteochondroma,

or synovial chondromatosis should be documented. Paget disease and osteonecrosis or bone infarction may be seen in addition to a secondary sarcoma. The presence of a pathologic fracture may influence the histological evaluation and should be documented. Other unrelated findings may include vasculitis, infection, coexistent chronic lymphocytic leukaemia (CLL) or incidental/unexpected metastatic carcinoma in the same specimen.

Back

Note 16 – Ancillary studies (Core)

All immunohistochemical stainings and molecular tests that contributed to the diagnosis should be documented. For instance, for Ewing sarcoma and other round cell sarcomas, lymphoma, adamantinoma and chordoma, these ancillary studies (immunohistochemical and/or molecular) are critical.

Back

Note 17 – Pathological staging (Non-core)

It is important that pathologist give the required ingredients for staging (according to UICC[3] or AJCC[4] 8th edition Staging Systems) in their reports. Ultimately, the final stage will be determined by the treating physician or in the multidisciplinary team, which will take both the pathological and imaging findings into account.

Back

References

1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.

2 WHO Classification of Tumours Editorial Board (2020). *Soft Tissue and Bone Tumours. WHO Classification of Tumours, 5th Edition, Volume 3*. IARC Publications, Lyon.

3 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.

4 Amin MB, Edge S, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed*. Springer, New York.

5 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin LH, Parkin DM, Whelan SL and World Health Organization (2000). *International classification of diseases for oncology*, World Health Organization, Geneva.

6 Evans HL, Ayala AG and Romsdahl MM (1977). Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. *Cancer* 40(2):818-831.

7 Cates JMM (2018). Modeling Continuous Prognostic Factors in Survival Analysis: Implications for Tumor Staging and Assessing Chemotherapy Effect in Osteosarcoma. *Am J Surg Pathol* 42(4):485-491.

8 Albergo JI, Gaston CL, Laitinen M, Darbyshire A, Jeys LM, Sumathi V, Parry M, Peake D, Carter SR, Tillman R, Abudu AT and Grimer RJ (2016). Ewing's sarcoma: only patients with 100% of necrosis after chemotherapy should be classified as having a good response. *Bone Joint J* 98-b(8):1138-1144.

9 Picci P, Rougraff BT, Bacci G, Neff JR, Sangiorgi L, Cazzola A, Baldini N, Ferrari S, Mercuri M, Ruggieri P and et al. (1993). Prognostic significance of histopathologic response to chemotherapy in nonmetastatic Ewing's sarcoma of the extremities. *J Clin Oncol* 11(9):1763-1769.

10 van der Woude HJ, Bloem JL, Taminiau AH, Nooy MA and Hogendoorn PC (1994). Classification of histopathologic changes following chemotherapy in Ewing's sarcoma of bone. *Skeletal Radiol* 23(7):501-507.

11 Oberlin O, Deley MC, Bui BN, Gentet JC, Philip T, Terrier P, Carrie C, Mechinaud F, Schmitt C, Babin-Boillettot A and Michon J (2001). Prognostic factors in localized Ewing's tumours and peripheral neuroectodermal tumours: the third study of the French Society of Paediatric Oncology (EW88 study). *Br J Cancer* 85(11):1646-1654.

12 Milano GM, Cozza R, Ilari I, De Sio L, Boldrini R, Jenkner A, De Ioris M, Inserra A, Dominici C and Donfrancesco A (2006). High histologic and overall response to dose intensification of ifosfamide, carboplatin, and etoposide with cyclophosphamide, doxorubicin, and vincristine in patients with high-risk Ewing sarcoma family tumors: the Bambino Gesù Children's Hospital experience. *Cancer* 106(8):1838-1845.

13 Pan HY, Morani A, Wang WL, Hess KR, Paulino AC, Ludwig JA, Lin PP, Daw NC and Mahajan A (2015). Prognostic factors and patterns of relapse in ewing sarcoma patients treated with chemotherapy and r0 resection. *Int J Radiat Oncol Biol Phys* 92(2):349-357.

14 Wagner MJ, Gopalakrishnan V, Ravi V, Livingston JA, Conley AP, Araujo D, Somaiah N, Zarzour MA, Ratan R, Wang WL, Patel SR, Lazar A, Ludwig JA and Benjamin RS (2017). Vincristine, Ifosfamide, and Doxorubicin for Initial Treatment of Ewing Sarcoma in Adults. *Oncologist* 22(10):1271-1277.