Paediatric Renal Tumours
Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

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

PRIOR THERAPY (Note 1)

- ◯ Information not provided
- ◯ No prior chemotherapy administered
- ◯ Prior chemotherapy administered

SPECIMEN LATERALITY (Note 2)

- ◯ Not specified/Not applicable
- ◯ Left
- ◯ Right
- ◯ Other (e.g., horseshoe kidney, single kidney), *specify*

OPERATIVE PROCEDURE (Note 3)

- ◯ Not specified
- ◯ Enucleation
- ◯ Partial nephrectomy
- ◯ Total or radical nephrectomy
- ◯ Other, *specify*

PRE-OPERATIVE RUPTURE OR INTRA-OPERATIVE SPILLAGE (Note 4)

- ◯ Not known
- ◯ Detected
- ◯ Not detected

ACCOMPANYING/ATTACHED STRUCTURES (Note 5)

(select all that apply)

- ◯ None submitted
- ☐ Adrenal gland
- ☐ Other, *specify*

SPECIMEN WEIGHT (Note 6)

g

- ◯ Cannot be assessed

TUMOUR FOCALITY (Note 7)

- ◯ Cannot be determined
- ◯ Unifocal
- ◯ Multifocal

Specify number of tumours

TUMOUR DIMENSIONS[a] (Note 8)

Nodule 1

Greatest dimension mm

Additional dimensions mm x mm

Nodule 2

Greatest dimension mm

Additional dimensions mm x mm

- ◯ Cannot be assessed, *specify*

[a] *Specify for each nodule.*

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BLOCK IDENTIFICATION KEY (Note 9)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

RENAL SINUS INVOLVEMENT (select all that apply) (Note 10)

- ◯ Cannot be determined
- ◯ Not identified
- ☐ Renal sinus vessel involvement by viable tumour with negative margin[b]
- ☐ Invasion of the wall of the ureter or collecting system outside of the kidney by viable tumour (but completely resected with negative margin)[b]
- ☐ More than minimal renal sinus soft tissue invasion present (but completely resected with negative margin)[b]
- ☐ Minimal renal sinus soft tissue invasion by viable tumour present (<5 mm in greatest dimension and >5 mm from a margin)[c]

[b] *Criteria for local stage II by both COG and SIOP.*

[c] *Allowed within local stage I by COG, considered stage II by SIOP.*

RENAL CAPSULE PENETRATION (Note 11)

- ◯ Cannot be assessed
- ◯ No viable tumour outside the renal capsule
- ◯ Viable tumour outside the renal capsule (including adrenal gland) that **is not** surrounded by a fibrous pseudocapsule, with negative margins[d]
- ◯ Viable tumour outside the renal capsule or within the adrenal gland that **is** surrounded by a fibrous pseudocapsule, with negative margins[e]

[d] *Supports local stage II by SIOP and COG.*

[e] *Supports local stage II for COG; allowed within local stage I for SIOP.*

PRIMARY TUMOUR EXCISED IN ONE PIECE[f] (Note 12)

- ◯ Cannot be assessed
- ◯ Tumour excised in one piece
- ◯ Tumour excised in more than one piece

[f] *Applicable only for COG staging; supports local stage III.*

NEPHROGENIC RESTS[g] (Note 13)

- ◯ Cannot be assessed
- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ Intralobar
    - ◯ Single
    - ◯ Multiple
  - ☐ Perilobar
    - ◯ Single
    - ◯ Multiple
    - ◯ Diffuse, hyperplastic
  - ☐ Unclassified

[g] *Nephrogenic rests are not included in staging criteria.*

HISTOLOGICAL TUMOUR TYPE (Note 14)
(Value list based on the World Health Organization Classification of Paediatric Tumours (2022))

- ◯ Wilms tumour
  - ◯ Favorable histology
  - ◯ Focal anaplasia
  - ◯ Diffuse anaplasia
- ◯ Nephrogenic rest only (without Wilms tumour)
  - ◯ Intralobar
  - ◯ Perilobar
- ◯ Mesoblastic nephroma
  - ◯ Cellular
  - ◯ Classic
  - ◯ Mixed
- ◯ Paediatric cystic nephroma
- ◯ Cystic partly differentiated nephroblastoma
- ◯ Metanephric stromal tumour
- ◯ Metanephric adenoma
- ◯ Metanephric adenofibroma
- ◯ Ossifiying renal tumour of infancy
- ◯ Clear cell sarcoma of the kidney
- ◯ Rhabdoid tumour of the kidney
- ◯ Anaplastic sarcoma of the kidney (DICER-1 associated)
- ◯ Other, *specify*

