Treatment Guidelines Collaborative Wilms Tumour Africa Project

Phase II

SOCIÉTÉ INTERNATIONALE D'ONCOLOGIE PÉDIATRIQUE
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

Document version 1.8
Date of issue: 9 May 2022

Disclaimer of Medical Advice

This document describes a consensus treatment guidelines for children with newly diagnosed Wilms tumour adapted to local circumstances in a low-income setting. Patients are registered and their outcome is evaluated in a prospective clinical study.

Hospitals with limited experience in Wilms tumour treatment in children should consider transferring the child to a more experienced centre.

Responsibility for the diagnosis, administration of protocol treatments and other interventions in patients lies with the participating clinician. Before entering patients into this protocol, clinicians must ensure that the protocol has received appropriate institutional and/or national regulatory approval.

This protocol has been written with greatest accuracy; however, errors cannot be completely excluded. Amendments may be necessary. Amendments will be circulated to known participating centres in the SIOP Africa / PODC (PODC has been renamed Global Health Network) Collaborative Wilms tumour project.

There is no central patient insurance for risks related to participating in this multi-centre international protocol. The centre in each country will ensure that treatment related injuries are managed in accordance with the applicable regulatory requirements for treating patients within that country.

Copyright

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About this document

For further information

Please see the website – https://siop-online.org/collaborative-wilms-tumour-africa-project/treatment-guidelines/

These guidelines are based upon the SIOP PODC adapted treatment guidelines for Wilms tumour and supportive care in low income countries. The SIOP PODC adapted treatment guidelines for Wilms tumour in low income countries are based upon the treatment guidelines of the SIOP Renal Tumour Study Group (RTSG). PODC has been renamed Global Health Network.

Who wrote this document

Dr. T. Israels, paediatric oncologist, Coordinator Collaborative Wilms Tumour Africa Project (Utrecht, The Netherlands).

Dr. V. Paintsil, paediatric oncologist (Kumasi, Ghana), Prof. I. Chitsike, paediatric oncologist (Harare, Zimbabwe) and Prof L Renner, paediatric oncologist (Accra, Ghana); current and previous members of the Steering Committee of the Collaborative Wilms Tumour Africa Project.

Prof. E.M. Molyneux and Prof. P.B. Hesseling, members of the Advisory Committee of the Collaborative Wilms Tumour Africa Project.

Dr. A.M.C. Mavinkurve-Groothuis, paediatric oncologist (Utrecht, The Netherlands) and Dr. F. Spreafico (Milan, Italy), members of the Relapsed Wilms Tumour subcommittee, SIOP-RTSG.

Prof. J. Parkes, radiotherapist (Cape Town, South Africa).

Dr. S. Kamiza, pathologist (Blantyre, Malawi).

Prof. E. Borgstein, paediatric surgeon (Blantyre, Malawi) and Prof. L Hadley, paediatric surgeon (Durban, South Africa).

Technical Editing: Neil Ranasinghe (Refinitiv and SIOP)

NOTE: This document has been produced by all the people listed above and, as such, is not an official SIOP document.

SIOP and SIOP Global Health Network (formerly PODC)

International Society of Paediatric Oncology (SIOP) is the only global multidisciplinary society entirely devoted to paediatric and adolescent cancer. The society has over 1,800 members worldwide including doctors, nurses, other health-care professionals, scientists and researchers. Our members are dedicated to increasing knowledge about all aspects of childhood cancer - https://siop-online.org/

Improving access to and care for children and adolescents with cancer is one of the fundamental goals of SIOP.

For more information about the SIOP Global Health Network (formerly Paediatric Oncology in Developing Countries (PODC)) and other Working Groups and Task Forces - https://siop-online.org/podc-working-groups/

SIOP PODC adapted treatment guidelines

The SIOP PODC (PODC has been renamed Global Health Network) adapted treatment guidelines that are the basis for these guidelines can be found here:

- SIOP PODC: Clinical guidelines for the management of children with a Wilms tumour in a low income setting: https://onlinelibrary.wiley.com/doi/full/10.1002/pbc.24321
- SIOP PODC: Recommendations for supportive care of children with cancer in a low income setting: https://onlinelibrary.wiley.com/doi/10.1002/pbc.24501

Chapter 1 Introduction

Wilms tumour (WT) is a relatively common and treatable kidney tumour. Survival in low income countries is much lower than in high income countries, with reported survival in low income settings in sub-Saharan Africa ranging from 11% - 50%.[1-5] Known challenges are late presentation with advanced disease, malnutrition, failure to complete treatment and poorer facilities both for the specific cancer treatment and for supportive care. [2,3,6] Treatment is multi-disciplinary and includes paediatricians, nurses, surgeons, radiotherapists, radiologist and pathologists. Social support to enable parents to complete treatment and adequate supportive care are essential.

Different settings need different strategies to be able to provide locally optimal care to children with WT. This treatment protocol is for children with WT in sub-Saharan Africa where the minimal requirements for treatment with curative intent are available. It is based on the SIOP PODC (PODC has been renamed Global Health Network) consensus treatment guidelines written by a multi-disciplinary group of African clinicians and 'state of the art' experts from Europe and North America.[7] Supportive care recommendations are largely based on the SIOP PODC recommendations for supportive care of children with cancer in low income countries.[8]

Collaborative Wilms Tumour Africa Project

The Collaborative Wilms Tumour Africa Project started implementing these guidelines in several centres in sub-Saharan Africa in 2014. Currently, the participating centres are in Blantyre (Malawi), Kumasi and Accra (Ghana), Mbingo, Banso and Mutengene (Cameroon), Harare (Zimbabwe) and Eldoret (Kenya). Several papers were published about the progress, principles and methods of the project.[9-12]

In the first four years of the project, 201 WT patients were included and treated. Compared to the baseline, programme implementation was associated with significantly higher survival without evidence of disease at the end of treatment (52% vs 68.5%, P=0.002, reduced abandonment of treatment (23% vs 12%, P = 0.009) and less death during treatment (21% vs 13%, P=0.06). Two-year event free survival was 49.9% ± 3.8% with abandonment of treatment as an event (median follow up 27 months, range 1-58). Relapse of disease occurred in 21% of patients.

This collaborative implementation of adapted WT treatment guidelines, using relatively simple and low-cost interventions, led to a significant decrease in treatment abandonment and increase in survival at the end of treatment, and also may have improved long term survival. Improved supportive care is needed to reduce death during treatment and to allow for some intensification and prolongation of treatment. In response to this obvious need, the Collaborative WT Africa Project group started SUCCOUR – a project to improve supportive care for children with cancer in Africa.[13] Late presentation and lack of radiotherapy likely contributed to the relapse rate. We need to keep advocating for early diagnosis and radiotherapy. Radiotherapy guidance is included in this Phase II version of the guidelines.

The aim is to decrease both abandonment of treatment and death during treatment to below ten percent and to increase survival of children with this common and curable tumour in sub-Saharan Africa to over 60%, in line with the Global Initiative for Childhood Cancer, launched by the World Health Organisation (WHO).

