Paediatric Rhabdomyosarcoma Histopathology Reporting Guide

Family/Last name

Given name(s)

Patient identifiers

Date of birth: DD – MM – YYYY

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 (Note 1)

◯ Information not provided

Preoperative treatment (select all that apply)

◯ Information not provided
◯ No known prior preoperative therapy
☐ Chemotherapy given
☐ Radiotherapy given
☐ Other, *specify*

First known cancer

◯ Yes
◯ No, *specify previous tumour(s)*

Known cancer predisposition syndrome, *specify*

Other clinical information, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

◯ Not specified
☐ Biopsy
☐ Intralesional excision
☐ Marginal resection
☐ Wide local resection
☐ Radical resection
☐ Amputation, *specify*

☐ Other, *specify*

TUMOUR SITE (Note 3)

◯ Not specified
◯ Bile duct
◯ Bladder/prostate
◯ Parameningeal
◯ Extremity
◯ Orbit
◯ Head and neck (excluding parameningeal), *specify*

◯ Genitourinary (excluding bladder/prostate), *specify*

◯ Other, *specify*

TUMOUR LATERALITY

◯ Left
◯ Right
◯ Not specified

TUMOUR DIMENSIONS (Note 4)
(Applicable for excision biopsies and resection specimens)

Greatest dimension [ ] mm

Additional dimensions [ ] mm x [ ] mm

◯ Cannot be assessed, *specify*

BLOCK IDENTIFICATION KEY (Note 5)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 6)
(Value list based on the World Health Organization Classification of Paediatric Tumours (2022))

- ☐ Embryonal rhabdomyosarcoma
- ☐ Alveolar rhabdomyosarcoma
- ☐ Pleomorphic rhabdomyosarcoma
- ☐ Spindle cell/sclerosing rhabdomyosarcoma
- ☐ Other, *specify*

___

ANAPLASIA (Note 7)
(Applicable for biopsy or post-treatment resection specimens)

- ○ Cannot be determined
- ○ Not identified
- ○ Present
  - ○ Focal
  - ○ Diffuse

  OR

  [____] % of cells

OTHER HISTOLOGICAL FEATURES (Note 8)

- ○ Not identified
- ○ Present, *specify*

___

TREATMENT EFFECT (Note 9)

- ○ No prior treatment
- ○ No response
- ○ Response
  - Microscopic viable tumour [____] %

  Rhabdomyoblastic differentiation
  - ○ Not identified
  - ○ Present
    - [____] % differentiation

MARGIN STATUS (Note 10)
(Applicable for resection specimens only)

- ○ Not involved
  - Distance of tumour from closest margin [____] mm

  Specify closest margin(s) (<10 mm), if possible

  ___

- ○ Involved
  - Specify margin(s), if possible

  ___

- ○ Cannot be assessed, *specify*

  ___

LYMPHOVASCULAR INVASION (Note 11)

- ○ Indeterminate
- ○ Not identified
- ○ Present

LYMPH NODE STATUS (Note 12)

- ○ 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

ANCILLARY STUDIES (Note 13)

- ◯ Not performed
- ◯ Performed
  - ▼
    Immunohistochemistry
    - ◯ Not performed
    - ◯ MyoD1
      - ▼
        - ◯ Negative
        - ◯ Positive
          - ▼
            | | % |
    - ◯ MYOGENIN
      - ▼
        - ◯ Negative
        - ◯ Positive
          - ▼
            | | % |
    - ◯ Desmin
    - ◯ Other, *specify test(s) and result(s)*
      - ▼
        | |
        | |

    Gene fusion studies
    - ◯ Not performed
    - ◯ Pending
    - ◯ No *FOXO1* rearrangement
    - ◯ *FOXO1* rearrangement present, fusion partner not known
    - ◯ *PAX3-FOXO1* gene fusion
    - ◯ *PAX7-FOXO1* gene fusion
    - ◯ Other rearrangement/fusion, *specify*
      - ▼
        | |
        | |

Molecular genetic studies

- ◯ Not performed
- ◯ Pending
- ◯ *MYOD1* L122R mutation
- ◯ *VGLL2/NCOA2* gene fusions, *specify*
  - ▼
    | |
    | |
- ◯ *EWSR1/FUS-TFCP2* gene fusion, *specify*
  - ▼
    | |
    | |
- ◯ p53
- ◯ *DICER1* mutation
- ◯ Other, *specify test(s) and result(s)*
  - ▼
    | |
    | |