POST-THERAPY HISTOLOGICAL CLASSIFICATION OF WILMS TUMOUR (Note 15)

- ◯ Not applicable[h]

Low risk tumours

- ◯ Completely necrotic (100% necrosis although residual tubules from nephrogenic rests may be present)

Intermediate risk tumours

- ◯ Favourable histology, epithelial type (<66% necrosis; >66% of viable component epithelial and <10% blastema)
- ◯ Favourable histology stromal type (<66% necrosis; >66% of viable component stromal and <10% blastemal)
- ◯ Favourable histology mixed type (<66% necrosis with viable component containing at least two components, none of which comprise more than two thirds of the viable tumour, or tumours that are 10-66% blastemal)
- ◯ Favourable histology, regressive type (66-99% necrosis)
- ◯ Focal anaplasia (except blastemal type)[i]

High risk tumours

- ◯ Blastemal type (<66% necrosis with >66% viable blastemal component)
- ◯ Diffuse anaplasia[i]

[h] *Not post-therapy or not Wilms tumour.*

[i] *Focal and diffuse anaplasia are included in the post-therapy risk stratification by SIOP, but are treated by separate clinical protocols by COG.*

MARGIN STATUS (Note 16)

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of viable tumour from closest margin ____ mm
  - Specify closest margin(s), if possible
- ◯ Involved by viable tumour[j] (select all that apply)
  - ☐ Renal vein margin
  - ☐ Ureteral margin
  - ☐ Inked soft tissue or parenchymal margin
  - ☐ Other, *specify*
- ◯ Involved by non-viable tumour (select all that apply)
  - ☐ Renal vein margin[j]
  - ☐ Ureteral margin[j]
  - ☐ Inked soft tissue or parenchymal margin[k]
  - ☐ Other, *specify*
- ◯ Presence of viable or non-viable tumour in peritoneal or abdominal or pelvic nodules or implants[k]

[j] *Supports local stage III by both COG and SIOP.*

[k] *Supports local stage III by COG, but not by SIOP.*

LYMPH NODE STATUS (Note 17)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found
- Number of lymph nodes examined ____
  - ◯ Not involved
  - ◯ Involved (viable or non-viable tumour)[l]
    - Number of involved lymph nodes ____
    - ◯ Number cannot be determined
    - Location of involved lymph nodes (select all that apply)
      - ☐ Regional
      - ☐ Non-regional (outside the abdomino-pelvic region)

[l] *Supports local stage III.*

COEXISTENT PATHOLOGY (Note 18)

- ◯ None identified
- ◯ Present, *specify*

ANCILLARY STUDIES (Note 19)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ Immunohistochemistry, *specify test(s) and result(s)*
  - ☐ Molecular genetic testing, *specify test(s) and result(s)*
  - ☐ Other, *record test(s), methodology and results*

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

HISTOLOGICALLY CONFIRMED DISTANT METASTASIS (Note 20)

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

PATHOLOGICAL STAGING (Note 21)

Pathologic staging system used

- ◯ Children's Oncology Group (COG)
- ◯ International Society of Paediatric Oncology (SIOP)

Local stage (based on the data elements for each stage)

◯ Local stage I	All staging elements are consistent with local stage I, and none indicate local stages II or III
◯ Local stage II	Presence of any staging element supporting local stage II and no parameters for local stage III
◯ Local stage III	Presence of any staging element for local stage III
◯ Local stage not determined	

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

The dataset has been developed for the examination of resection specimens from paediatric patients with nephroblastoma also known as Wilms tumour (used here from now on) and all other renal tumours of childhood except renal cell carcinomas, for which the ICCR Invasive carcinoma of renal tubular origin dataset should be used.[2] Rarely, other primitive tumours of childhood (including neuroblastoma, Ewing sarcoma/peripheral neuroectodermal tumour, desmoplastic small round cell tumour, among others) arise within the kidney but not within renal precursor cells; these should be staged and treated according to recommendations specific for their diagnosis. This dataset does not apply to these tumours.

For bilateral tumours, complete a separate dataset for each kidney. For multifocal unilateral tumours, complete a single dataset.