Summary of the treatment protocol

All WT patients referred to any of the participating hospitals will be included into the study with intention to treat. After diagnostic staging, the patients will receive preoperative chemotherapy consisting of vincristine and actinomycin D for four weeks for localized disease. This can be prolonged to 7 weeks and intensified (adding doxorubicin) for large tumours according to the clinician's discretion. If metastases are present, treatment is 6 weeks and consists of three drugs: vincristine, actinomycin D and doxorubicin. This treatment can be prolonged to 9 weeks to the clinician's discretion. Risk-stratified postoperative chemotherapy is delivered based on the SIOP PODC consensus guidelines, allowing for the absence of radiotherapy. Stratification is based on pathology staging and risk classification or, if this is not reliably and timely available, on surgical staging.

Additions and revisions in the Phase I guideline (2014)

If radiotherapy is available, it should be included and given according to local guidelines – general guidance is given in Chapter 11 Radiotherapy guidance on page 23.

In these Phase II guidelines, we added the option to prolong postoperative chemotherapy (AV14 and AVD14) from five 3-weekly courses to nine 3-weekly courses (AV26 and AVD26). We have insufficient evidence in our settings to state which one is better. Please see Chapter 9 Postoperative Chemotherapy (including stratification) on page 19.

Protocol history

Phase I - Version 1.1 was published in 2014.

Phase II – Version 1.7 was published in 2020.

Document history

Phase II – Version 1.8 was published in 2022.

- Changes to flow sheets on pages 23 and 33.
- Added Copyright section on page 2.

Chapter 2 Locally relevant clinical research questions

The SIOP Africa / PODC (PODC has been renamed Global Health Network) Collaborative Wilms Tumour project is implementing these guidelines as a multi-centre prospective clinical trial with uniform outcome evaluation. We aim to answer the locally relevant clinical questions as detailed below.

Treatment Guidelines

1. **Survival**
   - 2 and 5 year event free and overall survival

   Causes of treatment failure
   - Disease related (progression and relapse); death during treatment; abandonment of treatment.

2. **Response to preoperative chemotherapy**
   - % of unresectable disease after preoperative chemotherapy, reasons for unresectability
   - Stage distribution at surgery, including number of surgical ruptures

3. **Toxicity of preoperative chemotherapy**
   - % of children developing grade III or IV neutropenia (Common Toxicity Criteria (CTC)

4. **Treatment related mortality**
   - % of children who die during preoperative chemotherapy and around surgery

5. **Nutritional status and nutritional support**
   - Assessment of nutritional status at diagnosis, using mid-upper-arm-circumference

6. **Diagnostic work-up**
   - What is the percentage of correct and incorrect diagnosis after work-up and pre-treatment?

7. **Presentation of patients – Wilms tumour**
   - Size of tumour, % of patients with metastases (chest / liver)

Chapter 3 Inclusion and exclusion criteria

Inclusion criteria

All children under the age of 18 years presenting with a renal mass compatible with a new diagnosis of Wilms tumour based on clinical examination and ultrasonography will be included into the study protocol.

Exclusion criteria

- Relapse of disease
- Age under 6 months

Chapter 4 Diagnosis

The diagnosis can be made with reasonable certainty based on history, physical examination and ultrasonography of the abdomen.[7] Usually patients present with a flank mass and are well without fever, pain or severe general malaise. Hypertension and haematuria may be present.

Ultrasonography of the abdomen is essential to confirm the diagnosis.[14,15]

Ultrasound probes (3.5 MHz) that are usually used for adult patients are useful to scan large tumours. It is helpful to scan from the back and to try to visualise each kidney. In large (diameter more than 15 cm) WT, the affected kidney is often completely obliterated or only a rim of tissue remains. The destructive, heterogeneous, echogenic mass is cystic or a varying mixture of solid and cystic components.

Patients with abdominal Burkitt lymphoma (BL) are usually more malnourished than patients with WT.[16] Patients with BL often have masses elsewhere and tumour growth is fast. Ultrasound scans may reveal one or multiple solid masses that are nearly uniformly homogenous. BL can diffusely infiltrate the kidneys resulting in homogenous enlargement, in contrast to the renal destruction and heterogeneous tumours seen in WT.[17]

Children with neuroblastoma are generally in much poorer condition than children with WT. They are often in severe pain and have profound anaemia. They may have subcutaneous nodules or bilateral orbital hematomas, sometimes referred to as racoon eyes that are typical of neuroblastoma. A neuroblastoma often has calcifications which are visible on imaging (X-ray and ultrasonography).

Essential investigations at diagnosis

Essential investigations at diagnosis to be done and results documented as follows:

Patient details: Name, date of birth, home address, travel distance to treatment centre, contact information

Patient medical history: Duration of symptoms, previous surgery / chemotherapy for this disease, weight loss

Physical examination: Weight, height, Mid Upper Arm Circumference (MUAC), blood pressure, side of tumour (left, right) and estimated maximum diameter of the tumour using a ruler (from anterior axillary line to the edge of the tumour at its greatest diameter)

Laboratory tests: Urine dipstick (blood), thick smear for malaria parasites and Elisa antibody test for HIV

Imaging: Abdominal ultrasound and Chest X-ray

Imaging

An ultrasonographic examination of the abdomen is done to confirm the diagnosis and answer the following questions: Is the tumour intra-renal? Is the tumour cystic, solid or both? Are there intravascular extensions or thrombi (especially in the inferior vena cava)? Are there any tumours in the opposite kidney? Are there abdominal or liver metastases? If possible, estimate the size of the tumour by measuring the three dimensions (length x thickness x width x 0.523≈volume (cm^3).[18] If not possible, try to measure the single greatest measurement. If ultrasound Doppler examination is available, determining blood flow in the renal and inferior caval vein or see if these vessels are obstructed by tumour (thrombus) is useful.

Chest X-rays, postero-anterior (and, if available, lateral) are made to detect lung metastases that present as white round lesions often in the periphery of the lungs.

Diagnostic biopsy

Cytology by fine needle aspiration (FNA) or tru-cut biopsy (histology) at diagnosis is not recommended in this protocol.[7] It is at the clinician's discretion to do it when there is serious doubt about the diagnosis. Other tumours such as Burkitt lymphoma can usually be differentiated by clinical examination and ultrasonography. If a biopsy is indicated, an approach from the back is preferred both for percutaneous core needle biopsies (tru-cut) and FNA to avoid tumour seeding. According to the SIOP WT 2001 protocol, these biopsies / procedures do not upstage the tumour.[19] Diagnostic biopsy before preoperative chemotherapy is not standard practice according to the current SIOP Wilms protocol either.[20]

Multidisciplinary Team (MDT) meetings

Clinicians caring for children with cancer in low income countries often do so in isolation. Cancer diagnosis and care requires the expertise of several disciplines such as pathology, surgery, radiology, oncology, if available, radiotherapy and palliative care. It is very helpful to have the input of all these teams in decisions about diagnosis and in planning treatment. The best way of bringing these groups together is to hold regular meetings (e.g. weekly) together.

Chapter 5 Preoperative chemotherapy

Preoperative chemotherapy is given to shrink large tumours, reduce surgical complications, especially tumour rupture, and to downstage the tumour at surgery. This allows for less intense post-operative chemotherapy and reduces the need for radiotherapy.[21] Studies have shown that this is also true for small, seemingly easily resectable tumours.[22] This is a logical strategy for patients who have large tumours, in a setting where supportive care is limited and radiotherapy not available.[7]

Chemotherapy treatment regimens are detailed below.