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

| |
| |

HISTOLOGICALLY CONFIRMED DISTANT METASTASES
(Note 14)

- ◯ Not identified
- ◯ Present, *specify site(s)*
  - ▼
    | |
    | |

PATHOLOGICAL STAGING[a] ([Note 15])
(Applicable for resection specimens only)

Pathologic staging system used[b]

◯ Children's Oncology Group (COG)
◯ TNM

Children's Oncology Group (COG) staging[c]

◯ Stage I   Requires all of the following to be true: Tumour involves favorable site (i.e., biliary tract/ liver, orbit, head and neck [excluding parameningeal] or genitourinary site [excluding bladder/prostate]), and; Tumour metastatic to distant site not identified

◯ Stage II   Requires all of the following to be true: Tumour involves unfavorable site (i.e., bladder/ prostate, extremity, parameningeal or other site not mentioned in stage I), and; Tumour size ≤5 cm, and; Tumour involvement of lymph nodes not identified, and; Tumour metastatic to distant site not identified

◯ Stage III Requires that one of the following be true: Tumour involves unfavorable site, is ≤5 cm, and involves regional lymph nodes, but distant metastases are not identified, or; Tumour involves unfavorable site and is >5 cm, with or without regional lymph node involvement, but distant metastases are not identified

TNM staging (UICC TNM 8th edition 2016)[d]

TNM Descriptor (only if applicable)

◯ y   -   post-therapy

Primary tumour (pT)

◯ pT0   No evidence of tumour found on histological examination of specimen

◯ pT1   Tumour limited to organ or tissue of origin
Excision complete and margins histologically free

◯ pT2   Tumour with invasion beyond the organ or tissue of origin
Excision complete and margins histologically free

◯ pT3   Tumour with or without invasion beyond the organ or tissue of origin
Excision incomplete

    ◯ pT3a   Evidence of microscopic residual tumour
    ◯ pT3b   Evidence of macroscopic residual tumour
    ◯ pT3c   Adjacent malignant effusion regardless of size

◯ pTX[e]   Tumour status may not be assessed

Regional lymph nodes (pN)

◯ pN0   No evidence of tumour found on histological examination of regional lymph nodes

◯ pN1   Evidence of invasion of regional lymph nodes

    ◯ pN1a   Evidence of invasion of regional lymph nodes
         Involved nodes considered to be completely resected

    ◯ pN1b   Evidence of invasion of regional lymph nodes
         Involved nodes considered not to be completely resected

◯ pNX[e,f]   N status may not be assessed due to lack of pathological examination or inadequate information on pathological findings

[a] *Core for primary resection specimens; non-core for post-treatment resection specimens.*

[b] *Either COG or TNM, or both, can be used depending on local preference.*

[c] *Reprinted from Pediatr Blood Cancer, Crane JN, Xue W, Qumseya A, et al. Clinical group and modified TNM stage for rhabdomyosarcoma: A review from the Children's Oncology Group, 2022, with permission pending from Wiley.*

[d] *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.*

[e] *pTX and pNX should be used only if absolutely necessary.*

[f] *For evaluations pNX will be regarded as N0.*

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 by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Non-morphological testing e.g., molecular or immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) recommends that some ancillary testing in ICCR Datasets is included as CORE elements. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

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 DAC.

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Scope of this dataset

The dataset has been developed for the pathological reporting of biopsy and resection specimens of paediatric rhabdomyosarcoma. The dataset includes both pre- and post-treatment specimens.

For adult rhabdomyosarcoma refer to the ICCR soft tissue sarcoma datasets.[2,3]

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Note 1 – Clinical information (Core and Non-core)

Acquisition of clinical information is central to establishing accurate context for pathologic specimens. For rhabdomyosarcoma, acquisition of preoperative treatment (chemotherapy, radiation, etc.) data is important when considering the interpretation of histological findings, including treatment response. Additionally, non-core items such as primary cancer status, presence of cancer predisposition syndromes, or other clinical findings also enhance the completeness of specimen context.

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Note 2 – Operative procedure (Core)

This element is based on information from the operating report, independent of the final margin assessment by the pathologist. If lymph nodes or metastatic lesions are included with the specimen, these should be listed under 'other'.

Biopsy refers to a limited tumour sampling without the intention to resect the tumour. Tumour samples can be obtained through an open biopsy or a core needle biopsy.