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Note 1 – Prior therapy (Core)

The treatment of Wilms tumour may include the use of chemotherapy prior to resection or biopsy.[3-5] The staging systems for these different approaches, although similar, have significant differences. Further, the histological appearance differs following chemotherapy, as does the assessment of risk stratification.[6,7] Thus, it is critical that the status of pre-operative therapy is known so that the relevant staging and classification systems can be applied. When completing this element, only chemotherapy used to treat the current renal tumour is considered as 'prior treatment'.

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Note 2– Specimen laterality (Core)

The anatomic location of the tumour being evaluated is an elemental part of the accurate description of the tumour under consideration.

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Note 3 – Operative procedure (Core)

There are three overall approaches to the initial diagnosis of Wilms tumour: i) upfront neoadjuvant chemotherapy (with no biopsy) for presumed Wilms tumour (within specified clinical parameters) followed by post-therapy resection; ii) initial biopsy followed by chemotherapy and then resection; and iii) primary resection prior to therapy. The type and extent of the surgical procedure chosen depends on many factors, including the site, size and extent of the tumour. Total or radical nephrectomy includes resection of an intact kidney and any associated lymph nodes or tissue/organs adherent to the tumour. Partial nephrectomy seeks to completely excise a tumour with a margin of non-tumour tissue while sparing the remaining kidney. Enucleation seeks to remove the entire tumour, minimising the margin of non-tumoral tissue.

The choice of performing a biopsy has different implications depending upon which staging system is used. In the Children's Oncology Group (COG) staging system, biopsy of any type taken prior to therapy, including percutaneous core or needle biopsy, upstages the tumour to at least a stage III at the time of initial diagnosis and therapy.[8,9] In the International Society of Paediatric Oncology (SIOP)/Renal Tumour Study Group (RTSG) staging system, only open biopsy upstages the tumour to at least stage III[6]; needle or core biopsy does not upstage the tumour.[10]

It is important to note that in both COG and SIOP/RTSC staging systems, a biopsy performed at a previous procedure does not impact on the staging of subsequent procedures if interval therapy has been given. All procedures should be newly staged based on features for the tumour <u>at the time of resection</u> in order to best guide the subsequent therapy. For example, a needle/core biopsy taken prior to therapy in a COG patient supports a local stage of III at the time of the initial biopsy, but is <u>not</u> a criterion for stage III in a subsequent post-therapy resection unless the tumour undergoes another biopsy during that subsequent procedure.

Other rare operative procedures merit annotation. Wilms tumour rarely originates outside the kidney. Extrarenal Wilms tumour may be associated with other congenital anomalies and the operative approach should be provided.[11]

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Note 4 – Pre-operative rupture or intra-operative spillage (Core)

Wilms tumours, particularly prior to therapy, may rupture spontaneously or following preoperative or operative trauma.[12] In SIOP/RTSG and COG protocols, tumours that rupture either prior to surgery or at the time of surgery (an event more recently termed spillage by COG) are considered to have local stage III disease and to require additional therapy.[5,13] The pathologic appearance of rupture/spillage changes with the passage of time. Rupture near the time of resection results in disruption of the Gerota fascia and the underlying tumour. However, at times the pathologic evidence of the rupture may be limited and may only be evident to the surgeon. Furthermore, the same gross appearance may be seen following trauma to the specimen after operative removal of the tumour, requiring correlation with intraoperative findings. Rupture prior to surgery results in the same disruptive process, but with increasing passage of time several changes occur to varying degrees, including tumour devitalization, resolving haemorrhage, fibrosis, and inflammation within the perirenal soft tissue. With even further passage of time, the site of rupture may heal and may become inapparent pathologically. The determination of whether rupture/spillage has occurred is therefore often difficult based on pathologic findings alone and may require multidisciplinary input, particularly by the surgeon. Pathologists should seek the opinion of the surgeon prior to establishing the presence of rupture or spillage and should be aware that the surgeon may independently establish the presence and extent of rupture/spillage for treatment purposes.

It is important to note that the following situations do not constitute rupture: 1) penetration of the renal capsule, or the peritumoral pseudocapsule, and extension of the tumour into the perirenal soft tissue; and 2) appearance of rupture confined to the renal capsule (not involving the Gerota fascia). Further, in these situations, if the tumour then extends to the surgical margin, this is defined as a positive margin (see **Note 16 MARGIN STATUS**) and not rupture. This distinction may impact the type and amount of radiation therapy given.