Localized disease

Patients with localized disease will be treated for 4 weeks with two drugs:

- Vincristine 1.5 mg/m^2 (maximum dose 2 mg) weekly for 4 weeks (i.e. 4 doses in total).
- Actinomycin D 45 μg/kg (maximum dose 2 mg) at week one and three (i.e. 2 doses in total).

Both drugs are given by I.V. push.

Doses are reduced to 2/3 of the original dose in patients with a bodyweight < 12kg.

For dose modifications and / or the need to delay chemotherapy due to toxicity, please see below.

Treatment flow sheet - preoperative chemotherapy for localized disease

Actinomycin D 45 µg/kg	↓		↓		surgery
Vincristine 1,5 mg/m²	↓	↓	↓	↓	
Weeks	**1**	**2**	**3**	**4**	**5**

Metastatic disease

Patients with metastatic lung and/or liver disease will be treated with vincristine, actinomycin and doxorubicin for 6 weeks.

Chest X-ray and/or abdominal ultrasound scanning should be done at week six to reassess. If there is still evidence of metastatic disease and a good response with hope of complete response, then three additional weeks of chemotherapy can be considered. If metastases have not disappeared or not become resectable after nine weeks, we recommend stopping curative treatment. Parents may want to go home with their child who needs on-going palliative care.

Chemotherapy for metastatic disease

- Vincristine 1,5 mg/m2 (maximum dose 2 mg) weekly (i.e. 6 – 9 doses in total)
- Actinomycin D 45 μg/kg (maximum dose 2 mg) two weekly.(i.e. 3 – 5 doses in total)
- Doxorubicin 30 mg/m2 every four weeks (i.e. 2 – 3 doses in total)

All doses are reduced to 2/3 of the original dose in patients with a bodyweight < 12kg.

Vincristine and Actinomycin D are given as an I.V. push.

Doxorubicin is given in a 2 - 6 hours infusion.

For dose modifications and / or the need to delay chemotherapy due to toxicity, please see below.

Treatment flow sheet - preoperative chemotherapy for metastatic disease (2 options)

Dox 30 mg/m²	↓				↓					
Act D 45 µg/kg	↓		↓		↓	*	surgery			
Vinc 1.5 mg/m²	↓	↓	↓	↓	↓	↓				
Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**			

Dox 30 mg/m²	↓				↓		↓			
Act D 45 µg/kg	↓		↓		↓	*	↓		↓	surgery
Vinc 1.5 mg/m²	↓	↓	↓	↓	↓	↓	↓	↓	↓	
Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

* Chest X-ray and / or ultrasound abdomen to determine regression and resectability of metastases.

Preoperative chemotherapy for metastatic disease is 6 weeks. If there is a partial response of metastases after 6 weeks and the hope for a complete response after an additional 3 weeks of treatment, then this may be considered. (optional).

Localized disease - large tumours (optional prolongation and intensification of preoperative chemotherapy)

Children may present with large tumours (>15cm diameter). When there is the need to shrink tumours further to facilitate surgery, chemotherapy may be prolonged and intensified with an additional 3 weeks of treatments with three drugs (i.e. adding doxorubicin to the two drug regimen for localized disease). This can be chosen for children who have tolerated the first 4 doses of preoperative chemotherapy well.[21,23]

For dose modifications and / or the need to delay chemotherapy due to toxicity, please see below.

Treatment flow sheet – optional prolongation / intensification for localized tumours to improve resectability

Doxorubicin 30	mg/m²					↓			
Actinomycin D 45	µg/kg	↓		↓		↓		↓	surgery
Vincristine 1,5	mg/m²	↓	↓	↓	↓	↓	↓	↓	↓
	Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**

Dose modifications

A full blood count and differential should be done before each course of chemotherapy containing actinomycin D. Chemotherapy (if containing actinomycin D or doxorubicin) should be delayed if the absolute neutrophils count is below 1.0 x 109/L or if the child has a fever. Vincristine when given alone may be continued without taking the absolute neutrophil count (ANC) into account if the patient is clinically well. The platelet count must be > 100.000/mm3 to start a course. Anaemia alone is not an indication for delay or modification of the chemotherapy dose.

If neutropenia occurs, consider giving actinomycin D every three instead of two weeks, while continuing vincristine weekly at full doses. In severely acutely malnourished children, especially if they are in a poor condition, consider reducing doses of all drugs (e.g. by 1/3).

If there is any suspicion that hepatic veno-occlusive disease (VOD) has occurred, consider omitting the next dose of actinomycin D and then either cautiously re-introducing 50% of the dose on the following occasion or, if toxicity was severe, avoid actinomycin D altogether in the future. Symptoms of hepatic veno-occlusive disease are liver enlargement and tenderness of the liver, thrombocytopenia, ascites, and weight gain.

Chapter 6 Chemotherapy – administration and non-haematological side effects

Drugs should be stored and reconstituted according to the instructions given by the manufacturer. Vincristine should be kept in the refrigerator.

NOTE: Please reweigh the child before each new chemotherapy course.

Especially vincristine, but also actinomycin D, can cause painful, chemical burns with extravasation. To reduce the risk of extravasation, a fresh I.V. cannula should be placed in a vein where a leak is clearly visible. Check the correct placement by giving a bolus of normal saline before chemotherapy and check regularly during the infusion of doxorubicin.[8]

Adequate hydration should be given to all patients receiving actinomycin D, especially those less than 1 year of age, to avoid hepatic veno-occlusive disease. Hepatic veno-occlusive disease VOD (liver swelling / enlargement and tenderness, thrombocytopenia, ascites, and weight gain) is usually a self-limiting condition but can be fatal. Supportive care consists of careful fluid balance with fluid restriction. If there is any suspicion that VOD has occurred, consider omitting the next dose and then either cautiously re-introducing 50% of the dose on the following occasion or, if toxicity was severe, avoid actinomycin D altogether in the future.[7]

The specific side effects of vincristine, especially neuropathy (jaw pain, reduced / absent reflexes, foot drop, ptosis and constipation) increase with a cumulative dose and need to be sought during treatment.

Doxorubicin may be given in a 2 – 6 hour infusion, according to the local clinician's discretion. SIOP protocols favour a longer infusion (6 hours) to minimise cardiac toxicity. In COG (Children's Oncology Group in North America) protocols, doxorubicin in the same dose as this protocol is given through I.V. in 15 minutes. The disadvantage of longer infusions is the risk of extravasation during the infusion, logistic and nurse supervisory issues with a longer hospital stay which may affect patient compliance.

Chapter 7 Surgery

General surgeons, urologists, or paediatric surgeons may operate on a patient with a WT.[24] It is important that a prescribed, formal operative protocol is followed. As a general rule, the more experience the surgeon has of operating on patients with WT, the better.[25,26] The SIOP formal operative protocol used in high income countries is in Appendix A Formal SIOP Surgical protocol for reference.

Tumour resectability should be assessed by a team consisting of surgical, paediatric and anaesthetic staff that takes into account the complexity of the operation, the patient's general condition, co-morbidities and local facilities. Anaesthetists must be made aware of co-morbidities such as anaemia, hypertension, poor nutrition, pulmonary infection and the possible side effects of preoperative chemotherapy.[27]

Arrangements for close post-operative monitoring should be confirmed before any operation starts. Endotracheal intubation and muscle relaxation are essential. Blood should be available. Venous access should be in the upper limbs. A urinary catheter is essential to monitor intra-operative urine production and a nasogastric tube is helpful in keeping the stomach decompressed. It is wise to avoid resection of adjacent organs.[7] The mesocolon and a segment of descending colon can be safely resected en-bloc, but if it becomes obvious during the operation that the pancreas, duodenum or other organs are involved, it is better to stop the operation and consider giving more chemotherapy.[28] Para-aortic lymph node sampling is better done after the main tumour has been removed.