Intralesional resection is defined as a partial removal of the tumour with evidence of macroscopic residual tumour (this corresponds to Intergroup Rhabdomyosarcoma Study (IRS) III).[4]

Marginal resection is defined as the removal of the tumour and its pseudocapsule with a relatively small amount of adjacent tissue. There is no gross tumour at the margin; however, it is highly likely that microscopic tumour is present. Note that occasionally a surgeon will perform an 'excisional' biopsy, which effectively accomplishes the same outcome as a marginal resection. According to the IRS grouping system,[4] the tumour can be considered IRS II.

Wide local resection is defined as an intracompartmental resection. The tumour is removed with pseudocapsule and a cuff of normal tissue surrounding the neoplasm, but without the complete removal of an entire muscle group, compartment, or bone.

Radical resection is defined as the removal of an entire soft tissue compartment (for example, anterior compartment of the thigh, the quadriceps) or bone, or the excision of the adjacent muscle groups if the tumour is extracompartmental.

According to the IRS grouping system,[4] both wide and radical resection may be considered as complete resection if the pathologist confirms that resection margins are microscopically free of tumour.

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Note 3 – Tumour site (Core)

Rhabdomyosarcoma has a wide anatomical distribution. Rhabdomyosarcoma subtypes have a predilection for certain anatomical sites.

Embryonal rhabdomyosarcoma (ERMS) most often arises in the genitourinary tract, the abdomen, and the head and neck region, including the orbit. Botryoid subtype of ERMS often affects the mucosa of the bladder, vagina, extrahepatic bile ducts, and conjunctiva. Approximately half of ERMS occur in the head and neck, and about half in the genitourinary tract. ERMS only rarely occurs in the extremities. However, ERMS may present in any anatomical site.

Alveolar rhabdomyosarcoma (ARMS) predominantly affects the deep soft tissues of the extremities, but it can occur in the head and neck region, paraspinal sites, and perineal region.

In the paediatric age group, Spindle cell/sclerosing rhabdomyosarcoma (SSRMS) is more frequent in head and neck, and in the extremities. Spindle cell rhabdomyosarcoma is commonly seen in paratesticular site. Infantile Spindle cell rhabdomyosarcoma are frequent in the paraspinal region.

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Note 4 – Tumour dimensions (Core and Non-core)

As size is part in some staging systems, e.g., TNM, macroscopic tumour size should be measured on the resection specimen. At least the greatest tumour dimension should be reported; preferably all three dimensions should be evaluated.

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Note 5 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.

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Note 6 – Histological tumour type (Core)

Histologic diagnosis is based on the 2020 World Health Organization (WHO) Classification of Soft Tissue and Bone Tumours, 5th edition, and 2023 WHO Classification of Paediatric Tumours, 5th edition (Table 1).[5,20] The ICCR dataset includes 5th edition Corrigenda, November 2022.[6] The WHO classification is based on microscopic morphologic findings, variably combined with immunohistochemical and/or molecular findings.[5] If further testing is not available, then the possible diagnostic options should be described. The histopathologic report should include the supporting ancillary testing if performed.

Table 1: World Health Organization classification of soft tissue tumours.[5]

Descriptor	ICD-O codes[a]
Tumours with skeletal muscle differentiation	
Embryonal rhabdomyosarcoma NOS	8910/3
Alveolar rhabdomyosarcoma	8920/3
Pleomorphic rhabdomyosarcoma NOS	8901/3
Spindle/sclerosing rhabdomyosarcoma	8912/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third Edition, second revision (ICD-O-3.2).[7] 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. Incorporates all relevant changes from the 5th Edition Corrigenda, November 2022.[6]

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Soft tissue tumours are most often first sampled by biopsy. In some cases, the biopsy is not representative of the lesion. Molecular testing, including *FOXO1* fusion status, may be required to achieve a full molecular diagnosis, but the small tissue size, tissue processing issues, or suboptimal targeting of biopsy materials may preclude further testing. The pathologist should specify any, and all, limitations of the tissue interfering with an optimal diagnosis.

Embryonal rhabdomyosarcoma

Embryonal rhabdomyosarcoma (ERMS) is the most common subtype and, as its name suggests, mimics the appearance of embryonal skeletal muscle. There is frequently a myxoid background with alternating areas of loose and dense cellularity. Tumour cells are spindled or round, and may show elongated eosinophilic cytoplasm, sometimes with cross-striations ('strap-cells'). The botryoid pattern of ERMS shows condensation of tumour cells beneath a mucosal surface ('cambium layer'). Some tumours may show heterologous elements, including osteoid or cartilage (particularly common in tumours harbouring *DICER1* alterations).