Sufficient data are not currently available to utilise the presence of tumour cells detected within abdominal or pleural fluid in staging of Wilms tumour.

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Note 5 – Accompanying/attached structures (Core)

Depending upon the size and relationship of the tumour with the adrenal gland, the surgeon may choose to remove the adjacent adrenal gland with the goal of completely resecting the tumour. Whether or not the patient has one or two adrenal glands may be important in their care in the future. Similarly, to achieve total removal of the tumour, the surgeon may remove pieces of other organs adherent to the tumour (such as spleen, liver, bowel or diaphragm). This information may likewise be useful in the management of the patient in the future. When these accompanying structures are resected intact with the kidney, the presence of tumour within the accompanying structure does support a local stage of III unless the surgical margin of the resection of the specimen is positive for tumour.

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Note 6 – Specimen weight (Core)

Nephrectomy specimens should be weighed prior to sectioning or processing. Nephrectomy weight may be an eligibility factor for some clinical trial protocols[9] and may influence therapy decisions in certain circumstances.[14]

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Note 7 – Tumour focality (Core)

Most Wilms tumours are solitary, but multifocal unilateral and/or bilateral disease may occur in over 10% of cases.[14,15] Multifocal tumours are associated with an increased risk of Wilms tumour developing in the contralateral kidney, usually in association with nephrogenic rests.[16] The presence of multifocality often determines the treatment approach.[17] In case of multiple synchronous tumours in a specimen, a single dataset should be completed providing the number of tumours and their size. Within each kidney, each tumour should be individually staged and classified, and then the stage and classification should be determined for the entire kidney. For example, a kidney with a 40 millimetres (mm) tumour showing diffuse anaplasia, local stage I, and a 100 mm tumour with favourable histology, local stage III would receive a classification of diffuse anaplasia, local stage III. This example illustrates that there will be unusual combinations that need to be carefully discussed among a multidisciplinary team in order to determine the final treatment strategy. When bilateral tumours are sampled, a dataset should be recorded for each kidney.

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Note 8 – Tumour dimensions (Core and Non-core)

The macroscopic size of the tumour determines the pathological handling, whereby at least one microscopic section is taken per centimetre of maximal tumour diameter.[9,18,19] The pathologic and radiologic tumour dimensions may also be used to calculate the volume of the tumour, or the volume of the different histologic counterparts at the time of central review.[13] These are currently important questions being addressed within SIOP studies. For kidneys with more than two tumours, the two tumours impacting on the stage and histology should be provided.

At least the greatest tumour dimension should be reported; preferably all three dimensions should be evaluated, particularly if tumour volume is desired.

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Note 9 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should be documented in the final pathology report should the need for internal or external review arise. 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 is useful to have a digital macroscopic picture of the specimen and a record of the origin of the tumour blocks.

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 10 – Renal sinus involvement (Core)

The renal sinus is composed predominantly of adipose tissue and harbors nerves and vessels supplying and draining the kidney, and the extrarenal collecting system. The renal sinus also extends deeply into the contours of the kidney. The most important renal sinus sections are those taken from regions adjacent to the tumour. SIOP/RTSG and COG protocols separately evaluate the invasion of renal sinus soft tissue and the involvement of renal sinus vessels to provide tumour staging which dictates subsequent treatment. For both SIOP/RTSG and COG, only **viable** tumour within the renal sinus results in upgrading to local stage II, providing the margins are negative for viable and non-viable tumour.[13,18]

Sinus soft tissue: Unlike the majority of the kidney, the renal sinus lacks a fibrous capsule separating the kidney from the adjacent adipose tissue. Therefore, tumour that is confined to the kidney may directly abut the renal sinus fat, without truly invading the renal sinus soft tissue. Similarly, nephrogenic rests located deep in the kidney may also involve the renal sinus soft tissue and mimic involvement by Wilms tumour. COG protocols include an additional refinement that identifies patients with only minimal renal sinus soft tissue invasion that is distant from the soft tissue margin. Unless there are other features upstaging these patients, they are treated as local stage I tumours. In practice, 'minimal invasion' includes tumours that show tumour extension into the sinus that is less than 5 mm in greatest dimension, and is located greater than 5 mm from a surgical margin.