A report on the surgical staging, including difficulty of operation, abdominal metastases, sampled nodes and possible tumour spill or incomplete resection, is essential and will contribute to the determination of the intensity of post-operative chemotherapy. For the surgery staging system, please see below.

Postoperative analgesia is important. If feasible and an infusion pump is available, consider an opiate infusion; otherwise follow your institutional protocol. Intramuscular injections should be avoided.

Delays in surgery happen. These are caused by surgical emergencies, lack of staff or theatre equipment. Delays in surgery are one of the known reasons of 'abandonment' of treatment and are best avoided.[1,3] If a delay is unavoidable, we recommend continuing preoperative chemotherapy with vincristine only in an attempt to achieve some tumour control without risking neutropenia at the time of surgery.[7]

Documentation of surgical findings

The surgeon will determine surgical stage, tumour weight and, if indicated, inspect the contralateral kidney. The surgeon will record the appearance of the renal vein, vena cava, tumour capsule and lymph nodes: (normal, suspicious, wall infiltrated, thrombosis). Complete and incomplete excision or biopsy will also be recorded. Any other structures suspicious or invaded outside the resected kidney will also be recorded and excised or biopsied. The following surgery-related complications will be registered, if they occur: tumour rupture (major/minor), extensive haemorrhage (> 50 ml/kg), hypotension, cardiac arrest, vascular injury, inferior vena cava obstruction, bowel infarction, bowel injury, splenic injury, liver injury. Resection of any other visceral organ (due to injury) at time of nephrectomy will also be recorded.

SIOP Surgical staging system

- **Stage I** The tumour is resected with a clear margin
- **Stage II** The tumour is macroscopically completely resected
- **Stage III** There are (suspected) involved abdominal nodes
  The tumour is incompletely resected or ruptured or there is a vascular extension

Chapter 8 Pathology

If available, reliable and timely pathology services have an important role in making a histological diagnosis and in determining the postoperative chemotherapy. Postoperative chemotherapy is then based on the tumour type (risk classification) and stage of the specimen taken at surgery.[1,2]

Stratifying tumours into low, intermediate and high risk groups is based on histological sub-classification. Please see Appendix C Revised SIOP Working Classification of Renal Tumours of Childhood (2001) for Pre-Treated Cases [29]

Staging is based on the extent of the tumour outside the kidney:

- **Stage I** - tumour limited to the kidney, completely resected
- **Stage II** - tumour outside kidney, completely resected
- **Stage III** - incomplete resection

See Appendix B The SIOP Nephroblastoma Staging System (Pathology) for the detailed SIOP Pathology Staging System.

Correct staging is only possible if the specimen is inked and there is a block guide. Please see Appendix E SIOP Pathology – handling and study of the nephrectomy specimen for the complete and comprehensive SIOP guidelines how to handle the specimen and do the staging and risk group assessment.

The pathologist should have information regarding pre- or intraoperative tumour rupture (from the surgeon) and clinical information regarding distant metastases.

NOTE: Please keep the full set of slides of the pathology assessment. Regional meetings will be organised with the possibility of central pathology review of the cases.

If appreciated, the institutional pathologist will be invited to attend these meetings, bringing his / her own slides with him / her and taking them home again after the meeting.

Chapter 9 Postoperative Chemotherapy (including stratification)

If available, reliable and timely pathology services have an important role in making a histological diagnosis and in determining the postoperative chemotherapy. Postoperative chemotherapy is then based on the *tumour type* (risk classification) and *stage* of the specimen taken at surgery.[19,29]

For children with localized disease at diagnosis, postoperative chemotherapy can be based on the individual tumour's histological subtype (risk classification) and stage at surgery, if this is available. The risk stratification of postoperative chemotherapy based on pathology examination is shown below. Pathology staging and sub typing (especially stage I and low risk) must be reliable to follow this stratification. Treatment flow algorithms are in the end of this chapter.

- If reliable pathological staging and risk classification (tumour type) are not available in time to determine postoperative chemotherapy, postoperative chemotherapy will be stratified based on surgical staging. This includes assessment of the lymph nodes by gross inspection by the surgeon. Surgical staging involves not only reading the operation notes but also discussion with the surgeon. A difficult operation may mean that spillage occurred and the tumour should be upstaged. Stratification is then as shown below.[7]
- Surgical stage 1 or 2 (complete and easy tumour resection): SIOP Africa / PODC (PODC has been renamed Global Health Network) Wilms **AV 14** (or **AV26)**; i.e. 5 or 9 (optional) cycles of vincristine and actinomycin D.
- Surgical stage 3 (incomplete or difficult resection or rupture / spill): SIOP Africa / PODC Wilms **AVD14** (or **AVD26)**; i.e. 5 or 9 (optional) cycles of vincristine, actinomycin D and doxorubicin.

Children with metastatic disease at diagnosis but complete remission by the time of surgery should have the three drug – 5 or 9 (optional) cycle postoperative regimen **AVD14 or AVD26**.

The first dose of postoperative chemotherapy consists of vincristine alone and is given once gut peristalsis is re-established following surgery and within 21 days of the last pre-operative chemotherapy dose. The other drugs are added at week 2 of post-operative chemotherapy, if surgical recovery is complete. If not, a second dose of post-op vincristine only is given and the other drugs are delayed until week 3.[7]

The proposed interval between courses of chemotherapy is three weeks. If this is too intense - with treatment delays due to neutropenia - the interval should be extended to 4 weeks, especially if patients come from home and live far away.[7]

In these Phase II guidelines, we added the option to prolong postoperative chemotherapy (AV14 and AVD14) from five 3-weekly courses to nine 3-weekly courses (AV26 and AVD26). We have insufficient evidence in our settings to state which one is better.

The shorter postoperative chemotherapy has the advantage of less toxicity and less intense for families, possibly leading to less abandonment of treatment. The longer postoperative chemotherapy may prevent relapse of disease.
Centres can choose which option they prefer and are requested to do the same in all their patients. It is also possible for centres to randomise between the two options which will give us relevant information to decided which strategy is best.

Postoperative treatment strategies – risk stratification

The table below shows postoperative treatment strategies based on tumour type (risk classification) and pathology stage.

	Stage I	Stage II	Stage III
Low risk	No further treatment	**AV14 or AV26**	**AV14 or AV26**
Intermediate risk	**AV4**	**AV14 or AV26**	**AVD14 or AVD26**
High risk	**AVD14 or AVD26**	**AVD14 or AVD26**	**AVD14 or AVD26**

Chapter 10 Postoperative chemotherapy treatment schedules

SIOP Africa / PODC Wilms AV4

PODC has been renamed Global Health Network.

For patients with:
Localized disease at diagnosis and Stage I, intermediate risk (IR) pathology of tumour specimen

NOTE: Doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.