Alveolar rhabdomyosarcoma

Alveolar rhabdomyosarcoma is composed of monomorphic round cells which may cling to delicate fibrous septa resembling alveoli, or be arranged in a solid pattern. Frank skeletal muscle differentiation or strap cells are uncommon, but multinucleated giant cells are often seen in ARMS. Most ARMS harbour *PAX3-FOXO1* or *PAX7-FOXO1* gene fusions.

Spindle cell/sclerosing rhabdomyosarcoma

Spindle cell/sclerosing rhabdomyosarcoma (SSRMS) is a heterogeneous group of tumours. In infants, these tumours are characterised by *VGLL2* or *NCOA2* rearrangements and are composed exclusively of spindled cells resembling fibrosarcoma, although differentiated rhabdomyoblasts are often seen. Other SSRMS arise more often in adolescents and young adults, show purely spindled, purely sclerosing, or a combination of

morphologic patterns, and harbour *MYOD1* mutations. These tumours infrequently show rhabdomyoblastic differentiation. Tumours with extensive sclerosis may mimic osteosarcoma or other sarcomas. Primary bone rhabdomyosarcomas are recently described and are characterised by spindled and epithelioid tumour cells, and this subset harbours *TFCP2* or *MEIS1* fusions. Another subset of spindle cell rhabdomyosarcoma does not harbour any known molecular alterations; this subset may represent spindle cell predominant ERMS.

Pleomorphic rhabdomyosarcoma

Pleomorphic rhabdomyosarcoma is not well-defined in the paediatric population, and histologically overlaps significantly with rhabdomyosarcoma with diffuse anaplasia.

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Note 7 – Anaplasia (Core and Non-core)

Anaplasia in rhabdomyosarcoma is defined as the presence of large, hyperchromatic nuclei that are at least three times the size of neighbouring nuclei as seen at low power (10X objective), with or without atypical multipolar mitotic figures. It may be found in any histologic subtype, although it's most commonly seen in embryonal rhabdomyosarcoma. It can be further classified as focal (when rare scattered anaplastic cells are present) or diffuse (when clusters or sheets of anaplastic cells are present). The clinical significance of anaplasia remains unclear.[8] Nevertheless, anaplasia in rhabdomyosarcoma is associated with TP53 mutations, and the vast majority of tumours (approximately 70%) with TP53 mutations show histologic evidence of anaplasia. Screening for TP53 mutations (somatic and germline) is indicated in those patients that have rhabdomyosarcoma with anaplasia.

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Note 8 – Other histological features (Non-core)

The pathologist should report other abnormalities that are relevant for the diagnosis, and any other significant pathologic finding. For instance, a plexiform neurofibroma present in a resection for embryonal rhabdomyosarcoma may indicate the patient has NF1. Unrelated findings could include vascular malformations or hemangiomas, hamartomas or infection in the same resection specimen.

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Note 9 – Treatment effect (Non-core)

Descriptive assessment of the amount of residual viable tumour and type of histological response, necrosis, fibrosis/hyalinisation, and particularly cytodifferentiation, may be important and give reliable information in terms of efficacy of treatment.[9,10]

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Note 10 – Margin status (Core)

The status of the resection margins is important for TNM staging. If margins are involved one should distinguish between microscopic involvement and those that are clearly involved on gross examination and incompletely excised. If the margins are negative, the minimum that should be documented is the distance of tumour to the closest margins.

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Note 11 – Lymphovascular invasion (Non-core)

While sarcomas generally develop hematogenous metastases, rhabdomyosarcoma does belong to a small number of sarcomas which may also show lymphovascular infiltration, leading to metastasis to draining lymph nodes. In order to confirm true infiltration as opposed to 'carry-over' during tissue dissection, evidence of expansion of the vascular lumen by a tumour plug, and especially adhesion of tumour cells to the vascular endothelium are helpful findings. Confirmation of the nature of a vessel as lymphatic versus venous may be obtained with immunohistochemistry for podoplanin, which will react with lymphatic lining endothelial cells, while both blood and lymphatic vessels will stain with CD31.

Recent studies reviewing rhabdomyosarcomas in the broader context of sarcomas, have suggested a worse prognosis for patients whose tumours exhibit lymphovascular infiltration.[11,12] However, current standard practice does not stratify patients based on this histological finding.