Sinus vessels: Evaluating renal sinus vascular involvement may likewise be challenging. During processing, small fragments of tumour may be displaced into vascular structures and mimic true vascular involvement. Artifactually displaced tumour fragments are commonly highly irregular ragged, and may contain ink that is displaced by the knife or blade. True vascular involvement has a smooth surface and is often (but not always) adherent to the vessel. Any degree or size of true sinus vascular involvement is a criterion for local stage II. This is distinct from staging based on invasion of sinus soft tissue, as above.

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Note 11 – Renal capsule penetration (Core)

The SIOP/RTSG and COG protocols evaluate the invasion of tumour beyond the renal capsule in order to provide tumour staging which dictates subsequent treatment.[5,13] The renal capsule is a layer of collagen covering the entire kidney, except for the renal sinus. The renal capsule may be quite thin, particularly if compressed by an expanding tumour. The fibrous pseudocapsule formed by the tumour itself may merge with the renal capsule, making the distinction between the tumour pseudocapsule and the renal capsule difficult. The presence of the tumour beyond the renal capsule is best seen by taking sections of the triangular region where the normal kidney and renal capsule meets the confluence of the tumour with its pseudocapsule.

Beyond the renal capsule is a layer of adipose tissue, often containing dilated vessels, which is covered by the Gerota fascia. Viable tumour that penetrates the renal capsule and invades or is otherwise present within this soft tissue or vessels without invasion beyond, or rupture of, the Gerota fascia meet the criteria

for stage II. Non-viable tumour in this region, in the absence of other criteria, does not upstage to stage II. For institutions that treat patients according to SIOP/RTSG protocols, additional refinements have been made that identify a small number of patients with viable tumour within the perirenal fat or within the adrenal gland that is surrounded by a fibrous pseudocapasule, which is allowed within local stage I for SIOP/RTSG (but not for COG).

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Note 12 – Primary tumour excised in one piece (Core)

In the COG and National Wilms Tumour Study Group protocols, removal of tumour in more than one piece is a criterion for local stage III.[5] Some examples include: 1) primary tumour excised in more than one piece; 2) tumour identified in a separately excised adrenal gland; 3) a tumour thrombus within the renal vein that is removed separately from the nephrectomy specimen; and 4) tumour nodules within the perirenal fat (resembling lymph nodes) that are separately excised. The separately excised specimens may or may not represent contiguous tumour.

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Note 13 – Nephrogenic rests (Core)

Nephrogenic rests are foci of persistent embryonic tissue, and may be single, multiple, or diffusely distributed. More than 30% of Wilms nephrectomy specimens contain nephrogenic rests. Rests often appear paler than surrounding non-neoplastic kidney parenchyma and these areas should be sampled. The two fundamental categories of nephrogenic rests are based on the topography and histology; perilobar nephrogenic rests are located at the periphery of the lobule, are usually subcapsular and comprised predominantly of blastema or epithelial differentiation. Intralobar nephrogenic rests are usually located deep within the lobule. They have indistinct margins and contain blastemal, tubular, and prominent stromal elements interspersed among normal glomerular and tubular elements.[20,21] Diffuse hyperplastic perilobar nephroblastomatosis is a rare form of perilobar nephrogenic rests that forms a rind of nephroblastomatosis involving one or both kidneys, in whole or in part.[22,23] Nephrogenic rests have important implications concerning the risk of contralateral Wilms tumour development and association with certain syndromes.[16,24]

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Note 14 – Histological tumour type (Core)

Histologic diagnosis is based on the 2022 World Health Organization (WHO) Classification of Paediatric Tumours, 5th edition (Table 1).[25] Accurate histological diagnosis of paediatric renal tumours is critical in order to provide the optimal therapy and outcome. Because they are rare, they often present a diagnostic challenge. Over 85% of renal malignancies in children will be Wilms tumours (favourable and anaplastic suptypes); however, other paediatric renal tumours can have a similar appearance and the addition of immunohistochemical and molecular analyses will aid in differentiating the various tumour types. It is beyond the scope of this document to provide detailed descriptions of the subtypes of paediatric renal tumours (refer to WHO 5th edition).[25]

Table 1: World Health Organization classification of paediatric renal tumours.[25]

Descriptor	ICD-O codes[a]
Wilms tumour	8360/3
Nephrogenic rest	
Congenital mesoblastic nephroma	8960/1
Paediatric cystic nephroma	8959/0
Cystic partially-differentiated nephroblastoma	8959/1
Metanephric stromal tumour	8935/1
Metanephric adenoma	8325/0
Metanephric adenofibroma	8965/0
Ossifying renal tumour of infancy	8967/0
Clear cell sarcoma of kidney	8964/3
Rhabdoid tumour	8963/3
Anaplastic sarcoma of kidney (DICER-1 associate)	8800/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third Edition, second revision (ICD-O-3.2).[26] 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.