Both drugs I.V. push

Actinomycin D 45 µg/kg (max 2 mg)			↓		
Vincristine 1.5 mg/m² (max 2 mg)		↓	↓	↓	↓
	Week	**1**	**2**	**3**	**4**

SIOP Africa / PODC Wilms AV14 (or AV26)

For patients with:
Localized disease at diagnosis and Pathology Stage II IR or stage IILR or stage III LR
or
Surgical stage I or II

NOTE: Doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.

Both drugs I.V. push

Act D 45 µg/kg (max 2mg)		↓			↓			↓		
Vinc 2.0 mg/m² (max 2 mg)	↓	↓			↓			↓		
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
		11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
		20	**21**	**22**	**23**	**24**	**25**	**26**		

SIOP Africa / PODC Wilms AVD 14 (or AVD26)

For patients with:
Localized disease at diagnosis and **Pathology Stage I HR, II HR, III IR and III HR**
or
Surgical stage III

or
Metastatic disease at diagnosis

NOTE: Doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.

Actinomycin and Vincristine I.V. push, doxorubicin I.V. in 2 -6 hours.

Dox 30 mg/m²
Act D 45 µg/kg (max 2 mg)
Vinc 2.0 mg/m² (max 2 mg)

AVD 14

Dox		↓			↓			↓			↓		
Act D		↓			↓			↓			↓		
Vinc	↓	↓			↓			↓			↓		
Weeks	**1**	**2** **14**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**

AVD 26

Dox		↓						↓					
Act D		↓			↓			↓			↓		
Vinc	↓	↓			↓			↓			↓		
Weeks	**1**	**2** **14** **26**	**3** **15**	**4** **16**	**5** **17**	**6** **18**	**7** **19**	**8** **20**	**9** **21**	**10** **22**	**11** **23**	**12** **24**	**13** **25**

Rationale

The postoperative chemotherapy treatment schedule is simplified (omitting single vincristine injections and increasing the dose to 2 mg/m2) compared to SIOP schedules, in view of anticipated patient compliance.

Chapter 11 Radiotherapy guidance

Most centres in sub-Saharan Africa currently do not have radiotherapy available. It is an important and effective modality in the treatment of WT. General quality assurance guidelines for paediatric radiotherapy in low and middle income countries are published.[30]

Indications for Radiotherapy

When available radiotherapy should be considered in patients with metastatic disease (mostly lungs), incomplete resection or tumour rupture (stage III) and high risk disease (pathology report).

Timing of radiotherapy

Patients should be referred to a radiation oncologist within 1 week of surgery. Radiotherapy should start within 10 days of surgery or as soon as possible. (This tight timeline is less important for favourable histology than for patients with unfavourable histology.)

Sedation/anaesthesia

Most children 7 years old and older do not require sedation provided they are made to feel at ease in the radiotherapy suite. Play therapists and/or a buddy program may aid in avoiding the need for sedation. Children under the age of 6 years almost always require sedation and/or anaesthesia.

- Any pre-operative imaging, imaging reports, surgical notes and histology report (when available) should be available at the time of radiotherapy planning.
- Multi-disciplinary meetings prior to mark-ups are very helpful to discuss overall management, and to schedule mark-up slots immediately after surgery.
- Children may be planned using simulation or virtual simulation, using CT.
- Children are planned in the supine position. For abdominal radiotherapy, the arms are placed above the head, for whole lung RT, the arms are placed at the sides. A knee rest is used.
- The fields are delivered as parallel opposed anterior and posterior fields
- The fields depend on the type of radiotherapy required and are delivered according to SIOP and COG radiotherapy recommendations:
    - Flank radiotherapy, Whole abdomen radiotherapy, Whole lung radiotherapy.
    - Growing bones (e.g. the vertebral column) must be included symmentrically in the treatment volume to avoid asymmetrical growth in later years.
- Treatment is delivered using a Cobalt-60 or Linac (6MV) external beam radiotherapy unit.

Guidelines and dose recommendations

- Dose recommendations for sub-Saharan Africa are recommended according to COG radiotherapy guidelines. Rationale: This is because treatment courses are shorter, and easier to accommodate in a busy general RT department in LMIC.
- Specific guidelines and guidance can be requested from the authors of this chapter.

Chapter 12 Uniform treatment guidelines for relapse of disease

Introduction

Not many patients with relapse of disease survive in our centres in sub-Saharan Africa. Generally speaking, one will often need other drugs and more intense treatment than the first treatment to cure a child with resistant disease. More intense treatment can only be given, if tolerable, with the available level of supportive care.

We defined two groups of children with relapse of disease:

- Group 1 - patients who have only been treated with vincristine and actinomycin, not yet with doxorubicin. It can be considered to treat these patients with curative intent, a proposal for treatment is detailed below.
- Group 2 - patients who have been treated with vincristine, actinomycin and doxorubicin. It can be considered to treat these patients with palliative (quality of life) intent, a proposal for treatment is detailed below. Preference is given to oral treatment.

Group 1 – Relapse treatment with curative intent

Patients who have been treated with vincristine and actinomycin only during previous treatment

Carboplatin*200 mg/m2 day 1-2 I.V.

Etoposide 150 mg/m2 day 1-2 I.V.

Alternate with:

Cyclophosphamide 500 mg/m2 day 1-2 I.V.

Doxorubicin 30 mg/m2 day 1 I.V.

Every 3 weeks, 4 – 6 cycles, surgery when maximal response.

*Carboplatin can be replaced with Cisplatin 50 mg/m2 day 1 – 2, if carboplatin is not available.

If radiotherapy is available, consider in any case, at any site of relapse, according to local guidelines.

If G-CSF is available, consider giving carboplatin and etoposide 3 days instead of 2 days.

Group 2 – Relapse treatment with palliative intent

Patients who have been treated with 3 drugs (vincristine / actinomycin / doxorubicin) during previous treatment

Cyclophosphamide 25 mg/m2 day 1-7 oral*

Etoposide 100 mg/m2 day 1-2 oral

Every week, until further progression of disease.

*Alternatively, etoposide 50 mg/m2 daily (oral) can be given.

Chapter 13 Follow Up

Patients will be asked to come back for follow up half yearly until two years after the end of treatment.

At each visit

1. Examine for palpable masses in the abdomen

2. An abdominal ultrasonography should be done to check for a recurrence.

Please also see the suggestions in Chapter 16 Strategies to prevent failure to complete treatment to prevent failure to complete treatment which also apply to facilitating complete follow up.

Long term follow up is essential to assess outcome of this treatment protocol reliably. It may be necessary to arrange for active follow up to try to find the patients by phone or a visit at their homes to find out how they are doing.

Chapter 14 Supportive Care

These supportive care recommendations are largely based on the SIOP PODC (PODC has been renamed Global Health Network) recommendations for supportive care of children with cancer in low income countries.[8]

Patients are often severely and acutely malnourished at presentation and this is associated with more severe chemotherapy-associated toxicity and decreased immunity.[16,31,32]

Ideally, children with cancer should be on a separate ward from children with infectious diseases. Hand washing, prior to and after examining each patient, is essential to prevent spreading infections from patient to patient.[8]

Fever and neutropenia

Infections are the most common cause of treatment-related mortality in low income settings.[2,24] Bacterial infections in neutropenic children can rapidly develop into septic shock and death.