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Note 12 – Lymph node status (Core)

The regional lymph node status is a major determinant of risk stratification in rhabdomyosarcoma and can determine the intensity of chemotherapy and use of radiation therapy. Patients with regional lymph node involvement have a worse prognosis when compared to patients without lymph node involvement, especially in patients with ARMS.[13-15] Lymph node sampling using sentinel lymph node approach is often performed in patients with extremity tumours, and in patients ≥10 years of age with paratesticular tumours. In addition, clinically enlarged nodes may be biopsied as well. Nodes should either be sampled using excisional biopsy (preferably) or core needle biopsy. Fine needle aspirates are discouraged due to the potential for false negatives.

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Note 13 – Ancillary studies (Core and Non-core)

All immunohistochemical staining and molecular tests that contributed to the diagnosis should be documented. Desmin, myogenin and MyoD1 are antibodies used routinely in the diagnosis of rhabdomyosarcoma.[5,16,17] Both myogenin and MyoD1 are excellent nuclear myogenic markers with high sensitivity and specificity. The nuclear expression of myogenin is diffuse in >90% of cells in most cases of ARMS, with less staining seen in ERMS.[18] However, in dense cellular ERMS myogenin staining can be seen in >50% of tumour cells.

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Spindle cell/sclerosing rhabdomyosarcomas (SSRMS) are positive for immunohistochemical markers of skeletal muscle differentiation including desmin, myogenin (myf4) and MyoD1. *MYOD1* mutated SSRMS may lack staining for desmin or myogenin, but is often strongly and diffusely positive for MyoD1 immunostaining.[16,19]

The distinction between ERMS/ARMS has previously been based on histopathological features. It has now been shown that the clinically most significant difference is the presence of translocation involving *FOXO1* gene and either *PAX3* or *PAX7*. Various studies have shown that 'Fusion negative ARMS' are clinically and molecularly indistinguishable from ERMS. The WHO Classification of Paediatric Tumours, 5th edition,[20] defines *PAX3- FOXO1* and *PAX7-FOXO1* fusions as essential criteria for ARMS diagnosis.[21,22]

Thus, testing for these fusion genes in ARMS is regarded as standard practice.

However, if resources for molecular testing are not available, a morphological diagnosis together with immunohistochemistry is acceptable.

The third subgroup recognised by the WHO Classification of Soft Tissue and Bone Tumours, 5th edition,[5] includes the less common spindle cell/sclerosing variants. This is a molecularly heterogeneous group of tumours, including tumours with recurrent translocations involving *VGLL2* and *NCOA2*,[23] tumours with somatic mutations in *MYOD1,* and tumours lacking recurrent abnormality. Infantile Spindle cell rhabdomyosarcoma with VGLL2, and/or NCOA2 rearrangements are reported to have a good prognosis. *MYOD1* mutated tumours are reported to follow a highly aggressive course with high mortality.[19] More recently an intraosseous spindle/epithelioid cell rhabdomyosarcoma with *EWSR1* or *FUS* gene fusion to *TFCP2* or the *MEIS1-NCOA1* gene fusion has been described.[24,25]

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Note 14 – Histologically confirmed distant metastases (Core)

Documentation of known metastatic disease is an important part of the pathology report. Such information should be recorded with as much detail as is available, including the site, whether the specimen is a histopathology or cytopathology specimen, and with reference to any relevant prior surgical pathology or cytopathology specimens.

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Note 15 – Pathological staging (Core and Non-core)

Pathological staging should be provided in the pathology report in primary surgical excision but not in diagnostic biopsies of rhabdomyosarcomas. Pathological staging can also be reported in post-treatment surgical resections (non-core), but that this does not alter the pre-treatment stage.

The latest version of either the Children's Oncology Group (COG),[4] or TNM,[26,27] or both, can be used depending on local preferences. The Union for International Cancer Control (UICC)[26] or American Joint Committee on Cancer (AJCC)[27] versions of TNM are used in many parts of the world for rhabdomyosarcoma staging. Apart from minor discrepancies in terminology, the UICC and AJCC staging systems are broadly similar.

The COG staging system is used in the United States and by the College of American Pathologists (CAP)[28,29] for paediatric rhabdomyosarcoma. This staging is based on pre-treatment tumour characteristics. Clinical information required to definitively assign stage (e.g., nodal status or distant metastatic disease) may not be available to the pathologist and, therefore, pathological stage may not be possible.

In resection specimens following non-surgical treatment (for example, chemotherapy, radiotherapy); TNM staging (optional) should be prefixed by 'y' to indicate that this is a post-therapy stage.

Reporting of pathological staging categories is based on the evidence available to the pathologist at the time of reporting. The final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

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