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Note 15 – Post-therapy histological classification of Wilms tumour (Core)

The histologic response to prior therapy is taken into consideration by both SIOP and COG in order to guide future therapy of patients with post-therapy Wilms tumour.[19,27] Tumours are stratified into three risk groups based on the histology following preoperative chemotherapy and on the assessment of percentages of chemotherapy-induced changes and all viable components.

Low risk: Completely necrotic tumours showing no viable tumour are classified as low risk. Small foci of tubules, stroma and/or blastema representing residual nephrogenic rests may be present.

Intermediate risk: All favourable histology Wilms tumours falling outside of low and high risk as defined above are classified as intermediate risk. In addition, SIOP tumours with Focal Anaplasia are included in the intermediate risk category. COG tumours with focal and diffuse anaplasia are separately classified and treated. SIOP also separately classifies intermediate risk tumours by histology due to their potential prognostic implications.[28,29]

High risk: Tumours with Diffuse Anaplasia are classified as high risk by SIOP, and are separately classified and treated by COG. Favourable histology Wilms tumours that are ≥33% viable with ≥67% of the viable tumour composed of blastema are classified by both SIOP and COG as high risk.

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Note 16 – Margin status (Core and Non-core)

Margin status is critical for the staging of Wilms tumours. Margins positive for **viable tumour** upstage the tumour to stage III in all staging systems. The evaluation of non-viable tumour at the margin differs depending upon margin location and on the staging system used. In SIOP, **non-viable** tumour at the ureteral or renal vein margin or within abdominal or peritoneal implants is considered local stage III, whereas **non-viable** tumour at the soft tissue margin is not considered local stage III. COG considers **non-viable tumour** at all margins to represent local stage III.

The status of the renal parenchymal margin for partial nephrectomy is important, as positive margins are associated with consideration of the need for radiotherapy. However, after radiotherapy, the local recurrence rate was not greater in such patients.[30] The presence of nephrogenic rest at the parenchymal margin of partial nephrectomy specimen represents a challenge in interpretation, but is not considered to be positive.

The area with the closest margin and the distance of the closest margin from tumour, while not required, may aid in in planning post-operative therapy in non-treated tumours.[30,31]

Assessment of the renal vein margin may be challenging, particularly if there is bulging thrombus. If the thrombus is intact (by gross assessment and discussion with the surgeon), and if the renal vein wall is not attached to the thrombus at its most distal aspect, the margin can be assumed to be negative.[32]

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Note 17 – Lymph node status (Core and Non-core)

Lymph node involvement is a critical factor in determining stage, and lymph node involvement by either viable or non-viable tumour requires a designation of stage III in both the National Wilms Tumour Study Group/COG and SIOP/RTSG staging systems.[13,33] Positive lymph node status in any site is associated with a worse prognosis,[34] particularly for those patients with anaplasia.[33]

The recognition of lymph node metastasis in certain circumstances can be challenging. Small aggregates of tumour cells in the subcapsular sinuses may be overlooked, and these sites should be examined carefully for metastatic disease. In post-treatment tumours, lymph nodes may contain totally necrotic tumour, which still upstages the tumour to local stage III.[19,35] Such necrotic tumour foci should replace part of the nodal architecture; prominent sinus histiocytes should not be considered evidence for stage III tumour. Lastly, when tumour causes obstruction of the kidney, Tamm Horsfall protein may accumulate within the kidney and displaced into the regional lymph node. This may be accompanied by displaced non-neoplastic renal tubular epithelial cells and such foci may mimic lymph node metastasis. Such foci are cytologically consistent with reactive epithelial cells and do not resemble Wilms tumour.[32]

Involvement of abdominal or pelvic lymph nodes is a criterion for local stage III, whereas lymph node involvement in the thorax or other extra-abdominal sites is a criterion for stage IV.