Therefore, a local management plan has to be established in order to ensure that febrile patients who are possibly neutropenic will receive prompt and appropriate antibiotics. Fever is defined as twice a temperature > 38.0 °C or once > 39.0 °C. Fever in the presence of neutropenia (neutrophil count < 1.0 x 10^9/L with expectation of further neutrophil reduction) is defined as febrile neutropenia. Children may also be malnourished with associated impaired immunity. We recommend that all children with a neutrophil count below 1.0 x 109/L start antibiotics when they have a fever.[8] In settings where physicians are few and blood counts are not readily available, the nursing staff should take a blood culture whenever possible and start broad spectrum antibiotics immediately in any febrile child on treatment. If the health unit is in an area endemic for malaria, thick blood films for malaria parasites should be done (first). In many settings the available antibiotics are limited and second line, broad spectrum antibiotics such as third generation cephalosporins are reserved for severe or initially unresponsive infections. First-line antibiotics must cover common Gram positive and Gram negative bacteria.[8] In many settings, a broad-spectrum penicillin (e.g., ampicillin) plus an aminoglycoside (e.g., gentamicin) is a sensible and affordable first-line regimen. If a child remains febrile for longer than 48 hours, ceftriaxone or another third generation cephalosporin is a good second choice. Ciprofloxacin is an inexpensive alternative that usually covers pseudomonas which is not often sensitive to ceftriaxone. Be guided by local antibiotic sensitivities.

Nausea and vomiting

Anti-emetics may be needed to reduce vomiting. Metoclopramide (10 mg or 100 – 400 µg/kg) can be given orally 30 minutes before chemotherapy and has shown to be reasonably effective. If available, this can be replaced by or combined with diphenhydramine, which has the advantage of being relatively cheap and reducing the extrapyramidal symptoms associated with the use of metoclopramide. If available and needed, a selective serotonin antagonist (e.g., ondansetron, tropisetron) is an effective anti-emetic.[8]

Pain control

Adequate pain control is important, especially for children with progressive disease. Availability of oral morphine, the most effective and inexpensive pain control drug should be ensured. We recommend establishing a dedicated palliative care team with protected time to counsel families and organize care.[8]

HIV and other infections

We recommend treating children with HIV/AIDS like all other patients. Antiretroviral therapy (ART) should be continued or can be started simultaneously, if indicated, with the chemotherapy. Other co-infections, such as malaria, intestinal parasites and schistosomiasis, need to be identified and treated according to national guidelines. Screening for TB may be considered. If necessary, the anti-TB drugs can be started simultaneously with chemotherapy.[8]

Blood transfusions

Chemotherapy is expected to cause the haemoglobin to drop further. Transfusions may carry a risk of infections. If the Hb is less than 6 – 7 g/dl, then a blood transfusion is recommended.[8] Blood transfusions are recommended at higher Hb levels for children in poor general condition or who have a serious infection. Packed red cells (10 – 15 ml/kg) are given over 3- 4 hours.

Chapter 15 Nutritional assessment and nutritional support

Adequate nutritional assessment and nutritional support needs to be implemented.[31,33]

Acute malnutrition is associated with reduced immunity, an increase in severe chemotherapy-related side effects, altered pharmacokinetics such as higher serum levels of vincristine and other cytotoxic medications, additional surgical complications and increased morbidity and mortality.

In children with a large tumour, especially of the abdomen, weight can be a misleading measure of nutritional status. Clinical assessment of wasting is important in these children, but for a rapid, easy but reliable quantitative assessment at diagnosis, we recommend using mid upper arm circumference (MUAC).[8]

Most, if not all, of the children included in this study will be acutely malnourished at diagnosis and in need of nutritional support. The better their nutritional status at surgery, the less complications are to be expected.

A diet rich in energy (calories) and protein is important. Many poor families do not have the money to buy enough food while staying in hospital. Some hospitals provide meals for the children, but additional foods or supplements may be needed to provide sufficient calories, protein and micronutrients. Examples of locally acceptable and affordable protein-rich foods are ground nuts, beans, pigeon peas, small fish, eggs, soya, etc.

Peanut butter based ready-to-use-therapeutic foods such as “plumpy nut” or “chiponde” are often used on wards for malnutrition in sub-Saharan Africa and are, if affordable, valuable as additional nutritional support.[31,33]

Children who need acute nutritional rehabilitation should be managed according to the institutional guidelines. Temporary nasogastric tube (NGT) feeding may be needed in children who are incapable or reluctant to feed orally. F100 milk is available in many hospitals and can be given by NGT.

Chapter 16 Strategies to prevent failure to complete treatment

Failure to complete treatment is the most common cause of treatment failure for children with cancer in low income countries.[3,34] There are many reasons. One of the most important is cost. Usually parents do not have the money to pay for medical treatment and the associated costs (travel costs, food and lodging during stay in the hospital).[35] Whenever possible, treatment should be free of charge to poor families to enable them to finish the treatment. Social support is needed for families who cannot bear these additional costs. This may consist of a place to stay, meals for the patient and parents during hospitalisation and money for travel when they need to return. Adequate counselling on the nature of the disease and the importance of completing treatment are equally important.

Other suggestions

1. Carefully document all relevant and available contact information at admission.
2. Keep this documentation in the file (preferably on a sheet with a different colour).
3. If available, mobile phones can be very useful to keep in touch with families.
4. Keep a diary with an overview of scheduled patient visits. Patients can be called or contacted if they fail to attend.
5. If possible, a photograph taken of every child at diagnosis can help to identify the child and to trace the child actively when he/she has not come for further treatment or follow up.

Chapter 17 All Treatment Flow Sheets

Preoperative chemotherapy

Localized disease

Actinomycin D 45 µg/kg	↓		↓			surgery
Vincristine 1.5 mg/m²	↓	↓	↓	↓	*	
Weeks	**1**	**2**	**3**	**4**		

* Chest X-ray and / or ultrasound abdomen to determine regression and resectability of metastases.

Metastatic disease

Dox 30 mg/m²	↓				↓			
Act D 45 µg/kg	↓		↓		↓			surgery
Vinc 1.5 mg/m²	↓	↓	↓	↓	↓	↓	*	
Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	

* Chest X-ray and / or ultrasound abdomen to determine regression and resectability of metastases.

Optional I– Prolonged and intensified preoperative chemotherapy for localized disease to improve resectability

Doxorubicin 30	mg/m²					↓				
Actinomycin D 45	µg/kg	↓		↓		↓		↓		surgery
Vincristine 1,5	mg/m²	↓	↓	↓	↓	↓	↓	↓	↓	
Weeks		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	

Optional II – Prolonged preoperative chemotherapy for metastatic disease to improve resectability

Dox 30 mg/m²	↓				↓		↓				
Act D 45 µg/kg	↓		↓		↓	*	↓		↓	*	surgery
Vinc 1.5 mg/m²	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		

* Chest X-ray and / or ultrasound abdomen to determine regression and resectability of metastases.

Postoperative chemotherapy

SIOP Africa / PODC Wilms AV4 – only if based on reliable pathology report

For patients with localized disease at diagnosis and Stage I, intermediate risk (IR) pathology report

Actinomycin D 45 µg/kg		↓			
Vincristine 1.5 mg/m²	↓	↓	↓	↓	
Weeks	**1**	**2**	**3**	**4**	

SIOP Africa / PODC Wilms AV14 or AV26

For patients with localized disease at diagnosis and Stage II, IR or stage II, LR or stage III, LR pathology report.

Or

Surgical Stage I or Stage II

Actinomycin D 45 µg/kg		↓			↓			↓		
Vincristine 2.0 mg/m²	↓	↓			↓			↓		
Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
		11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
		20	**21**	**22**	**23**	**24**	**25**	**26**		

SIOP Africa / PODC Wilms AVD14 or AVD26

For patients with localized disease at diagnosis and Stage I HR, Stage II HR, Stage III IR, Stage III, HR (path)

Or

Surgical stage III

And for patients with metastatic disease at diagnosis

Actinomycin and Vincristine I.V. push, doxorubicin I.V. in 2 -6 hours.

Dox 30 mg/m²
Act D 45 µg/kg (max 2 mg)
Vinc 2.0 mg/m² (max 2 mg)

AVD14

Dox		↓			↓			↓			↓	
Act D		↓			↓			↓			↓	
Vinc	↓	↓			↓			↓			↓	
Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		14											

AVD26

Dox		↓						↓					
Act D		↓			↓			↓			↓		
Vinc	↓	↓			↓			↓			↓		
Weeks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		14	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
		26											

Appendix A Formal SIOP Surgical protocol

Surgery will be performed within 10 days of the completion of preoperative treatment. It will consist of a radical nephrectomy via a trans abdominal approach. For staging purposes, examination and sampling of at least one hilar and one para-aortic node, and any suspicious lymph nodes, and careful exploration of the other intradiaphragmatic organs and the opposite kidney is mandatory.

Preoperative imaging

The surgeon must know the extent of the tumour, its location within the kidney, and its relation to the central vessels, diaphragm, liver, pancreas, spleen and adrenal glands **before operation**. This can be done with high quality ultrasonography. Enlarged intra-abdominal (mainly para-aortic) lymph nodes, intra-abdominal metastases (mainly hepatic) and thrombus in the renal vein or vena cava should be looked for. Chest CT is advised if there is any doubt about the X-ray and if metastatectomy is planned.

The Operation

Access

Long transverse trans abdominal incision.

Inspection of the abdominal cavity

The abdominal cavity should always be inspected prior to tumour removal. Metastases in the liver, lymph nodes and peritoneum should be searched for. Since SIOP 6 and 9 studies have shown the value of excision for both pulmonary and intra-abdominal metastases, every effort must be made to remove these completely. Every lesion should be excised (if resectable) or biopsied (if unresectable) and its position marked. This includes lymph nodes which should be sampled even if they appear normal (see below). Excised material must be sent to the pathologist in a separate container and its origin clearly indicated. Complete excision should be attempted even if the diagnosis of nephroblastoma is uncertain. If the tumour is considered inoperable, it should be biopsied, preferably with a Tru-cut needle.

Thorough inspection of the opposite retroperitoneal space is obligatory **only** if pre-operative imaging indicates bilateral localisation of the tumour. In other cases, it rarely gives more information than good quality imaging. The operating surgeon should decide whether to do it in individual cases.

Nephrectomy

Early ligation of the renal vessels should be the aim and is possible in nearly every case. The renal artery should be ligated first in order to avoid swelling of the tumour with increase of its fragility and the possibility of dissemination via perforating perinephric veins. An extensive Kocher-manoeuvre of the duodenum is a convenient approach to the renal vessels for a large tumour whether on the right or left. An approach via the peritoneum lateral to the colon is also acceptable. The technique of the approach should be indicated in the surgery form. If the tumour is very large and infiltrating and the primary ligation of renal vessels is difficult and considered too risky, the tumour should be dissected from surrounding structures first, and vessels ligated when possible. This should be precisely described in the surgery form. The tumour should be removed together with adipose capsule and, if possible, with all invaded surrounding structures. Heroic and mutilating resections such as pancreatectomy are not recommended because these tumours are chemosensitive.

Renal Vein, Vena Cava

Although intravascular extension of the tumour is usually apparent on the pre-operative imaging, the vena cava and renal vein should be carefully examined during the operation. If thrombus is found, it should be removed. A short thrombus in the renal vein may be resected together with the vein. A thrombus extending to the infra-hepatic vena cava should be removed through a vena cavotomy, after occluding the contra lateral renal vein and cava above and below the thrombus. The thrombus should be removed and the venotomy closed.

Adrenal Gland

The adrenal gland can be left in situ if a safe resection margin between the tumour and the gland can be guaranteed.

Ureter

The ureter should be resected as close to the bladder as possible.

Lymph Nodes

NOTE: Sampling and histological examination of lymph nodes is imperative for accurate staging and subsequent treatment.

Hilar and para-aortic lymph nodes at the origin of the renal artery (regional nodes) and nodes below or above this level (extra regional nodes) should be sampled even if not suspicious. Involved or suspicious lymph nodes must be excised without rupture. They must be carefully labelled and sent to the pathologist separately with an accurate description of their position and character.

NOTE: The above information affects staging, treatment and therefore outcome. Radical lymph node dissection does not enhance survival and therefore is not part of the surgical therapy.

The sampling of hilar and para-aortic lymph nodes is just as important in patients with metastases.

Appendix B The SIOP Nephroblastoma Staging System (Pathology)

Stage I

1. The tumour is limited to kidney or surrounded with a fibrous (pseudo)capsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated by the tumour but it does not reach the outer surface.
2. The tumour may be protruding ('bulging') into the pelvic system and 'dipping' into the ureter but it is not infiltrating their walls.
3. The vessels or the soft tissues of the renal sinus are not involved.
4. Intrarenal vessel involvement may be present.

Notes

- Fine needle aspiration or percutaneous core needle ('tru-cut') biopsy does not upstage the tumour but the size of the needle gauge should be mentioned to the pathologist.
- The presence of necrotic tumour or chemotherapy-induced change in the renal sinus and/or within the perirenal fat should not be regarded as a reason for upstaging a tumour providing it is completely excised and does not reach the resection margins.
- Infiltration of the adrenal gland does not upstage tumour if the external capsule of the adrenal gland is intact.
- Liver: tumour might be attached to the liver capsule and this should not be regarded as infiltration of the adjacent organ; only if clear infiltration of the liver parenchyma is present, tumour should be regarded as stage III.

Stage II

1. Viable tumour penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins 'clear').
2. Viable tumour infiltrates the soft tissues of the renal sinus.
3. Viable tumour infiltrates blood and lymphatic vessels of the renal sinus or in the perirenal tissue but it is completely resected.
4. Viable tumour infiltrates the renal pelvic or ureter's wall.
5. Viable tumour infiltrates adjacent organs or vena cava but is completely resected.

Stage III

1. Viable or non-viable tumour extends beyond resection margins.
2. Any abdominal lymph nodes are involved.
3. Tumour rupture before or intra-operatively (irrespective of other criteria for staging).
4. The tumour has penetrated through the peritoneal surface.

5. Tumour implants are found on the peritoneal surface.
6. The tumour thrombi present at resection margins of vessels or ureter, trans-sected or removed piecemeal by surgeon.
7. The tumour has been surgically biopsied (wedge biopsy) prior to pre-operative chemotherapy or surgery.

NOTE: The presence of necrotic tumour or chemotherapy-induced changes in a lymph node or at the resection margins is regarded as proof of previous tumour with microscopic residue and therefore the tumour is assigned stage III (because of the possibility that some viable tumour is left behind in the adjacent lymph node or beyond resection margins).

Stage IV

Haematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region.