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Note 18 – Coexistent pathology (Non-core)

In some situations, inclusion of coexisting conditions such as glomerulopathy may support clinico-pathological correlation or patient management.

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Note 19 – Ancillary studies (Core and Non-core)

Wilms tumour: Ancillary studies are usually not necessary for the diagnosis of Wilms tumour in resection specimens. However, immunohistochemical staining for WT1 and/or PAX8 may be useful for problematic cases when differentiating blastemal-predominant Wilms tumour from other embryonal soft tissue tumours presenting within the kidney (which are not covered by this dataset). Similarly, no single recurrent genetic abnormality has been found in Wilms tumour, although molecular genetic tests may be performed for diagnostically difficult cases. Several studies suggest that the common underlying marker of anaplasia is mutation of the p53 protein.[36-38] Mutation of p53 often (but not always) results in abnormal p53 protein accumulation and strong nuclear positivity for p53 by immunohistochemistry. However, the diagnostic utility of immunohistochemistry for p53 protein is limited by difficulties in performing and interpreting the test. Furthermore, some p53 mutations do not cause abnormal protein accumulation. However, strong nuclear p53 protein accumulation identified in a tumour that is suspicious for anaplasia may contribute to the diagnosis.[39]

Molecular tests such as loss of heterozygosity (LOH) at chromosomes 1p and 16q, gain of 1q, and 11p15 loss have prognostic significance in certain patient populations. Augmentation of therapy has been shown to be effective for Wilms tumours with combined LOH at 1p and 16q, therefore analysis of these loci, most commonly by targeted or genome-wide microarray that includes evaluation of zygosity (SNP array), has become routine practice in North America.[40,41] While 1q gain is associated with adverse prognosis, the benefit of increased therapy is an area of active investigation.[42] LOH and imprinting abnormalities of 11p15 have been associated with increased risk of relapse in young patients with stage I favourable histology Wilms tumour treated with nephrectomy alone without adjuvant therapy.[43,44] On occasion, ancillary germline genetic testing may be useful after the diagnosis has been made. For example, there is an association between perilobar nephrogenic rests, LOH for IGF2 and overgrowth syndromes; and between intralobar nephrogenic rests, mutations of the WT1 gene and the WAGR and Denys-Drash syndromes (reviewed in Beckwith 1998[24]).

Clear cell sarcoma of kidney: CCSKs often show expression of BCOR, cyclin D1, NGFR, and TLE1 by immunohistochemistry; however none of these are either fully sensitive nor specific.[45-48] Clear cell sarcoma of the kidney frequently contain *BCOR*-ITD mutations or other BCOR alterations;[49] a minority have *YWHAE-NUTM2B* fusions.[50,51]

Rhabdoid tumour: Rhabdoid tumours of the kidney are most often characterised by alterations in *SMARCB1*, causing loss of INI1 expression by immunohistochemistry.[52]

Paediatric cystic nephromas (but not cystic partially differentiated nephroblastomas) are often associated with germline or somatic mutations in *DICER1* and are associated with pleuropulmonary blastoma familial cancer syndrome.[53-55] Rarely, sarcomas with varying degrees of anaplasia histologically similar to pleuropulmonary blastoma may also be identified within the kidney,[25,56] at times arising within a cystic nephroma.[57,58]

Metanephric adenomas, adenofibromas, and stromal tumours often carry somatic *BRAF* mutations.[59]

Congenital mesoblastic nephromas containing a cellular component often demonstrate *ETV6-NTRK3* fusions (as well as other variant fusions); alterations of *EGFR*, *BRAF* and other genes have also been reported in ETV6-NTRK3 negative cases.[59]

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Note 20 – Histologically confirmed distant metastases (Core)

Documentation of known metastatic disease correlates with outcome and is an important part of the pathology report.[60] Such information, if available, should be recorded with as much detail as is available including the site, specimen type, and histologic pattern.

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Note 21 – Pathological staging (Core)

Staging of Wilms tumour remains one of the most important factors in determining prognosis and in making therapeutic decisions. Two main systems are in use: the SIOP/RTSG staging system is predominantly used for pre-treated tumours; and the National Wilms Tumour Study Group/COG staging system is used for tumours undergoing primary resection as well as following therapy.[13,19] The evaluation of tumour viability is only taken into consideration following therapy.