Stage V

Bilateral renal tumours at diagnosis. Each side should be sub-staged according to the above criteria.

Appendix C Revised SIOP Working Classification of Renal Tumours of Childhood (2001) for Pre-Treated Cases

Low risk tumours

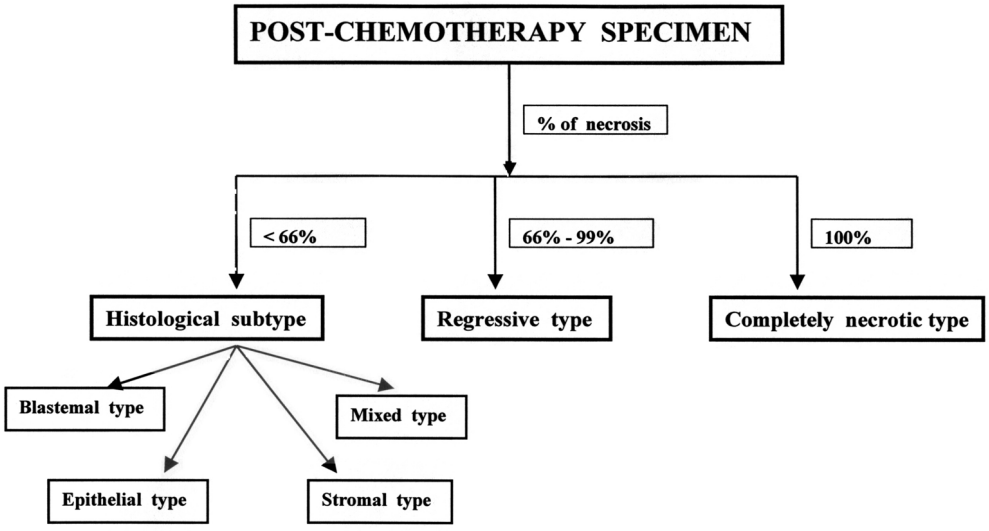
- Mesoblastic nephroma
- Cystic partially differentiated nephroblastoma
- Completely necrotic nephroblastoma

Intermediate risk tumours

- Nephroblastoma - epithelial type
- Nephroblastoma - stromal type
- Nephroblastoma - mixed type
- Nephroblastoma - regressive type
- Nephroblastoma - focal anaplasia

High risk tumours

- Nephroblastoma - blastemal type
- Nephroblastoma - diffuse anaplasia
- Clear cell sarcoma of the kidney
- Rhabdoid tumour of the kidney



Appendix D SIOP Surgical Staging System

Surgical staging

- **Stage I** The tumour is resected with a clear margin
- **Stage II** The tumour is macroscopically completely resected
- **Stage III** There are involved abdominal nodes
  The tumour is incompletely resected or ruptured or there is a vascular extension

Appendix E SIOP Pathology – handling and study of the nephrectomy specimen

Handling the fresh specimen

The following steps must be followed when handling the fresh specimen

1. **Weigh**, **measure** and **photograph** the whole specimen. Look carefully for ruptures and fissures and locate any suspicious areas and/or ink it in different colours from the rest of the specimen. Decapsulation makes determination of growth beyond the capsule impossible and therefore should not be done.
2. Look for and dissect the peri-renal and perihilar **lymph nodes**. Block these separately recording the site. (These are rare).
3. **Identify renal vein, artery and ureter** and take transverse section block of each near the resection margin.
4. **Ink** the surface of the whole specimen (or at least areas in which excision margins are dubious) and renal sinus with Indian ink and let it dry **before** opening the specimen. This is a critical step and should always be done as otherwise it might be impossible to stage the tumour correctly and give adequate therapy.
5. **Open** by a longitudinal incision to bivalve the specimen and reveal the tumour and its relation to the kidney, capsule, and renal sinus.
6. **Photograph** the cut surface, record macroscopic appearance. **Measure** the size of the tumour. It is crucial to **assess the percentage of a necrotic tumour** and also to describe and photograph the multicystic cut surface, if present.
7. **The specimen** should be ***fixed*** in 4% buffered formalin for 24 to 48 hours, according to the usual procedure of the laboratory. Several additional cuts can be made parallel to the initial cut to divide the specimen into “slabs” for better fixation. (*Alternatively, instead of parallel longitudinal sections, you may find that making horizontal sections and sampling the tumour in this way will give a better view of the renal sinus and a tumour-sinus relationship*.)

Samples for histological examination

Samples for histological examination should include:

1. At least one longitudinal slice of tumour and kidney surface, completely sampled (see Figure 1). Please consider using mega-blocks because it makes histological assessment much easier and they are less time-consuming for both pathologists and their labs.
2. In addition, please sample the following too:
3. The macroscopically different areas of the tumour (it is advised to take at least one block per cm of the largest diameter of the tumour, not forgetting to take blocks from grossly necrotic areas, too); mostly from the periphery rather than from the central areas of the tumour;
4. Dubious areas have to be marked by the surgeon and need special attention of the pathologist (they have to be marked with Indian ink or methylen blue);
5. Sinus lymph nodes when present;
6. Other lymph nodes;
7. Renal pelvis and pelvic fat, ureter and sinus vessels; especially the renal vein should be inspected for evidence of tumour thrombus; if present, it is critical to assess whether it is completely resected;
8. Each nodule away from the main mass (in multifocal tumours);

9. Tumour-kidney interface;
10. Tumour-kidney capsule;
11. Areas of the capsule that are suspected of being invaded by the tumour;
12. Areas of perirenal fat suspected for tumour infiltration (important for assessment whether the tumour is completely resected);
13. Areas of adhesions of the tumour to surrounding tissues;
14. At least 2 blocks of the normal kidney and blocks from abnormal looking areas in the remaining renal tissue.

Please have a 'block guide' (as in Figure 1 below), i.e., all the samples should be numbered and their sites recorded as well as all other samples taken at the time of operation, i.e. adrenals, lymph nodes and various biopsies. If there is no photo, please use **a pre-prepared diagram in the Pathology Form.**

Please clearly state all relevant findings in the histopathology report and document block/slide number. This make central pathology review easier.

For example, "there is renal sinus invasion in block A7"

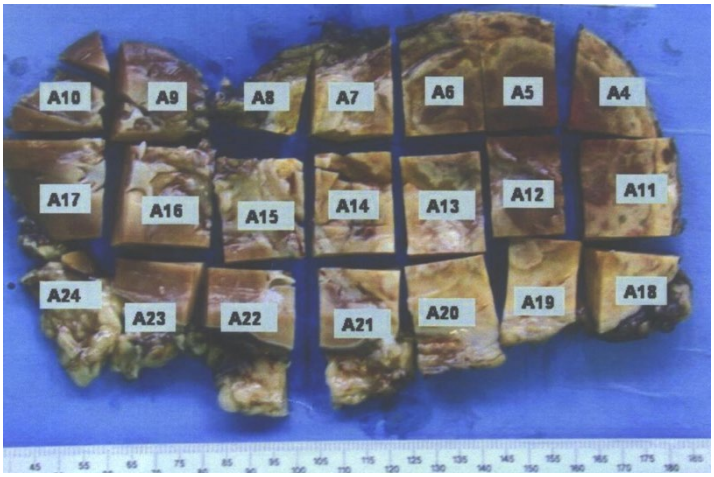


Figure 1. Recommended sampling of renal tumours

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