When bilateral tumours are sampled, a separate dataset should be recorded for each kidney.

The local staging criteria for COG are provided below:

COG Local stage I: Tumour (viable) is limited to the kidney with negative margins and lymph nodes. All criteria listed below are met:

a) Renal capsule is not penetrated by viable tumour.
b) Tumour may protrude (botryoid) into the renal pelvis or ureter but does not infiltrate their walls.
c) The vessels of the renal sinus are not involved by viable tumour.
d) The soft tissue of the renal sinus is not more than minimally involved by viable tumour.
e) Necrotic tumour may be present within the renal sinus or beyond the renal capsule and remain local stage I provided the margins are negative for viable and non-viable tumour.

COG Local stage II: The tumour is resected in one piece; the margins and lymph nodes are negative for tumour (viable or non-viable); at least one of the following is present:

a) Viable tumour is present in the perirenal fat or adrenal gland.
b) Viable tumour infiltrates the blood or lymphatic vessels outside the renal parenchyma, including the renal sinus.
c) Viable tumour more than minimally infiltrates the soft tissue of the renal sinus.
d) Viable tumour infiltrates the wall of the renal pelvis or the ureter.
e) Viable tumour may infiltrate the adrenal gland or be adherent to adjacent structures but remain stage II if surgical margins are negative for tumour.

COG Local stage III: Residual non-haematogenous tumour present after surgery and confined to the abdomen. At least one of the following is present:

a) Tumour (viable or non-viable) involves abdominal/pelvic lymph nodes.
b) Tumour (viable or non-viable) is present at a surgical margin of resection (documented by microscopic examination).
c) Pre- or intra-operative tumour rupture/spillage has occurred (documented histologically or confirmed by the surgeon).
d) The tumour is resected in more than one piece (piecemeal).
e) The tumour is biopsied before surgery regardless of biopsy type: tru-cut, open, or fine needle aspiration. (Only applies to staging at time of biopsy, should not be used as a criterion for stage III in a post-therapy resection specimen).
f) Tumour (viable or non-viable) has penetrated through the peritoneal surface.
g) Tumour implants (viable or non-viable) are found anywhere in the abdomen.

The local staging criteria for SIOP are provided below:

SIOP Local stage I: Viable tumour is limited to the kidney with negative margins and lymph nodes. All criteria listed below are met:

a) Renal capsule intact, not penetrated by viable tumour.
b) Tumour might protrude (botryoid) into the renal pelvis or ureter but does not infiltrate their walls.
c) The vessels of the renal sinus are not involved by viable tumour.
d) The soft tissue of the renal sinus is not involved by viable tumour.
e) Necrotic tumour may be present within the renal sinus or beyond the renal capsule and remain stage I.
f) Viable tumour may remain Stage I if present in the perirenal fat or within the adrenal gland but surrounded by a fibrous pseudocapsule.

SIOP Local stage II: The margins are negative for viable tumour and the lymph nodes are negative for viable or non-viable tumour; at least one of the following is present:

a) Viable tumour is present in the perirenal fat or adrenal gland and is not covered by a pseudocapsule.
b) Viable tumour infiltrates the blood or lymphatic vessels outside the renal parenchyma.
c) Viable tumour infiltrates the soft tissue of the renal sinus.
d) Tumour may be adherent to adjacent structures but remain stage II if the surgical margin is negative.
e) Viable tumour infiltrates the vena cava or adjacent organs (except the adrenal gland), but is completely resected.
f) Viable tumour infiltrates the wall of the renal pelvis or the ureter.

SIOP Local stage III: Residual non-haematogenous tumour present after surgery and confined to abdomen. Any one of the following may occur:

a) Tumour (viable or non-viable) involving abdominal-pelvic lymph nodes.
b) Tumour (viable only) present at a soft tissue surgical margin of resection.
c) Tumour (viable or non-viable) present at resection margins of ureter, renal vein or inferior vena cava.
d) Pre- or intra-operative tumour rupture/spillage, if confirmed by microscopic examination (positive margin in area of the rupture).
e) Tumour thrombus (viable or non-viable) attached to the inferior vena cava wall removed piecemeal.
f) Wedge/open tumour biopsy prior to pre-operative chemotherapy or surgery.
g) Tumour implants (viable or non-viable) are found anywhere in the abdomen.
h) Tumour (viable or non-viable) has penetrated through the peritoneal surface.

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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